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

Data Safety Monitoring Committee (DSMC) Charter

Principal Investigators:
Oleksa G. Rewa MD MSc, University of Alberta

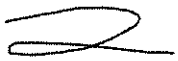
Oleksa Rewa is conducting the Midodrine for the Early Liberation from Intravenous Vasopressor Support in the ICU (LIBERATE) randomized clinical trial.

Steering Committee:
Sean Bagshaw
D'Arcy Duquette
Kirsten Fiest
Constantine Karvellas
Vincent Lau
Dawn Opgenorth
Janek Senaratne
Jocelyn Slemko
Wendy Sligl
Fernando Zampieri

DSMC Member Signature Page

Study Name	Midodrine for the Early Liberation from Vasopressor Support in the ICU (LIBERATE): A Multi-Centre, Randomized, Controlled Trial
Principal Investigator	Dr. Oleksa Rewa
Sponsor	University of Alberta Hospital Foundation Kaye Fund

I agree to be a part of the Data Safety Monitoring Committee (DSMC) for the LIBERATE study. I understand and agree to all the terms and conditions outlined in the DSMC charter. I confirm that I am not a part-time or full-time, paid or unpaid employee of any organizations that are involved in the LIBERATE trial. I am aware of my responsibilities for maintaining the confidentiality of any non-public information that I receive or become aware of through this activity, and for avoiding using such information for my personal benefit, the benefit of my associates, or the benefit of organizations with which I am connected or with which I have a financial involvement. I have no conflicts of interests to disclose that make me ineligible to serve on the DSMC. I agree that in the event that any of the above changes during my tenure as a member of the DSMC, I will disclose and discuss the risk with the Sponsor/Principal Investigators upon discovery of a risk and sign a new Conflict of Interest and Disclosure Statement form and will include a description of the conflict. This includes the discovery that an organization with which I am affiliated meets the criteria for a conflict of interest.

DSMC Members		
Name	**Signature**	**Date**
Dr. Alexander Zarbock		Feb. 15. 2024
Dr. Melissa Parker		Feb 13, 2024
Dr. Caio de Assis Moura Tavares		Feb 13, 2024
Principal Investigators		
Dr. Oleksa Rewa		February 12, 2024

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1. Introduction

The following outlines the Data Safety Monitoring Committee's (DSMC) terms of reference for the LIBERATE study. These terms of reference will govern the review of data on participants enrolled and treated under this protocol.

The DSMC is an independent group, appointed in an advisory capacity to the **Steering Committee** (SC) of the LIBERATE study. The DSMC will remain standing until the end of trial accrual. All DSMC members are expected to remain free from perceived or actual conflict of interest throughout their involvement in the trial and will be asked to complete a conflict of interest form at the start of their participation in the DSMC.

2. Protocol Overview

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
Clinical Sites	25 ICUs in Canada and Brazil. Additional clinical sites will be included as needed.
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 > 18 years • Ongoing vasopressor support (i.e., norepinephrine ≥0.05 mcg/kg/min and/or epinephrine ≥ 0.05 mcg/kg/min and/or vasopressin ≥0.04 U/min and/or phenylephrine ≥0.1 mcg/kg/min) • Decreasing vasopressor dose(s)

Exclusion Criteria	• Vasopressor peak dose(s) > 24 hours • Contraindication to 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 1,000 patients. Sites are expected to enroll at least 2 • patients per month.
Follow-up	Daily during ICU stay for up to 30 days and at 90 days after study eligibility.

3. DSMC Aims and Roles

The DSMC is responsible for safeguarding the interests of study participants, and assessing the safety of study procedures, and to provide recommendations about continuing or stopping the study, based on safety considerations.

Specific roles: Every six months the DSMC will:

- Assess data quality, including timeliness and completeness
- Monitor compliance with the protocol
- Monitor participant recruitment, accrual and retention
- Review adverse events and serious adverse event data
- Review protocol modifications, if applicable
- Assess the impact and relevance of external data that may affect the safety of the participants or ethics of the trial
- Monitor compliance with previous DSMC recommendations.

The DSMC will monitor serious adverse events as they occur (see below) and at the above stated intervals.

As per the protocol, interim analysis will take place after 33.3% and 66.6% of the trial cohort has completed 90-day follow-up. The DSMC will meet to review data from this analysis.

The agenda for DSMC meetings will be drafted by the LIBERATE Study Coordinating Centre, University of Alberta) along with the Clinical Trials Office (CTO) at the University of Alberta. The CRO is the Health Canada regulated body at the University of Alberta. The CTO will provide overall trial monitoring and oversight. The agenda and data reports will be distributed by the Coordinating Centre at least 10 business days before any DSMC meeting.

4. Safety Endpoints

It is recognized 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 recognized 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.

i) *Adverse drug reactions (ADR)*: With respect to 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.
- 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 DSMC.

ii) *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 hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that jeopardizes the study participant and requires intervention to prevent one of the other outcomes listed in the definition above.

The classification of 'serious adverse drug reaction' is not related to the assessment of the severity of the reaction. A reaction that is mild in severity may be classified as a serious adverse reaction based on the above criteria. Given that critically ill patients may be likely to fulfill one or more of the above listed criteria in the course of their ICU admission, only serious reactions that are judged to be related to study treatment will be reported. Examples of these may include, but are not limited to bowel ischemia, limb ischemia, cardiac events and cerebrovascular events.

iii) *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.

For this study, a reportable Safety Endpoint must meet one of the definitions noted above and also be considered:

- An atypical reaction, defined as clinically significant and unexpected in the context of critical illness, AND;

- A reaction that is at least possibly related to study procedures.

All safety endpoints must be reported to the DSMC in aggregate form at least 10 days in advance of a scheduled meeting. All safety endpoints should be reported to the DSMC chair in an expedited fashion as per the procedures described below.

Procedures for reporting a safety endpoint

Each site research coordinator will liaise with the clinical team and review the medical records of study participants to identify potentials safety endpoints. The site research coordinator will notify the site investigator and the local Ethics Board (according to local requirements) about the occurrence of significant safety endpoint (i.e., SADRs or SUSARs). Clinicians will treat the study patient affected by a safety endpoint as per the usual standard of care.

The site investigator has primary responsibility for the safety of individual study participants at their study site. Upon recognition of a safety endpoint, the site research coordinator or site investigator will notify the LIBERATE coordinating centre within 1 business day of becoming aware of the SADR or SUSAR. Follow-up of any SADR or SUSAR be provided within 7 calendar days. Follow-up of the outcomes of safety endpoints will continue until clinical recovery is complete and laboratory results have returned to baseline, or until progression has been stabilized. Follow-up will continue for the duration of the participant's inclusion in the study. Any documents relating to safety endpoints will be reviewed at the coordinating centre, to ensure that they do not contain sensitive or confidential participant information, in accordance with privacy requirements.

In the event of a reported safety endpoint, the study manager will contact the PI (Oleksa Rewa) and the DSMC Chair (Dr. Alexander Zarbock) to alert them of the forthcoming documentation regarding the safety endpoint. Upon receiving all relevant clinical notes and case report forms from the site, research personnel at the coordinating centre will collate this material into a detailed report for distribution to the PIs and the DSMC Chair within 5 business days of the original notification to the coordinating centre.

After reviewing the clinical notes and CRFs, the DSMC chair will determine whether immediate input from other DSMC members is required and will contact them as needed. The DSMC will send its determinations to the PIs.

The DSMC will also review aggregate safety endpoints every six months and upon enrollment of 33.3% and 66.6% of patients. At this time, the DSMC will recommend to the SC whether to:

1. continue patient enrolment,
2. suspend enrolment until careful review by the SC, or
3. request additional information before making a recommendation.

5. Membership

The DSMC consists of members who are experts in critical care and trial methodology. Members are independent of the investigators and have no financial, scientific, or other conflict of interest with the trial, as noted in written documentation on file with the coordinating center located at the University of Alberta in Edmonton.

Alexander Zarbock is the Chair, responsible for overseeing the meetings and the contact person for the DSMC.

The DSMC is independent of the PIs and SC with respect to recommendations made, but is supportive of the aims and methods of the trial. The DSMC serves in an advisory role. The DSMC, PIs, and Project Manager will work collaboratively to ensure rigorous, safe, and timely conduct of the trial.

Quorum

It is expected that all DSMC members will attend every meeting. At minimum, the chair and one members must participate in order for a quorum to exist. If one member is unable to attend the meeting, the DSMC Chair will follow up by phone or email afterwards, as feasible. The sponsor or designated representative must always be available for the open session as well. If voting is required, then all members must participate.

6. Meeting Format

Each meeting will start with an **open session** that may be attended by 1-2 SC members (including one of the PIs) and selected trial staff. Issues discussed will include conduct and progress of the study, including patient accrual, compliance with the protocol, and any problems encountered. Patient-specific data and treatment group data may not be presented in the open session.

Only DSMC members will attend the **closed session**; others (e.g., study statistician) may attend by invitation. All safety data will be presented at this session. The discussion at the closed session is confidential.
After each meeting, the DSMC will recommend whether to:

1. continue enrollment;
2. consult immediately with the PIs and SC with a view to terminating enrollment; or
3. request additional information before making a recommendation.

Results from the interim analysis will also be submitted to the DSMC to assist in forming their recommendations for continuation of the trial. The DSMC will inform the PIs if, in their view, major safety issues have arisen that are likely to convince a broad range of clinicians, including those supporting the trial and the general clinical community, that on balance, continued use of one of the study interventions in a particular group or sub-group would be widely seen as unethical, BOTH for clinical care AND for any further investigation.

The DSMC will follow these guidelines in formulating a recommendation:

- the Chair will encourage consensus and all members will attempt to achieve consensus
- members will consider the ethical, scientific, statistical, practical, and financial implications for the trial in making recommendations.

7. Stopping Rules

Should the DSMC contemplate a recommendation to terminate the study, they will provide the SC with the opportunity to halt enrollment (without terminating the trial) and investigate any concerns during the halt period. If the DSMC subsequently decides to recommend termination, after considering the SC's report of the issues raised, a vote of all DSMC members will be required. The DSMC will attempt to come to a consensus before taking a vote. In the event of a divided vote, majority will rule and a minority report should be appended. There will be no stopping rules for perceived benefit.

8. Compensation

DSMB members will receive a stipend, in Canadian dollars, for the contribution of their time and professional expertise as part of the DSMB.
Stipend breakdown per meeting:

- DSMC Chair: $500
- Other members: $250

9. Reports

1. **Interim Reports:** Interim reports are distributed to the DSMC membership every six months and at least 10 days before a scheduled meeting. These interim reports will be numbered and provided by encrypted secure email as the DSMC member prefers. The contents of the report are determined by the DSMC. Additions and other modifications to these reports may be directed by the DSMC on a one-time or continuing basis. Interim data reports generally consist of two parts:
    I. Part 1 (Open Session Report) provides information on study aspects such as accrual, baseline characteristics, and other general information on study status, including protocol amendments.
    II. Part 2 (Closed Session Report) will include safety data. The Closed Session Report is considered confidential and should be destroyed at the conclusion of the meeting.

2. **Reports from the DSMC:** A formal written report containing recommendations for continuation or modifications of the study from the DSMC Chair will be sent to the full DSMC within 4 weeks of the meeting. It is the responsibility of the PI to distribute the formal DSMC report with any recommendations to all site investigators (and funding agencies, if required) and to ensure that sites are advised to submit the reports to their local Ethics Board.

The formal DSMC report should conclude with a recommendation to continue or to terminate the study. This recommendation should be made by formal majority vote after an attempt is made to reach consensus. A termination recommendation may be made by the DSMC at any time by majority vote. In the event of a split vote in favor of continuation, a minority report should be contained within the regular DSMC report. The report should not include unblinded data.

Access to Interim Data: Access to the accumulating endpoint data should be limited to as small a group as possible. Limiting the access to interim data to the DSMC members relieves the PIs of the burden of deciding whether it is ethical to continue to randomize patients and helps protect the study from bias in patient entry or evaluation.

10. Confidentiality

All materials, discussions and proceedings of the DSMC are completely confidential. Members and other participants in DSMC meetings are expected to maintain confidentiality.

Archiving of DSMC Activities and Related Documents

All DSMC documentation and records will be retained by the Department of Critical Care Medicine, Faculty of Medicine and Dentistry, University of Alberta until the completion of the study, at which point they will be transferred to and stored by the PI, for a time period of minimum of 15 years after completion of the study. Access to archived data will be controlled by the Department of Critical Care Medicine until the completion of the study, at which point they will be transferred to and stored by the PI, and will be released only as specified in this charter or as required by law.