Midodrine for the early liberation from vasopressor support in the ICU – LIBERATE

A multi center concealed-allocation parallel-group blinded randomized controlled trial to ascertain the effect of midodrine compared to placebo on intravenous vasopressor duration and ICU length of stay for critically ill patients

Principal Investigator:
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LIBERATE PROTOCOL
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Sponsor:
University of Alberta Hospital Foundation Kaye Fund

ClinicalTrials.gov:
NCT05058612

SPONSOR STATEMENT of COMPLIANCE

My signature confirms the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP), Division 5 of Health Canada's Food and Drug Regulations, the ethical principles that have their origins in the Declaration of Helsinki, and applicable privacy laws.

Personnel listed below are authorized to sign the protocol and any subsequent protocol amendments on behalf of the sponsor:

Name:
(Print) Oleksa G. Rewa

Title:
(Print) Principal Investigator

Signature: 

Date of Approval: 24-May-2023
(dd-mmm-yyyy)

PROTOCOL SIGNATURE PAGE

I have read this protocol in its entirety and its appendices. I agree to comply with the requirements of the study protocol and procedures for data recording/reporting and acknowledge my responsibility for the well-being of each research participant and to ensure that all persons involved in study activities are adequately informed about the protocol, the investigational product, and their trial-related duties. The signature below constitutes the agreement to conduct this study in accordance with the REB approved protocol, GCP and applicable regulatory requirements, including confidentiality, ethical guidelines and regulations regarding the conduct of research in humans.

Qualified Investigator:

Name:
(Print) _____

Title & Institution:
(Print) _____

Signature: _____

Date of signature _____
(yyyy-mmm-dd)

TABLE OF CONTENTS

SPONSOR STATEMENT OF COMPLIANCE …….....2
PROTOCOL SIGNATURE PAGE 3
TABLE OF CONTENTS 4
LIST OF TABLES 6
LIST OF ABBREVIATIONS 7
STUDY SUMMARY 8
1. INTRODUCTION 9
    1.1 Hemodynamic support in the ICU 9
    1.2 Hemodynamic support with midodrine 9
    1.3 Rationale for the study 9
2. STUDY OBJECTIVES 10
    2.1 Primary Objectives 10
    2.2 Secondary Objectives 10
    2.3 Tertiary Objectives ….....10
3. STUDY DESIGN 10
4. METHODS 10
    4.1 Study Setting 10
    4.2 Eligibility Criteria 10
        4.2.1 Inclusion Criteria 10
        4.2.2 Exclusion Criteria 10
    4.3. Recruitment Strategy 11
    4.4 Randomization Methods 11
    4.5 Blinding 11
    4.6 Interventions 11
        4.6.1 Experimental Arm 11
        4.6.2 Control Arm 11
        4.6.3 Study Drug Administration..... 11
        4.6.4 Co-Interventions 12
    4.7 Management of Potential Risk to Participants 12
    4.8 Outcome Measures 12
        4.8.1 Primary Outcome 12
        4.8.2 Secondary Outcomes 12
        4.8.3 Tertiary Outcomes 13
        4.8.4 Safety Endpoints 13
    4.9 Data Collection and Participant Follow-up 13
    4.10 Cohort Retention 13
5. DATA MANAGEMENT 14
    5.1 Case Report Forms 14
    5.2 REDCap Database 14
    5.3 Data Discrepancy Inquiries 14
    5.4 Security and Back up of Data 15
6. ETHICS AND DISSEMINATION 15
    6.1 Health Canada Authorization 15
    6.2 Research Ethics Approval 15

6.3 Consent 15
6.4 Confidentiality 16
6.5 Protocol Amendments 16
6.6 Safety Endpoints 16
6.6.1 Adverse Drug Reactions 17
6.6.2 Serious Adverse Drug Reaction 17
6.6.3 Suspected Unexpected Serious Adverse Reactions 17
6.6.4 Reporting SADR and SUSARs 18
6.7 Discontinuation of the Study 18
6.8 Dissemination Policy 18
7. STUDY COMMITTEES 18
7.1 Executive Committee 18
7.2 Steering Committee 19
7.3 Data Safety Monitoring Committee 19
8. STATISTICAL ANALYSIS 19
8.1 Sample Size Determination 19
8.2 Statistical Methods 19
8.2.1 Patient Centered Analysis 19
8.2.2 Health Economic Analyses 20
8.2.3 Interim Analyses 20
8.2.4 Subgroup Analysis 20
8.2.5 Reduction of Bias 20
9. SUBSTUDIES 20
10. REFERENCES 22

LIST OF TABLES

Previous Trials Evaluating the Role of Midodrine for Hypotension..... 21

LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
APACHE	Acute Physiology and Chronic Health Evaluation
CRF	Case Report Form
CTA	Clinical Trials Application
DIN	Drug Identification Number
DSMC	Data Safety Monitoring Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ICU	Intensive Care Unit
IRB	Institutional Review Board
IV	Intravenous
LoS	Length of Stay
NOL	No Objection Letter
RCT	Randomized Controlled Trial
REB	Research Ethics Board
SADR	Serious Adverse Drug Reaction
SUSAR	Serious Unexpected Serious Adverse Reaction
SAE	Serious Adverse Event
SDM	Substitute Decision Maker
UAH	University of Alberta Hospital

STUDY SUMMARY

Title	Midodrine for the early liberation from vasopressor support in the ICU
Short Title	LIBERATE
Coordinating Centre	Department of Critical Care Medicine, University of Alberta
Background	Resuscitation and hemodynamic support with intravenous (IV) vasopressors is a prime indication of treatment in intensive care unit (ICU) settings. Oral vasopressors, such as midodrine, have been historically used for hemodynamic support in non-critically ill patients, but their study in patients as a potential IV vasopressor sparing therapy has been limited. Previous studies evaluating the use of midodrine have been small in scale and limited to septic patients. The LIBERATE study will evaluate the expanded role of midodrine for any vasoplegic patient supported in ICU settings.
Primary Outcome	• ICU length of stay
Secondary Outcomes	• All-cause mortality at 90 days • Hospital length of stay • Length of IV vasopressor support • Re-initiation of IV vasopressors • Rates of ICU readmission
Tertiary Outcomes	• ICU costs • Hospital costs • Total healthcare costs • Cost-effectiveness
Safety Outcomes	• Adverse Events • Severe Adverse Drug Reactions • Suspected Unexpected Serious Adverse Reactions
Study Design	Parallel group blinded randomized controlled trial
Inclusion Criteria	• Age $\geq$ 18 years • Ongoing vasopressor support (i.e., norepinephrine $\geq$0.05 mcg/kg/min, epinephrine $\geq$ 0.05 mcg/kg/min, vasopressin $\geq$0.04 U/min or phenylephrine $\geq$0.1 mcg/kg/min) • Decreasing vasopressor requirements
Exclusion Criteria	• Vasopressor peak requirements > 24 hours • Contraindication to midodrine or enteral medications • Previous receipt of midodrine in last 7 days • Expected death or anticipated withdrawal of life-sustaining therapies • Pregnancy
Study Intervention	Experimental arm: midodrine 10mg PO every 8 hours. Control arm: placebo
Randomization	Eligible patients will be randomized in a 1:1 ratio to midodrine or placebo. We will use permuted blocks of undisclosed and variable size. We will stratify by randomization by site.
Sample Size	We will enroll a total of at least 350 patients. Sites are expected to enrol at least 4 patients per month.
Follow-up	Daily during ICU stay for up to 30 days and 90-days after study eligibility.

1. INTRODUCTION

1.1 Hemodynamic support in the ICU

Resuscitation and hemodynamic support with intravenous (IV) vasopressors is a prime indication of treatment in intensive care unit (ICU) settings.(1) Hemodynamic support is typically provided with intravenous (IV) vasopressors.(2-4) However, these have been shown to have significant negative effects including tissue necrosis, tissue thrombosis, cardiac dysrhythmias and dysfunction as well as bowel ischemia. Further, the presence of central venous catheters required for the infusion of IV vasopressors can lead to increased central venous catheter line associated infections, venous thrombosis and impaired mobility.(5-8) Oral vasopressors, have been historically used for hemodynamic support in non-critically ill patients, but their study in patients as IV vasopressor sparing therapy has been limited.(9-11). One such oral vasopressor is midodrine (midodrine hydrochloride), which is an alpha agonist that has previous been used to attenuate symptoms of chronic orthostatic hypotension.

1.2 Hemodynamic support with midodrine

Previous studies have evaluated the use of midodrine for vasopressor support in the ICU (Table 1). (12-16) The first of these studies by Levine et al. was a single centre, prospective cohort study of 20 patients which evaluated the effect of concurrent administration of midodrine on vasopressor requirements. They ultimately found that when using midodrine it was possible to decrease the amount of phenylephrine required for hemodynamic support.(13) Following this, Poverno et al. evaluated the use of midodrine in 188 patients in a single center retrospective cohort study, where the primary outcome was the duration of IV vasopressor therapy. Importantly, in patients receiving midodrine, there was a significant reduction in vasopressor durations (decreased by 1.2 days in the midodrine group compared with control, $p<0.05$). There was no change in ICU or hospital lengths of stay, nor in rates of ICU readmissions.(14) The MIDAS study, a multicenter pilot study conducted by Santer et al. involving 136 patients did not demonstrate any difference to time to vasopressor discontinuation between study groups.(15) However, this trial was small and required over 7 years to achieve target recruitment, greatly impacting the validity and significance of these results. The largest of randomized trial to date was conducted by Whitson et al. that evaluated 275 patients, and found that midodrine use decreased IV vasopressor duration by 0.9 days ($p<0.001$) and decreased ICU length of stay (LoS) (9.4 vs. 7.5 days, $p=0.017$).(16) However, while this study showed a reduction in ICU LoS, it was only limited to septic patients. The LIBERATE study will evaluate the expanded role of midodrine for any vasoplegic patient in the ICU.

1.3 Rationale for the study

Oral midodrine may lead to earlier liberation from IV vasopressor support in critically ill patients. Currently literature evaluating the effects of oral midodrine on weaning from IV vasopressor support is unclear and conflicting and the trials conducted to date underpowered to detect a significant difference (12-16) In the environment of strained healthcare resources, limited ICU capacity and constant pressure on ICUs worldwide, the ability to safely wean patients from IV vasopressors with transition to oral hemodynamic supporting agents may improve how patients navigate through the healthcare system. (12)

2. STUDY OBJECTIVES

To determine the efficacy and safety of use of the enteral vasoactive agent (i.e., midodrine hydrochloride) to facilitate earlier liberation from continuous infusion of IV vasopressor therapy in critically ill patients with vasoplegia.

2.1 Primary Objectives

To compare the effect of enteral midodrine vs. placebo in critically ill patients with vasoplegia receiving continuous IV vasopressor therapy on *ICU length of stay*.

2.2 Secondary Objectives

To evaluate important patient-centered outcomes of enteral midodrine vs. placebo in critically ill patients with vasoplegia receiving continuous IV vasopressor therapy.

2.3 Tertiary Objectives

To determine the health economic effects of the usage of midodrine vs. placebo in critically ill patients with vasoplegia receiving continuous IV vasopressor therapy.

3. STUDY DESIGN

The LIBERATE Trial is a multicentre, concealed-allocation parallel-group blinded RCT. The trial will randomly allocate 350 to either midodrine (enteral, 10mg every 8h) or placebo for the duration of their IV vasopressor therapy and 24 hours after discontinuation of their IV vasopressor therapy.

4. METHODS

4.1 Study Settings

The study will be centrally coordinated by the Research Office in the Department of Critical Care Medicine at the University of Alberta Hospital. The study will be performed at mixed medical/surgical ICUs throughout Alberta. Additional sites outside of Alberta may be added, as necessary.

4.2 Eligibility Criteria

4.2.1 Inclusion Criteria

- Age ≥ 18 years
- Ongoing vasopressor support (i.e., norepinephrine ≥0.05 mcg/kg/min, epinephrine ≥ 0.05 mcg/kg/min, vasopressin ≥0.04 U/min or phenylephrine ≥0.1 mcg/kg/min)
- Decreasing vasopressor dose(s) (i.e., current dose less than peak dose(s))

4.2.2 Exclusion Criteria

- Greater than 24 hours from peak vasopressor dose
- Contraindication to enteral medications
- Previously received midodrine in last 7 days
- Expected death or anticipated withdrawal of life-sustaining therapies in next 24 hours
- Pregnancy
- Known allergy or other contraindication to midodrine
- Treating clinician does not believe enrolment would be in the best interest of the patient

4.3 Recruitment Strategy

As per standard practice for critical care research, local research personnel will approach the patient if he/she is able to consent. If not, the surrogate decision-maker (SDM) will be approached in person for consent. If no SDM is present at bedside, the research staff will enroll and obtain consent subsequently as per local Research Ethics Board (REB) recommendations under a deferred consent model. Once consent is obtained, participants will be randomized, and treatment will start immediately as per trial allocation.

4.4 Randomization Methods

Eligible patients will be randomized in a 1:1 ratio to midodrine or placebo. We will use permuted blocks of undisclosed and variable size. We will stratify randomization by site.

4.5 Blinding

Intensivists, research personnel, ICU personnel, participants, members of the Executive and Steering Committees, and the data analysts will be blinded to the treatment allocations.
Only the pharmacist at the Research Pharmacy who will prepare the study drug (i.e., midodrine or placebo) will not be blinded. In a situation needing unblinding, only the unblinded coordinate centre research coordinator will have access to the treatment allocation.

The complete blinding of the intervention will be achieved by using midodrine and placebo capsules that are indistinguishable. An unblinding procedure will be made available when necessary. This will only be done when knowledge of the treatment allocation is necessary for the continued safe management of the participant. The treating clinician or investigator should contact the coordinating centre if there is need for unblinding and the request will be adjudicated in a timely fashion by the study principal investigator or nominated delegate.

In any case of unblinding, data collection and follow-up schedule will be maintained.

4.6 Interventions

4.6.1 Experimental Arm

The experimental arm will involve midodrine administration 10mg enterally q8h from time of study inclusion to 24 hours post IV vasopressor support termination. This will be administered as a capsule containing the active substance. There is no maximum duration of treatment.

4.6.2 Control Arm

Participants in the control arm will receive a placebo capsule to match the midodrine.
Participants will be given the placebo enterally q8h from time of study inclusion to 24 hours post IV vasopressor support termination. This will be administered as a capsule containing the inactive substance.

4.6.3 Study Drug Administration

The administration of experimental arm and control arm capsules will be the responsibility of the blinded bedside nurse. If participants have an oral/nasal feeding tube, the contents will be removed from the study capsule, mixed with water and administered through the participant's feeding tube.

4.6.4 Co-Interventions

The study design is for a pragmatic, real-world trial evaluating the use of concurrent midodrine administration for the early liberation from vasopressor support. Other than the study intervention, co-interventions (i.e., steroids, IV fluids, additional vasopressors) are at the discretion of the clinical team. Co-enrollment in other studies will be permitted when that investigational product has little known hemodynamic effects and will be reviewed on a case-by-case basis.

4.7 Management of Potential Risks to Participants

The safety profile for midodrine is well established. No side effects have been reported in the previous studies on midodrine with its use for the treatment of hypotension in critically ill patients. We do not anticipate any significant drug interactions. The most serious adverse reaction with midodrine is a marked elevation of blood pressure which, if sustained, may contribute risk to stroke, myocardial infarction, congestive heart failure, renal insufficiency or similar disorders. Midodrine has also been associated with reflex bradycardia. During the intervention and while in ICU, all participants will receive standardized vital and physiological monitoring. This monitoring will include continuous heart rate, 3-lead ECG, pulse oximetry and intravascular blood pressure monitoring. Additional vitals and physiological parameters, including but not limited to respiratory rate, non-invasive bleed pressure monitoring, Glasgow Coma Scale and urine output, are monitored hourly or more frequently as needed.
Midodrine has been reportedly associated with paraesthesia, piloerection, dysuria, pruritus, chills, pain and rash. We will monitor all study participants for any of these potential adverse reactions.

The placebo will contain microcrystalline cellulose. This is a purified, partially depolymerised cellulose prepared by treating alpha-cellulose**,** obtained as a pulp from strains of fibrous plant material, with mineral acids. It has no specific adverse reaction profile.

Any serious adverse event (SAE) will be managed immediately by the treating team. Unexpected events will be reported to the research team within 24 hours of knowledge of the event.

A urine or serum pregnancy test for females of childbearing potential will be done to exclude pregnant women, as per the clinical team.

4.8 Outcome Measures

4.8.1 Primary Outcome

The primary outcomes is:

1. The length of ICU stay as measured in hours.

4.8.2 Secondary Outcomes

The secondary outcomes will include:

1. Total and Post-ICU hospital length of stay in hours
2. Duration of IV vasopressor support in hours
3. 90-day all-cause mortality
4. Rates of ICU re-admission
5. Rate of re-initiation of IV vasopressor

4.8.3 Tertiary Outcomes

The tertiary outcomes will include:

1. ICU costs
2. Hospital costs
3. Total healthcare costs
4. Cost-effectiveness

4.8.4 Safety Endpoints

1. Adverse drug reactions (ADR)
2. Serious adverse drug reactions (SADRs)
3. Suspected unexpected serious adverse reactions (SUSARs)

4.9 Data Collection and Participant Follow-up

Potentially eligible participants will be referred to the research team by intensivists and other ICU staff. The research team will confirm eligibility and the site principal investigator or co-investigators will confirm whether the patient or SDM may be approached for consent. If that is the case, the research team will obtain consent from the patient or SDM or will enroll and obtain consent as per local REB recommendations under a deferred consent model.

Daily data will be collected from day 1 until ICU discharge or 30 days, whichever occurs first. Outcome data will also be collected at 90 days. All study outcomes (as defined in sections 4.8.1 and 4.8.2) will be documented on the electronic CRFs (eCRF).

Time Points:

1. Baseline data: patient demographics, etiology for hypotension, severity of illness, pre-existing comorbidities, clinical frailty scale
2. Daily data until ICU discharge or 30 days (whichever comes first): protocol adherence, co-interventions (administration of mechanical ventilation, renal replacement, vasopressors, corticosteroids, intravenous fluids, blood products, sedatives)
3. 90-day data: death or persistent organ dysfunction (defined as dependency on mechanical ventilation, renal replacement, or ongoing IV vasopressor use)

4.10 Cohort Retention

Once a participant is enrolled in the trial, the clinical site will make every reasonable effort to follow the participant for the entire duration of the study period. To minimize loss to follow-up at 90 days, consent forms will encompass permission to collect alternate contacts information. Participants may withdrawal their participation in the LIBERATE trial at any time. If a participant wishes to withdraw their consent from the study, we will use the following strategies to minimize the impact on the validity of the trial, meanwhile respecting the participants right to withdraw. We will seek a better understanding of the patient's wishes and offer the following alternatives to complete withdrawal, which would include no further study drug exposure and data deletion:

1. Discontinue study drug but allow data collection (i.e., clinical data, follow-up);
2. Discontinue study drug and in-person follow-up but allow ongoing data collection.

Should any participants withdraw from the study, we will not seek participant replacement. We will adhere to the intention-to-treat principle and data from patients will be analyzed in the group to which they have been allocated irrespective of protocol adherence. Reasons for protocol

deviations, should they arise, will be recorded. In the special case of participants mistakenly randomized, we will allow post-randomization exclusions if: 1) the information about ineligibility was available at randomization; 2) two members of the Steering Committee agree that the participant was mistakenly randomized; 3) participants did not receive the intervention; and 4) participants remain blinded to their allocation. All of the above criteria must be present for participants to be excluded post-randomization.

Participant eligibility will be adjudicated when either a clinical site or the coordinating centre suspects ineligibility. Two members of the Steering Committee will review all relevant information (i.e., hospital records) available at the time of randomization and adjudicate if the participant is eligible or ineligible. To be considered ineligible, the participant must have been ineligible at the time of randomization. If the adjudicators determine that the participant is eligible, the participant will remain in the trial. If they determine that the participant is ineligible, the participant will be withdrawn from the trial. Participants should not be withdrawn until confirmation is received from the Coordinating Centre.

5. DATA MANAGEMENT

Multiple measures are in place for data quality control. These measures include: 1) on-site or remote training of research and clinical personnel; 2) standard operating procedures to guide storage, preparation and administration of the study drug; 3) ongoing assessment of performance and periodic feedback to the clinical sites on performance with benchmarking from other sites; 4) site monitoring visits (remotely or in person); 5) ongoing review of missing data and outliers; and 6) rapid dissemination of responses to frequently asked questions via our study website and monthly newsletter. Coordinating centre personnel and the Principal Investigators will be available 24/7 to answer study-related questions.

5.1 Case Report Forms

The CRFs or eCRFs will be the primary data collection tool for the study. All data requested on the CRF must be recorded either on paper CRFs or on the eCRFs within the REDCap system (see next section).

5.2 REDCap Database

Clinical site research personnel will enter all participant data into the REDCap system. The REDCap system will be managed and housed within the Department of Critical Care Medicine (DCCM) Research Office, located at the University of Alberta, Edmonton, Alberta, Canada. Personnel within DCCM Research Office will be responsible for programming and maintaining the database. With the support from DCCM Research Office, personnel with the coordinating centre will be responsible for daily data management.

5.3 Data Discrepancy Inquiries

Once data errors are submitted, errors will be detected by the program within the REDCap system to detect missing data or errors. With the support from DCCM Research Office, personnel at the Coordinating Centre will review and validate each data field for errors and/or inconsistencies.

Clinical site personnel will be notified of these errors through regular quality control reports, which include the follow:

1. Listing of participants entered into the trial at their clinical site
2. Listing of participants who have completed follow-up at their clinical sites
3. Outstanding data queries and data clarification requests
4. Listing of missing data
5. Protocol adherence to study drug administration.

Clinical site personnel will be required to respond promptly to each query on the quality control report. To respond to queries study personnel should check the original forms for inconsistency and check other sources of participant records to determine the correction. Clinical site personnel will then modify the data in the REDCap system to reflect the correction and resubmit data to the REDCap system to resolve the query.

5.4 Security and Back-Up of Data

All CRFs must be kept secure in locked cabinets or other enclosures that are accessible only to study personnel. All electronic data must be password-protected and accessible only to study personnel. The DCCM Research Office will be responsible for backing up all submitted data within the REDCap system.

6. ETHICS AND DISSEMINATION

6.1 Health Canada Authorization

Since the proposed use of midodrine in the present study is outside the parameters of the Drug Identification Number (DIN) application, a Clinical Trial Application (CTA) was submitted to Health Canada and a No Objection Letter (NOL) obtained (HC6-24-c257473, November 18th 2021).

6.2 Research Ethics Approval

All participating clinical sites will receive REB or Institutional Review Board (IRB) approval prior to commencing participant enrollment. Depending on local standards, centralized or local REBs/IRBs will approve the study protocol of each site. Before launching the trial, each clinical site will provide the coordinating centre with a copy of their ethics approval letter.

6.3 Consent

All consecutive eligible patients will be invited to participate in the trial following referral by the treating ICU team. If the patient is unable to provide consent within the time window allowed by the protocol, his or her SDM may be approached in person or, if necessary, contacted by telephone. The local research team could also enroll eligible patients and obtain consent subsequently as per local REB recommendations under a deferred consent model.

To obtain informed consent, study personnel should follow the following steps:

- Present information on the study in a simple and understandable manner;
- Answer questions in a simple and understandable manner;
- Allow the potential participant/SDM an opportunity to reflect and discuss study participation with their family, friends, or family physician if desired; Confirm that the participant/SDM understands the risks and benefits of participating in the study and that their participation is voluntary;

- Complete and obtain signatures for informed consent form and obtain contact information from the participant/SDM, alternate contacts.

If SDM are contacted by telephone, documenting written informed consent should involve the following steps:

- Provide explanations on the study using the validated telephone script for SDM telephone consent;
- Answer questions in a simple and understandable manner;
- Allow the SDM an opportunity to reflect and discuss study participation with their family, or friends if desired;
- Confirm that h/she understand the risks and benefits of the study and that participation is voluntary;
  Complete and sign the telephone consent form section and obtain contact information;
  Make reasonable efforts to obtain a signature by setting an appointment with the SDM, or by sending the consent form by mail/email.

6.4 Confidentiality

Information about study participants will be kept confidential and will be managed in accordance with the following rules:

- All study-related information will be stored securely.
- All study participant information will be stored in locked file cabinets, or locked room, as applicable, and accessible only to study personnel.
- All paper and eCRFs will be identified only by a coded participant number.
- All databases will be password protected.

If a participant revokes authorization to collect or use personal health information, the clinical site retains the ability to use all information collected prior to the revocation of participant authorization unless otherwise specified.

6.5 Protocol Amendments

Any amendments to the study protocol which may affect the conduct of the study, or the potential safety of or benefits to participants (i.e., changes to the study objectives, inclusion/exclusion criteria, study design, sample size, or study procedures) will require a formal amendment to the protocol. Any protocol amendments will be approved by the Principal Investigator and will require approval by the REB at the University of Alberta and Health Canada before it becomes effective. Clinical sites will also be required to submit amendment requests to their local ethics boards to obtain approval for the amendment and to provide the Coordinating Centre with a copy of this approval. Administrative changes (i.e., minor corrections or clarifications that have no effect on the way the study is conducted) will not need to undergo a formal amendment process and will be communicated to clinical sites when applicable. Health Canada will be informed of these changes with a CTA-Amendment or a Notification depending on the extent of the changes.

Safety Endpoints

It is recognised that the patient population in the ICU will experience a number of aberrations in laboratory values, signs, and symptoms due to the severity of the underlying disease and the impact of standard treatments in the ICU. These will not necessarily constitute adverse events or

serious adverse events unless they are considered to be related to study treatment or in the principal investigator's clinical judgement are not recognised events consistent with the participants underlying critical illness and/or chronic diseases and expected clinical course.
In Canada, reporting of adverse events will follow the 5 recommendations for rational reporting of serious adverse events in investigator-initiated critical care trials of drugs in common use.(17)

6.5.1 Adverse drug reactions (ADR)

In respect of marketed medicinal products, a well-accepted definition of an adverse drug reaction is:

- *A response to a drug which is noxious and unintended, and which occurs in doses normally used in humans for prophylaxis, diagnosis or therapy of disease or for modification of physiological function.*
- Any adverse reaction thought to be study treatment related will be reported to the Regional Coordinating Centre within 7 days of discovery. The site principal investigator will be responsible for determining the causal relationship as either possible, probable or definitely study treatment related. Notification will be by fax (with follow-up email confirmation of receipt), scanned document sent by email or by completing an ADR form on the web-based data management system.
- All adverse reactions will be reviewed by staff at the coordinating centres and recorded in a safety database and will be periodically reported to the independent data safety monitoring committee (DSMC).

6.5.2 Serious adverse drug reactions (SADRs)

Serious adverse events are defined as any untoward medical occurrence that meets one of more of the following criteria:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that jeopardises the study participant and requires intervention to prevent one of the other outcomes listed in the definition above.

The classification of 'serious adverse event' is not related to the assessment of the severity of the event. An event that is mild in severity may be classified as a serious adverse event based on the above criteria. Given that critically ill patients are likely to meet any of the above listed criteria in the course of their ICU admission, only serious events that are thought to be related to study treatment will be reported.
It is requested that SADRs are reported to the coordinating centre within 24 hours of participating site study staff becoming aware of the occurrence. A member of the coordinating centre will be available 24 hours a day for out of 'business hours' reporting.

Suspected unexpected serious adverse reactions (SUSARs)

A SUSAR is a SADR which is considered *unexpected*. A SADR whose nature, severity, specificity, or outcome is not consistent with the term or description used in the product

information, should be considered unexpected. These will also be reported to the coordinating centre within 24 hours of participating site study staff becoming aware of the occurrence.

6.5.3 Reporting SADR and SUSARs

The minimum information to report will include:

- Participant initials and study number
- Nature of the event
- Commencement and cessation of the event
- Outcome of the event
- The principal or co-investigator's opinion of the relationship between study drug and the event (possibly, probably or definitely related)
- Whether treatment was required for the event and what treatment was administered

The coordinating centre staff will be responsible for following-up all SADRs and SUSARs to ensure all details are available. The coordinating centres are also responsible for alerting other participating sites to the reported SADR or SUSAR and reporting to the regulatory authorities within required time frames.

It is the responsibility of each principal investigator to inform the responsible human research ethics committee (HREC)/Research Ethics Boards (REB) of all SADR and SUSAR events which occur at their hospital, in accordance with local requirements. Copies of any reporting and correspondence to and from the relevant HREC/REB or research governance officer (RGO) should also be sent to the coordinating centre.

6.6 Discontinuation of the Study

In the event of a premature discontinuation of the clinical trial (e.g. sponsor decision to discontinue the trial due to safety concerns, alternative therapy newly available that may benefit research subjects), a notification will be sent to Health Canada no later than 15 days after the date of the discontinuation. A discontinuation procedure will be made available when necessary.

6.7 Dissemination Policy

Dissemination will be done via an integrated knowledge translation strategy.
Plans for end-of-study dissemination include presentations at major international conferences, publications in high-impact journals and, building on experience with social media developed during previous trials, dissemination of our results via social media platforms and discussion forums managed by partner organizations.

7. STUDY COMMITTEES

7.1 Executive Committee

The Executive Committee is comprised of Drs. Rewa and Bagshaw. Dr. Rewa is the principal study investigator while Dr. Bagshaw is a co-investigator. The committee is responsible for day-to-day management and is accountable to the Steering Committee.

7.2 Steering Committee

The Steering Committee consists of intensivists, investigators and health economists and will meet quarterly by teleconference. The Steering Committee with provide guidance and direction to the overall trial.

7.3 Data Safety Monitoring Committee

As per the FDA guidance document the Establishment and Operation of Clinical Trial Data Monitoring Committees for Clinical Trial Sponsors, a DSMC will oversee the safety of the trial participants. The DSMC is comprised of three members who remain completely independent of the study investigators. The DSMC members all have extensive trial experience and include a senior methodologist who has served as Chair on numerous DSMCs for international RCTs, a senior biostatistician, and an intensivist. The DSMC will be responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and for monitoring the overall conduct of the study. The DSMC will periodically review enrollment and demographic summaries, listings of protocol deviations, and summaries and listings of SAEs. In accordance with a prespecified DSMC Charter, the DSMC will advise the Executive and Steering Committees on any concerns related to participant safety and trial conduct, and will make recommendations for the study to continue as designed, for study termination, for study continuation with major or minor modifications, or temporary suspension of enrollment until some uncertainty is resolved.

8. STATISTICAL ANALYSIS

All participants will be analyzed as randomized in accordance with the intention-to-treat principle. However, we will also plan a secondary efficacy analysis including patients who received all study drug doses (per protocol analysis). The criterion for statistical significance will be based on alpha = 0.05. All tests will be two-sided, and all analysis will be performed using STATA v16 or later.

8.1 Sample Size Determination

Using an alpha of 0.05 and a power of 80% and assuming a 20% deduction in the length of stay associated with midodrine based on previous pilot work by Anstey et al., we would need a sample size of 161 participants per arm.(18) To compensate for loss to follow up, we will plan for 175 participants per arm for a total treatment size of 350 participants.

8.2 Statistical Methods

8.2.1 Patient centered Analysis

All analyses will follow the intention-to-treat (ITT) principle. Analyses of the primary and secondary outcomes (i.e., patient centered outcomes) will involve summary measures obtained by aggregating the endpoints using Stata software package (StataCorp, Texas, USA). We will compare median differences along with their 95% confidence intervals. Baseline comparisons will be performed using chi-squared test for equal proportions with results to be reported as numbers, percentages, and 95% confidence intervals. Continuous normally distributed variables will be compared using paired t-tests and reported as means with 95% confidence intervals, while non-normally distributed will be compared using Wilcoxon rank sum tests and reported as medians and interquartile ranges

8.2.2 Health economic Analysis

Analyses of the tertiary outcomes (i.e., health economic outcomes) will be based on health economic information obtained from public and private databases. Cost-effectiveness and cost-utility will be analyzed by estimating incremental cost and effectiveness based on ICU lengths of stay and average daily ICU costs.

8.2.3 Interim Analyses

SAEs will be reviewed in real time by the PIs and the DSMC chair on a case-by-case basis. They will be reported to the REB shortly after being identified. As our population is critically ill and the baseline incidence of death is high, each death will be adjudicated by the co-PIs and chair of the DSMC as related to the intervention or not.

The DSMC will review data on all possibly related AEs and SAEs after 175 patients (i.e., 50% of total planned recruitment). If the one-sided p-value is <0.1 for cumulative SAE, then an interim two-sided analysis of the primary outcome will automatically be conducted. This analysis will generate a conditional power for showing efficacy in the final analysis of the primary outcome, assuming that the group-specific event rates observed to date remain the same in the total sample size. If the conditional power for efficacy is $<20\%$, in the context of a one-sided $p<0.1$ for any of the safety outcomes, then the DSMC will recommend stopping the trial to the SC. The DSMC may make a similar recommendation even if these exact thresholds are not met, based on its interpretation of the balance between safety and efficacy.

8.2.4 Subgroup Analysis

Secondary analyses will examine the effects for length of ICU stay and duration of IV vasopressors within subgroups defined at baseline by age (<65 vs. ≥ 65 years), sex, frailty (Clinical Frailty Scale 1-4 vs. ≥ 5), severity of illness (quartiles of predicted risk of death from baseline APACHE II and/or SOFA score), and types of shock (i.e., septic, hypovolemic, cardiogenic, obstructive or neurogenic). We will also evaluate subgroup based on comorbid conditions (i.e., pre-existing cirrhosis and acute kidney injury on admission). The subgroup analyses will use logistic regression with terms for treatment arm, subgroup, and subgroup by treatment interaction. We hypothesize that midodrine is more beneficial in young patients, in those with lower frailty and illness severity at baseline, those with pre-existing cirrhosis, those with acute kidney injury and those who meet strict criteria for septic shock.

8.2.5 Reduction of Bias

Risk of selection bias will be reduced by concealed randomization using variable and undisclosed blocks. Physicians, nurses, patients and family members, all research personnel, and outcome assessors and adjudicators will be blinded. Pharmacists will not be blinded as they are assigning group allocation; however, they will remain independent of clinical team Accordingly, decisions to discontinue life-sustaining therapies and other outcomes that require subjective assessments will not be affected by individually held beliefs regarding the effects of midodrine. In addition, we will record co-interventions to detect potential performance bias.

SUBSTUDIES

There are currently no sub-studies planned for the LIBERATE trial. However, any proposed sub-studies will be presented to the Executive Committee and require unanimous approval. They will then be presented to the Steering Committee and will require majority approval prior to proceeding.

TABLES:

Table 1. Previous Trials Evaluating the Role of Midodrine for Hypotension

Author	Year	Patients	Population	Study type	Outcomes	Results
Levine et al.	2013	20	Surgical	Single Center Prospective Cohort	• **Dose of IV vasopressor**	• Decrease of -1.58 mcg/min of phenylephrine with use of midodrine
Poverno et al.	2016	188	General	Single Center Retrospective Cohort	• **Duration of IV vasopressor** • ICU LoS • Hospital LoS • ICU readmission	• Midodrine patients required IV vasopressors for 1.2 days following initiation of midodrine • No change in ICU length of stay • Increased hospital length of stay with midodrine (12.0 vs. 9.5d) • No difference in ICU readmission between groups
Whitson et al.	2016	275	Medical	Single Center Retrospective Cohort	• **Duration of IV vasopressor** • ICU LoS • Hospital LoS • IV vasopressor reinstitution • Mortality	• Decrease duration of IV vasopressors by 0.9 days • Decrease ICU length of stay (7.5 days vs. 9.4 days) with midodrine • Decrease hospital length of stay (21.9 days vs. 24.2 days) with midodrine • No mortality difference between groups
Santer et al.	2020	136	General	Multicenter RCT	• **Duration of IV vasopressor** • ICU LoS • Hospital LoS • ICU readmission • Adverse Events	• No difference in duration of IV vasopressors • No difference in ICU or hospital LoS • No difference in ICU readmissions between groups

Table 1. Previous trials show conflicting results regarding the effects of midodrine on ICU patients. Primary outcomes are indicated in bold lettering. ICU – intensive care unit; IV – intravenous; LoS – length of stay; RCT – randomized controlled trial.

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