Feasibility of melatonin for prevention of delirium in critically ill patients: a protocol for a multicentre, randomised, placebo-controlled study

Lisa Burry,1 Damon Scales,2 David Williamson,3 Jennifer Foster,4 Sangeeta Mehta,5 Melanie Guenette,6 Eddy Fan,7 Michael Detsky,8,9 Azar Azad,10 Francis Bernard,11,12 Louise Rose13

ABSTRACT

Introduction: Delirium is highly prevalent in the intensive care unit (ICU) and is associated with adverse clinical outcomes. At this time, there is no drug that effectively prevents delirium in critically ill patients. Alterations in melatonin secretion and metabolism may contribute to the development of delirium. Administration of exogenous melatonin has been shown to prevent delirium in non-critically ill surgical and medical patients. This trial will demonstrate the feasibility of a planned multicentre, randomised controlled trial to test the hypothesis that melatonin can prevent delirium in critically ill patients compared with placebo.

Methods and analysis: This feasibility trial is a randomised, 3-arm, placebo-controlled study of melatonin (2 vs 0.5 mg vs placebo, administered for a maximum of 14 days) for the prevention of delirium in critically ill patients. A total of 69 patients aged 18 years and older with an expected ICU length of stay >48 hours will be recruited from 3 Canadian ICUs. The primary outcome is protocol adherence (ie, overall proportion of study drug doses administered in the prescribed administration window). Secondary outcomes include pharmacokinetic parameters, incidence, time to onset, duration of delirium, number of delirium-free days, adverse events, self-reported sleep quality, rest-activity cycles measured by wrist actigraphy, duration of mechanical ventilation, ICU length of stay and mortality. Data will be analysed using an intention-to-treat approach.

Ethics and dissemination: The study has been approved by Health Canada and the research ethics board of each study site. Trial results will be presented at international conferences and published in a peer-reviewed journal.

Trial registration number: NCT02615340: Pre-results.

INTRODUCTION

Delirium is a syndrome of acute brain dysfunction characterised by fluctuations in attention, mental status, disorganised thinking and altered level of consciousness.1 Specific symptoms such as delusions and hallucinations, agitation, restlessness, and sleep disturbance are distressing for patients, families and clinical staff.2 3 Delirium is highly prevalent in the intensive care unit (ICU) where rates range from 40% to 90%.4 Critically ill patients who develop delirium experience worse outcomes including increased mortality, prolonged mechanical ventilation, increased duration of ICU and hospital length of stay, functional and cognitive decline, and increased likelihood of placement in long-term care facilities.5–10 These adverse clinical and systems-level implications underscore the imperative of identifying safe and effective strategies for the prevention of delirium in critically ill patients. At this time, however, no pharmacological agent has been shown to effectively
prevent delirium or favourably alter related outcomes in this patient population.4

The pathophysiology of delirium is not fully understood. Current hypotheses include neuroinflammation, impaired cerebral oxidative metabolism and disturbances of neuroendocrine and neurotransmitter systems.11 12 In particular, there is considerable research on dopaminergic, cholinergic, γ-aminobutyric acid and serotonergic neurotransmitter pathways, as these modulate cognition, behaviour, mood and sleep. Although disturbances of the sleep–wake cycle are not diagnostic of delirium, changes in sleep patterns are incorporated into delirium screening tools, and studies indicate that sleep changes occur in over 75% of delirious patients.13

Melatonin (N-acetyl-5-methoxytryptamine) is a neurohormone sequentially derived from tryptophan and serotonin and is secreted by the pineal gland during hours of darkness.14 It has multiple biological effects, most notably in the regulation and synchronisation of circadian rhythms, where it works as a hypnotic in accelerating the initiation and improving the maintenance and efficiency of sleep.14 Disturbances in circadian melatonin secretion have been described in a number of patient populations at high risk of delirium, including general medicine, critically ill with sepsis and post-operative.15–21 Given these findings, the abnormal secretion and metabolism of melatonin may play a role in delirium pathogenesis.13 15 16 18 22–24

Unlike other hypnotics, melatonin causes no significant changes in sleep architecture and has no hangover effects or abuse potential.25 The administration of exogenous melatonin may therefore prevent delirium through its effects on circadian rhythm and sleep.19 20 Exogenous melatonin has also been shown to be sedative sparing,26 an important factor in reducing delirium risk in critically ill patients.4 27 28

The hypothesis that exogenous melatonin may prevent delirium has been explored in three randomised controlled trials.29–31 In one study, hospitalised general medicine patients (N=145, aged 65 years and older) given low-dose melatonin (0.5 mg) at bedtime displayed significantly less delirium (3.6% vs 19%, p=0.014) compared with placebo controls.31 In a surgical population (N=222, aged 65 years and older) comparing melatonin (5 mg), midazolam (7.5 mg) and clonidine (0.1 mg) to no premedication administered the night prior to and again 90 min before surgery, patients receiving melatonin experienced significantly less delirium in the post-operative period compared with no premedication, midazolam or clonidine (melatonin 9.4% vs no premedication 32.7% vs midazolam 44.0% vs clonidine 37.3%, p<0.05).29 In contrast, a large trial (N=444, aged 65 years and older) of hip fracture patients reported that a 3 mg dose of melatonin at bedtime did not reduce delirium compared with placebo (29.6% vs 25.5% placebo, p=0.4); however, fewer patients treated with melatonin experienced long-lasting delirium, defined as more than 2 days (25.5% vs 46.9%, p=0.02).30 Furthermore, a trial of ramelteon, a melatonin agonist, showed a significant reduction in delirium incidence compared with placebo (3% vs 32%, p=0.003) when administered to a mix of ICU and acute ward patients (N=67).32

A recent systematic review found that melatonin did not reduce delirium incidence (relative risk (RR) 0.41, 95% CI 0.15 to 1.13; p=0.08).33 However, in the subgroup of elderly patients treated in acute medical wards, melatonin decreased delirium incidence by 75% (RR 0.25, 95% CI 0.07 to 0.88; p=0.03), but did not reduce sleep–wake disturbance (RR 1.24, 95% CI 0.51 to 3.10; p=0.64). Given the small number of melatonin studies for delirium prevention, more research is needed. This is particularly important in the critically ill population which is considered at highest risk and among the most burdened by delirium from a clinical and resource usage standpoint.

Study objectives
Exogenous melatonin may decrease delirium incidence in non-critically ill patients. However, there are no trials focused solely on the critically ill population. On the basis of the available evidence, we hypothesise that exogenous melatonin, administered on a scheduled nightly basis, will be efficacious and safe in the prevention of delirium in critically ill adults.

This pilot study will serve to determine the feasibility of conducting a future large-scale, multicentre, randomised, placebo-controlled trial in critically ill patients at risk of delirium. Additionally, we aim to determine appropriate melatonin dosing.

Specific study objectives are to:
1. Identify the proportion of administered doses of the prescribed study drug (ie, study protocol adherence);
2. Identify the proportion of screened study participants who meet the inclusion criteria;
3. Identify the consent rate of eligible participants (ie, feasibility and time frame of enrolment: number screened, number excluded, number consented);
4. Describe, per patient, the time required to complete study enrolment and all data collection;
5. Describe the pharmacokinetic properties of enterally administered melatonin at a dose of 0.5 mg compared with 2 mg;
6. Describe the proportion of participants who experience adverse drug effects; and
7. Compare delirium incidence (Intensive Care Delirium Screening Checklist (ICDSC)34 score of 4 or more) and duration, self-reported sleep quality, rest-activity cycles (with wrist actigraphy), duration of mechanical ventilation, length of ICU and hospital stay, and ICU and hospital mortality.

METHODS AND ANALYSIS
Study design
We will conduct a three-arm, randomised, placebo-controlled feasibility trial comparing the safety and efficacy
of two doses of melatonin (low dose=0.5 mg and high dose=2 mg) versus placebo for the prevention of delirium in patients with an anticipated ICU admission of >48 hours.

**Study outcomes**

**Feasibility outcomes**
1. Protocol adherence: we will calculate protocol adherence using the overall proportion of doses administered in the prescribed dose administration window divided by the total number of study days. We will define adherence as administration of \( \geq 85\% \) of prescribed doses within the drug administration window \( qHS \) (\( quaque hora somni \) defined as 21:00–23:59);
2. Trial recruitment: we will calculate the proportion of screened ICU patients meeting study inclusion criteria, the number of and reasons for patient exclusions, and the consent rate of eligible participants; and
3. Time-in-motion study: we will capture the amount of time required to screen for, consent and enrol patients, as well as to complete study procedures and data collection for the first 10 patients at each site.

**Pharmacokinetic outcomes**
Plasma melatonin levels will be measured by mass spectrometry including:
1. Peak concentration;
2. Time of peak concentration;
3. Morning concentration;
4. Half-life;
5. Mean apparent clearance;
6. Mean apparent volume of distribution and
7. Area under the concentration-time curve.

**Clinical outcomes**
1. Adverse events: we will screen for the following adverse events previously associated with melatonin: morning drowsiness (Sedation Agitation Scale (SAS))\(^a\) scores <3 or patient self-report of drowsiness between 7:00 and 12:00), headache and vivid dreams
2. Delirium incidence (ICDSC\(^b\) score \( \geq 4 \)) and sub-syndromal delirium (ICDSC score of 1–3)
3. Time to onset of delirium, delirium duration and delirium-free days (at ICU discharge)
4. Self-reported sleep quality (Richards Campbell Sleep Questionnaire (RCSQ))\(^c\) and rest-activity cycles with wrist actigraphy)
5. Duration of mechanical ventilation
6. Length of stay (ICU and hospital) and
7. Mortality (ICU and hospital)

**Location and setting**
We will conduct the trial in three mixed-patient population ICUs in three university-affiliated hospitals (Sunnybrook Health Science Centre (Toronto), Mount Sinai Hospital (Toronto) and Hôpital du Sacré-Cœur de Montréal (Montreal)). These ICUs have existing research infrastructure and extensive experience with clinical trial conduct, including studies related to delirium.

**Participant selection and recruitment**
The study participants will be adult critically ill patients admitted to the ICU at any of the three study sites.

**Inclusion criteria**
1. Critically ill patients aged 18 years or older and
2. Anticipated ICU stay >48 hours

**Exclusion criteria**
1. ICU admission >48 hours at the time of screening
2. Unable to assess for delirium (eg, coma or deep sedation (SAS score 1 or 2 or ‘no response’ score A or B on ICDSC); receiving neuromuscular blocking drugs) at the time of screening
3. Screened delirium positive (ICDSC score \( \geq 4 \)) prior to randomisation
4. Anticipated withdrawal of life-sustaining therapy
5. History of severe cognitive or neurodegenerative disease (eg, dementia, Parkinson’s disease) or severe structural brain injury (eg, traumatic brain injury, intracranial haemorrhage) as the ICDSC assessment tool has not been validated in these patient populations
6. Unable to communicate in English or French (Montreal site) as we will be unable to assess for delirium using the ICDSC in non-English-speaking/French-speaking patients
7. Absolute contraindication to enteral nutrition (eg, gastrointestinal obstruction, perforation, recent gastrointestinal surgery, deemed strict nil by mouth, lack of enteral access)
8. Active seizures
9. Known pregnancy
10. Legally blind
11. Known allergy to melatonin

**Eligible non-randomised criteria**
1. Patient or substitute decision-maker (SDM) declines consent
2. Patient unable to give consent and no SDM available
3. ICU physician declines consent
4. Consent not obtained due to another reason
Research personnel at each study site will screen for potential participants daily, Monday to Friday. Written informed consent will be sought from competent eligible participants, or SDMs, if incompetent. Consent will be documented in the patient’s medical record.

**Randomisation and blinding**
Following informed consent, participants will be randomly assigned in a 1:1:1 manner to one of the three study arms using a computer-generated, permuted-block randomisation schedule, stratified according to site. The clinical trial pharmacists and/or trial pharmacy technician at each site will randomise patients to treatment groups using the REDCap interactive randomisation technology. Study personnel, the ICU team, participants and family members will be blind to study group
allocation, except in an emergency and only after unblinding is approved by the principal investigator. In this instance, the principal investigator and attending physician will discuss whether unblinding is necessary to provide medical care to the patient.

A target sample of 15 participants (5 from each study arm) from the Mount Sinai Hospital site will be recruited for inclusion in the pharmacokinetic analysis. There are no additional inclusion or exclusion criteria for participation in the pharmacokinetic analysis.

Interventions

After randomisation, a preprinted study medication order will be placed in the patient’s medical chart. Study participants will receive the study drug (melatonin 0.5 mg, melatonin 2 mg or placebo) once daily qHS, between 21:00 and 23:59. Study medication will be administered by mouth or, if necessary, by feeding tube (nasogastric, orogastric, jejunal or percutaneous endoscopic gastrostomy) with subsequent flushing with 20 mL of sterile water. All study drugs will be administered starting on the day of study enrolment and continued until ICU discharge, death or up to a maximum of 14 days, whichever occurs first. This maximum duration of study drug administration was selected because critically ill patients are at greatest risk of developing delirium within the first 2 weeks of ICU admission.8

The optimal dose of melatonin for the prevention of delirium has yet to be determined. Published trials for delirium prevention in hospitalised, non-critically ill adults have administered oral nightly doses of melatonin ranging from 0.5 to 3 mg.20-31 Trials of melatonin for sleep disorders have used higher doses, up to 10 mg.38-41 A small study evaluating melatonin for sleep in mechanically ventilated adults (N=24) found that a 10 mg nightly dose excessively increased plasma concentrations and resulted in morning drowsiness. The authors therefore suggested that doses of 1–2 mg may be more appropriate in critically ill patients.42 For jet lag in non-clinical populations, melatonin doses between 0.5 and 5 mg have been shown to be similarly effective; however, doses above 5 mg were not found to be more effective than lower doses.43 Given the relatively sparse data on melatonin for delirium prevention and the lack of trials in ICU patients, we have chosen doses we feel are reasonable given the available data, while also ensuring sufficient difference to identify an effective dose.

We will not protocolise administration of any co-interventions in this study. The clinical team will remain responsible for all other aspects of patient care, including any pharmacological or non-pharmacological interventions for delirium prevention and treatment, or interventions that may be associated with delirium development. As such, the management of pain, agitation, sedation, delirium and sleep will be performed according to local practice, the details of which will be captured through study data collection. The use of open-label melatonin will not be permitted in this study.

Study medication

The clinical trial pharmacist and/or pharmacy trial technician at each site will compound melatonin 1 mg/mL oral suspension in accordance with Good Manufacturing Procedures (GMP) guidelines. All sites will use a non-animal synthetic source of melatonin (Jamieson Laboratories, NPN 80015041 immediate release) to compound doses. The compounded 1 mg/mL solution will be further diluted with Oral Mix SF (sugar-free flavored suspending vehicle) (MEDISCA Pharmaceutique Inc. product code 2600) to prepare study doses identical in appearance (milky white colour and identical final volume). Each 5 mL dose will be dispensed in amber oral syringes labelled as ‘melatonin/placebo study drug’. Only the clinical trial pharmacist and/or pharmacy trial technician specified on the delegation of responsibility log will prepare and dispense the study drug.

The study drug will be stored, tracked and counted in accordance with standard pharmacy dispensing practices by the clinical trial pharmacist and/or pharmacy trial technician. The pharmacy department at each site will maintain a dispensing list kept in the study operations binder that records the identity of participants for each study randomisation number. The randomisation number will be indicated on the prescription in the participant’s chart and on the dispensing label, allowing the bedside nurse to verify that the patient receives the appropriate study medication. The nurse will record the administration of the study drug in the medication administration record, in accordance with standard ICU practice.

Data collection

To ensure consistency and optimisation of the data collection process, case report forms and standard operating procedures will be included in each site’s study resource binder. Study training sessions will be held at each site, and attendance of research staff will be documented. Only trained and qualified research staff will be permitted to collect study data.

Protocol adherence and feasibility assessment

Each morning, the research team will review the medication profile of study participants to ascertain if the study drug was administered and, where applicable, identify the reasons for late (ie, protocol deviation) or missed (ie, protocol violation) doses. Each site will maintain a screening log documenting patients: (1) screened, (2) ineligible, (3) eligible, (4) consented and enrolled, and (5) declined. Using a time-in-motion template41 by the Canadian Critical Care Trials Research Coordinator Group, the time required to complete patient screening, maintain the study log, and complete all consent and study-related procedures, including data capture, will be recorded on a daily basis for the first 10 patients enrolled at each site.
Pharmacokinetics
A pharmacokinetic analysis of plasma melatonin concentration will be conducted at the Mount Sinai Hospital site in participants who consent to the required blood samples. A target sample of 15 participants (5 from each study arm) will be enrolled. On the first study day, research personnel will collect eight blood samples of 4 mL each using BD vacutainer tubes (K2 EDTA 7.2 mg, DB Franklin Lakes, New Jersey, USA). The first sample will be taken prior to the first dose of the study drug, and subsequent samples will be collected throughout the night at predefined intervals (t0 (baseline), t0.5 hour, t1 hour, t2 hours, t4 hours, t6 hours, t8 hours, t12 hours) terminating 12 hours later (ie, the next morning). Specimens will be screened for haemolysis and redrawn if needed. All samples will be centrifuged and stored at −80°C until assays are performed by Mount Sinai Hospital Services Laboratory. Plasma melatonin concentration will be measured using mass spectrometry, and sample dilution to within the linear range of the assay will be performed as necessary. Non-compartmental pharmacokinetic analysis (PKSolution 2.0; Summit Research Services, Montrose, Colorado, USA) will be used to compare the three study doses. The timing of the blood samples was chosen based on pharmacokinetic studies using similar methodology, in critically and non-critically ill patients.45–47

Since melatonin release is regulated by the presence of light, research personnel will also measure light intensity at the time of (ie, in the 5 min prior to) each blood sample. Light intensity will be measured near the head of the patient’s bed at eye level using a lux-meter (Environment Meter SHSEHY002, Shimana, Digital Measurement Metrology, Brampton, Ontario, Canada).

Clinical outcomes
Delirium: The ICDSC34 is an eight-item checklist that requires initial evaluation of the patient’s level of consciousness, with subsequent delirium screening if the patient is neither comatose nor stuporous. It has been shown to have a pooled sensitivity of 74% and specificity of 82%.48 Clinical staff will screen for delirium once daily until the patient is discharged from the ICU. If the bedside staff have not completed the ICDSC, research staff will prompt the completion of the assessment. All ICDSC scores will be recorded on the case report form for the duration of the patient’s ICU admission, enabling the determination of the incidence and duration of delirium and subsyndromal delirium.49

Sleep: The RCSQ is a simple, validated survey instrument used to evaluate perceived depth, latency, efficiency and quality of sleep in intensive care patients.50 51 Patients will be asked to complete the RCSQ each morning of study participation, independently or with the assistance of their bedside nurse. If the patient is unable to complete the RCSQ, no sleep data will be collected for that day because of poor correlation between the patient and their nursing scores.50 Although polysomnography51 52 is the reference standard for measuring sleep, its requirement for specialised technology and expert staff for interpretation render it logistically challenging in the ICU setting. Polysomnograms are also particularly difficult to interpret in ICU patients because of considerable polypharmacy and pathophysiology associated with their critical illness.

Patients enrolled at the Hôpital du Sacré-Coeur de Montréal site (N target=21) will have rest-activity cycles measured using wrist actigraphy. The actigraph is a small watch-like device that contains an accelerometer, which records physical motion in all directions with a sensitivity of 0.05 g. Motion is converted into an electric signal, which is digitally integrated to derive an activity count per 1 min epoch. The rest-activity cycle consolidation will be estimated with the ratio of daytime activity to total 24-hour activity. For each 24-hour day and for each participant, the activity counts will be summed separately for daytime (07:00–21:59) and nighttime (22:00–6:59) periods. Night time is defined according to the schedule of the hospital unit, and is characterised by lower levels of activity and light. The percentage of activity occurring in the daytime will be divided by the total 24-hour activity to obtain the daytime activity ratio. According to previously published data,53 a daytime activity ratio of 80% will be chosen to designate an adequate consolidation of the rest-activity cycle, synchronised to the day–night cycle.

Adverse events: We will adhere to published guidelines54 55 for reporting serious adverse events in academic drug trials in critical care. As such, the only adverse events recorded will be those reasonably thought to be a consequence of study participation, and judged by investigators to be unrelated to the patient’s underlying disease or an unexpected complication of critical illness.

Other data: Other data recorded daily will include the Glasgow Coma Scale (GCS)56 and SAS55 scores, psychoactive drug exposure (ie, type and dose of sedative, analgesic, antianxiety and antipsychotic medications), sedation protocols or sedation interruption, mobilisation out of bed, physical restraint, accidental device removal, presence of a visible clock or window, use of a television, computer or iPad, single versus shared room, isolation precautions, and strategies to preserve day–night orientation including light and noise reduction (ie, earplugs and eye masks). Patient demographics (age, sex), comorbidities, use of visual and auditory aids, severity of illness score (Sequential Organ Failure Assessment [SOFA])57, admission diagnosis, best possible medication history,58 duration of mechanical ventilation, ICU and hospital length of stay, and ICU and hospital mortality will also be recorded.

Statistical considerations
Sample size
The sample size for this pilot study has been determined to measure adherence to the prescribed study drug, with adherence defined as administration of ≥85% of prescribed doses within the administration window using a
margin of error of ±5%. For an average daily drug administration lasting 4 days and an intracluster correlation of 0.115 (adjusting for the clustering effect of repeated drug administration within the same participant), 69 patients (or 276 drug administration adherence opportunities) will enable determination of successful adherence (rate 85%; margin of error of ±5% at a 95% confidence level).

Statistical analysis
Data will be analysed using an intention-to-treat approach. Simple descriptive statistics will be used to report feasibility outcomes, pharmacokinetics, as well as baseline demographic and clinical variables. Continuous variables will be described using measures of central tendency and spread (means and SDs or medians and IQRs, dependent on data distribution). Frequencies, proportions and their 95% CIs will be used to describe categorical variables. Except for analyses of repeated measures, Kruskal-Wallis tests will be used to compare continuous variables, and χ² tests to compare categorical variables. Methods that account for clustering will be used when analysing repeated observations from the same participant. Time-to-event analyses will be used to compare the effects of the study drug on the onset of delirium, duration of mechanical ventilation, ICU and hospital length of stay.

Analyses will be considered significant when p ≤ 0.05 (two-tailed). All analyses will be performed by an independent statistician using SAS V.9.3.

Ethics and dissemination
This trial is funded by the Centre for Collaborative Drug Research at the University of Toronto, and will be conducted in accordance with the ethical principles outlined by the Canadian Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans and the Declaration of Helsinki. Trial methods and results will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines.

Ethical considerations
The trial will be conducted in accordance with Good Clinical Practice following published tri-council guidelines, the Canada Natural Health Products Regulations, the Canadian Personal Health Information Protection Act (PHIPA) and the International Conference on Harmonization Good Clinical Practice (ICH GCP). All data will be de-identified and will be presented in summary form to preserve the anonymity of individual participants.

All patients or their SDM will sign an informed consent form before trial participation and will be given a copy for their records. Research staff will provide an appropriate lay explanation of the proposed aims, methods, objectives and possible harms of the study. A specific section outlining the acquisition and storage of blood samples is included in the informed consent form. We will complete routine quality control to ensure that the study is being conducted according to protocol. This routine quality control will include verification of (1) inclusion and exclusion criteria; (2) source data checks, to ensure accuracy of data collection; (3) adverse events checks to confirm that these are recorded, assessed and reported according to protocol; and (4) case report form review, to ensure completion according to protocol.

CONCLUSION
Delirium is a common syndrome in critically ill patients and is associated with numerous adverse clinical outcomes. At this time, no effective drug treatment exists for delirium, making the identification of a safe and effective prevention therapy a clinical imperative. Exogenous melatonin is inexpensive to administer and demonstrates a wide safety margin across adult and paediatric clinical populations. This feasibility trial is the first to explore the effect and pharmacokinetics of high-dose and low-dose melatonin against placebo in critically ill adults. The results of this study are expected in 2018 and if feasibility is proven, we plan to conduct an adequately powered pragmatic randomised controlled trial of similar design.

Author affiliations
1Department of Pharmacy, Mount Sinai Hospital, and Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Canada
2Department of Critical Care Medicine, Sunnybrook Health Sciences Centre, and Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Canada
3Department of Pharmacy, Hôpital du Sacré-Cœur de Montréal, and Faculté de pharmacie, Université de Montréal, Montréal, Canada
4Department of Critical Care, IWK Health Centre, and Dalhousie University, Halifax, Canada
5Department of Medicine and Interdepartmental Division of Critical Care Medicine, Mount Sinai Hospital and University of Toronto, Toronto, Canada
6Department of Pharmacy, Mount Sinai Hospital, Toronto, Ontario, Canada
7Interdepartmental Division of Critical Care Medicine and Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada
8Department of Medicine, University of Toronto, Toronto, Canada
9Department of Medicine, University of Toronto and Department of Medicine, Mount Sinai Hospital, Toronto, Canada
10Mount Sinai Services, Mount Sinai Hospital, and Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Canada
11Département de Médecine, Hôpital du Sacré-Cœur de Montréal, and Département de Médecine, Université de Montréal, Montréal, Canada
12Département de Médecine, Université de Montréal, Montréal, Quebec, Canada
13Department of Critical Care Medicine, Sunnybrook Health Sciences Centre, and Lawrence S. Bloomberg Faculty of Nursing and Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Canada

Acknowledgements
Michael Christian MD, MSc; Heather Boon, PhD; Wei Xiong, MSc; Elizabeth Wilcox, MD; Catherine Duclos, BA, PhD (candidate); Nadia Gosselin, PhD; Salmaan Kanji, PharmD; Michelle Rodrigues, BSc; Hilde Vandenberghe, PhD

Contributors
LB, DS, DW, JF, SM, MG, EF, MD, AA, FB and LR made substantial contributions to the conception and/or design of the study protocol. LB, DS, DW and LR conceived of the overall study and wrote the
first draft of the protocol and this manuscript. LB, DS, DW, AA and LR provided critical input pertaining to the design of the study interventions, procedures and outcomes. LB, DS, MG, AA and LR designed the data analysis and management plan. LB, DS, DW, JF, SM, EF, MD, FB and LR critically revised the protocol for important intellectual content and approved the final version to be published. LB, DS, DW, JF, SM, MG, EF, MD, AA, FB and LR agree to be accountable for all aspects of the work, ensuring its accuracy and integrity.

Funding
This work was supported by the Centre for Collaborative Drug Research at the University of Toronto (Pilot Project Fund 2015).

Competing interests
None declared.

Ethics approval
Health Canada (No Objection Letter, #197507, 7 November 2016) and the research ethics board of each participating centre have approved the protocol (Sunnybrook Health Sciences Centre #086-2016; Mount Sinai Hospital #16-0097-A and Hôpital du Sacré-Cœur de Montréal #2017-1385).

Provenance and peer review
Not commissioned; externally peer reviewed.

Open Access
This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

REFERENCES


