LIBERATE

Manual of Procedures

Midodrine for the early liberation from vasopressor support in the ICU

Version 5.0

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Clinical Trials.gov NCT05058612

Contents

Chapter 1: Introduction

1.1 Study Overview

The LIBERATE Trial is a multicentre, concealed-allocation parallel-group blinded RCT. The trial will randomly allocate 1000 subjects 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.

Subjects will be assessed daily while hospitalized up to ICU discharge or 30 days after enrollment, whichever occurs first. Subjects will be followed-up for vital status at 90 days after enrollment.

The LIBERATE Manual of Procedures (MOP) was developed to serve as a reference to all research team members involved in the conduct of this study.

The MOP provides guidance by outlining the various procedures and processes required to ensure compliance with the study protocol and regulatory requirements. Each process involved in the conduct of this study has instructions detailing the steps required to perform each procedure, acting as a "How To" manual for research team members.

1.2 Glossary of Terms

ACE	Aid to Capacity Evaluation
ADR	Adverse Drug Reaction
AE	Adverse Event
APACHE	Acute Physiology and Chronic Health Evaluation
CC	Coordinating Center
CTA	Clinical Trials Application
CTO	Clinical Trials Office
CRF	Case Report Form
DCCM	Department of Critical Care Medicine
DIN	Drug Identification Number
DSMB	Data Safety Monitoring Board
DMCC	Data Management and Coordination Centre
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMR	Electronic Medical Record
GCP	Good Clinical Practice
HC	Health Canada
IB	Investigational Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive Care Unit
IP	Investigational Product
IV	Intravenous
ITT	Intention to Treat
LoS	Length of Stay
MRP	Most Responsible Physician
NG	Nasogastric Tube

NOL	No Objection Letter
NPO	Nothing By Mouth
OG	Orogastric Tube
QI	Qualified Investigator
RCT	Randomized Control Trial
REB	Research Ethics Board
RN	Registered Nurse
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SIV	Site Initiation Visit
SUSARs	Serious Unexpected Serious Adverse Reaction
SDM	Substitute Decision Maker
SOP	Standard Operating Procedure
TCPS2	Tri-Council Policy Statement
TDL	Task Delegation Log

Chapter 2: General Information

2.1 Study Chair

Name and Institution	Address, Phone, Email
Oleksa Rewa, MD MSc FRCPC Department of Critical Care Medicine Faculty of Medicine and Dentistry University of Alberta	2-124E Clinical Sciences Building, 8440-112 ST NW, Edmonton, T6G 2B7 CANADA T: 780.263.3280 E: rewa@ualberta.ca

2.2 LIBERATE Steering Committee

The Steering Committee is responsible for providing overall oversight of the LIBERATE trial. Its membership includes the study chair and other individuals with specialized knowledge in critical care and experience in running and oversight of clinical trials.

2.3 Data and Safety Monitoring Board

The LIBERATE trial has a Data and Safety Monitoring Board (DSMB) to monitor subject safety, data quality, and the general progress of the study. The DSMB membership includes experts in critical care, clinical trial methodology, and biostatistics.

Members of the Data and Safety Monitoring Board:

Dr. Alexander Zarbock
Dr Melissa Parker
Caio de Assis Moura Tavares
Dr. Oleksa Rewa

2.4 Data Management and Coordination Centre (DMCC)

The University of Alberta Critical Care Research Office will serve as the Data Management and Coordination Centre for the LIBERATE study. The study database will be housed on secure servers at the University of Alberta in Edmonton, Alberta.

For questions about study operations please contact:

Dawn Opgenorth, Project Manager
Department of Critical Care Medicine
University of Alberta
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8440 112 Street
Edmonton, AB T6G 2B7
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Chapter 3: Screening

3.1 Pre-Screening

Sites are encouraged to pre-screen patients in the ICU on a daily basis. Pre-screening should occur in the morning and ideally again in the afternoon. Theoretically, there is no limit on the frequency or number of times a patient may be re-screened. You may re-screen patients who are not initially eligible for the trial as several conditions for eligibility are inherently dynamic. For example, vasopressor dose may be increasing when patient is admitted to the ICU but may stabilize after a day or two. Or, patients not initially eligible because of anticipated withdrawal of life support within 24 hours whose prognosis subsequently improves may become eligible for inclusion in the study.

3.2 Screening

Screened patients who meet all the conditions for inclusion should be entered in the screening log. If a patient does not meet ALL the inclusion criteria, the patient should not be entered in the screening log.

Patients entered in the screening log should only be entered in the log once a final decision has been made regarding their study entry (i.e., those in the process of re-screening due to a potentially dynamic exclusion criterion should not be finalized until a final decision has been made regarding their eligibility for the trial). Clearly document the reasons patients do not meet criteria and reasons eligible patients are not enrolled. This information is important for the Sponsor to make informed protocol revisions and assist sites with recruitment initiatives.

Each month's screening log should be uploaded into the site-specific REDCap regulatory binder on the FIRST business day of the subsequent month. Save the document as a new file using "Save As" and name the document "LIBERATE -<insert site number> - <insert yyyy-mmm>

Chapter 4: Eligibility Criteria

4.1 Overview of Eligibility Criteria

Part of the screening process will include gathering information and results from past and present procedures, since the patients may not be physically able to answer questions. These pieces of information will help assess suitability and determine eligibility to participate in the trial. All patients entering the ICU should be assessed for enrollment, including patients who are re-admitted into the ICU who did not previously meet eligibility criteria. Only after all inclusion criteria have been met, and all exclusion criteria have not, will the patient be considered eligible to participate in the trial. Eligible patients are then reviewed with the attending physician(s) caring for the patient (i.e., the ICU physician). Eligibility of a patient rests on the non-objection of the attending physician(s) to the patient's participation in the trial.

4.2 Eligibility Criteria

Inclusion Criteria

1. Age ≥ 18 years
   - Patient's age on the day of eligibility screening.
2. Ongoing vasopressor support
   - 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
3. Decreasing vasopressor dose(s) (i.e. current dose less than peak dose(s))

Exclusion Criteria

1. Greater than 24 hours from peak vasopressor dose
   - doses of any prescribed vasopressors have not increased for the past 24 hours
2. Contraindication to enteral medications
   - i.e. - NPO order, treating physician's preference
3. Previously received midodrine in last 7 days
   - Confirmed using available patient medical records and/or patient/substitute decision maker when available
4. Pregnancy
5. Known contraindication to midodrine
6. Known allergy to midodrine
7. Expected death or anticipated withdrawal of life-sustaining therapies in next 24 hours
   - based on the treating physician's opinion
8. Treating physician does not believe enrollment would be in the best interest of the patient

IF THE PATIENT MEETS ALL OF THE ABOVE INCLUSION CRITERIA AND NONE OF EXCLUSIONS, THEN THE PATIENT IS DEEMED <u>ELIGIBLE</u> AND THE TREATING PHYCISIAN WILL THEN BE APPROACHED BY THE RESEARCH TEAM TO CONFIRM THEIR AGREEMENT WITH TRIAL

4.3 Documentation of Eligibility

Use page 1 “SCREENING FOR ELIGIBILITY” of the CRF to document assessment of eligibility. For all eligibility criteria, source documents must exist in either the subject’s clinical chart or study file. Examples of relevant source documents may include medical history including lists of known allergies and current medications, hospital intake notes, and discussions with the Substitute Decision Maker (SDM) or Most Responsible Physician (MRP) regarding medical history.

In instances where paper source is not available, for example when medical charts are electronic, please have the Qualified Investigator (QI) or Co-Investigator include a progress note in the subject’s electronic medical record (EMR) documenting eligibility review.

In addition the site QI should e-sign and lock the screening form in the REDCap database.

If your process differs from Health Canada regulatory requirements, please describe your process for eligibility review (e.g., confirmation emails) in a Note to File. File these documents in your REDCap regulatory binder.

If a contraindication to eligibility occurs between the signing of the ICF and time of randomization, the subject must be deemed ineligible and not enrolled into the study.

If a contraindication to a study assessment develops during the course of the study (i.e., after enrollment), subjects will be asked to continue their participation in the study so that data from the other assessments can be gathered. Eligibility will not be re-assessed throughout the study – meaning that the subject does not need to continue to meet all the initial eligibility criteria throughout the length of the study. If at any time during the study, a subject no longer meets study inclusion/exclusion criteria due to a change in medication or to the development of a new medical condition, this will be noted, and they will be allowed to continue participation at the discretion of the QI.

Chapter 5: Informed Consent

5.1 Informed Consent Process

Informed consent is an ongoing process that must be obtained and maintained for each subject throughout the study. Consent to participate in the study **must** be obtained prior to any study procedures taking place unless the use of deferred consent is approved by the site Research Ethics Board (REB). Consent should be maintained by providing subjects or their Substitute Decision Maker (SDM) with opportunities to ask questions throughout the duration of the study. Only ICFs and updates that have been approved by the local REB may be used.

The individual obtaining informed consent must be a research team member that has been trained in and delegated this responsibility as recorded on the *Task Delegation Log (TDL).*

5.2 Substitute Decision Maker (SDM) Determination

As potential study subjects may be intubated and thus lack the capacity to consent, an SDM will need to consent on their behalf prior to enrollment. The site will need to refer to local regulations and policies to determine who can be used as an SDM. Any questions regarding the appropriateness of a potential SDM should be directed to the site's REB. Additionally, if the emergency contact person listed on the subject file is not a direct family member (e.g., employer, friend, etc.), sites are encouraged to contact their REB before calling the emergency contact person, even if the purpose of contacting them is to collect SDM information. File any REB correspondence in the REDCap regulatory binder or subject research file.

5.3 Obtaining Consent

Initiating the consent process

POLICIES REGARDING CONSENT MECHANISMS MAY DIFFER BETWEEN STUDY SITES. PLEASE FOLLOW LOCAL POLICY.

Patients and/or their SDM will be approached by the QI or Research Nurse/Coordinator. Ideally, a member of the clinical treating team for the patient will provide a brief introduction to the study prior to the patient/SDM being approached by the research personnel.

One or more Study Investigators may be involved in the clinical care of some prospective subjects. In this scenario and whenever possible, the Investigator(s) in question will excuse him/herself from involvement in the consent process in order to avoid an impression of a conflict of interest or undue influence.

Prior to initial contact with the patient, the study team also will ensure that the patient/SDM has been informed regarding the patient's clinical condition and diagnoses and potential eligibility for a research study by a member of the clinical treating team (MRP/RN).

Assessing capacity for consent

Every attempt should be made to explain the rationale and potential risks of the study to the patient, or if he/she is incapacitated, to an SDM.

Assessing patient capacity requires considerable clinical judgment. The modified Aid to Capacity

Evaluation (ACE) screening tool is recommended as a guideline but sites may use whatever processes are in place at their site (see Appendix 1).

Examples of Consent scenarios

The following consent situations may arise:

Patient has capacity to provide consent. Provide the patient with a copy of the most current and approved informed consent form (ICF) to read and review. Review the details and all pertinent aspects of the study with the patient and confirm that the study is understood. Answer any questions that may arise. Ensure they are aware that they can withdraw consent at any time without changes to the quality of their healthcare. Ensure ample time has been given to make a decision regarding participation, and that all questions pertaining to the study have been sufficiently answered.

After the patient has read the ICF, ascertain their willingness to consent to the study. If the patient agrees, obtain their written consent. The designated study team member must also sign and date the ICF. Provide a copy to the subject and keep the original in a separate file. Document the date and time of consent as per local site policy. Document whether the patient declines or accepts on the Screening Log.

Patient does not have capacity and SDM available. If patient is deemed not to have capacity then a SDM should be sought using the patient's pre-determined wishes. If the patient's SDM is unavailable, then a standard hierarchical order of persons authorized to make medical decisions for an incapacitated patient, based on local practices, should be considered. If a SDM is identified, attempt to obtain consent from this individual using the most recently REB approved ICF. Review the details and all pertinent aspects of the study with the SDM and confirm that the study is understood. Answer any questions that may arise. Ensure they are aware that they can withdraw consent at any time without changes to the quality of the patient's healthcare. Ensure ample time has been given to make a decision regarding participation, and that all questions pertaining to the study have been sufficiently answered.

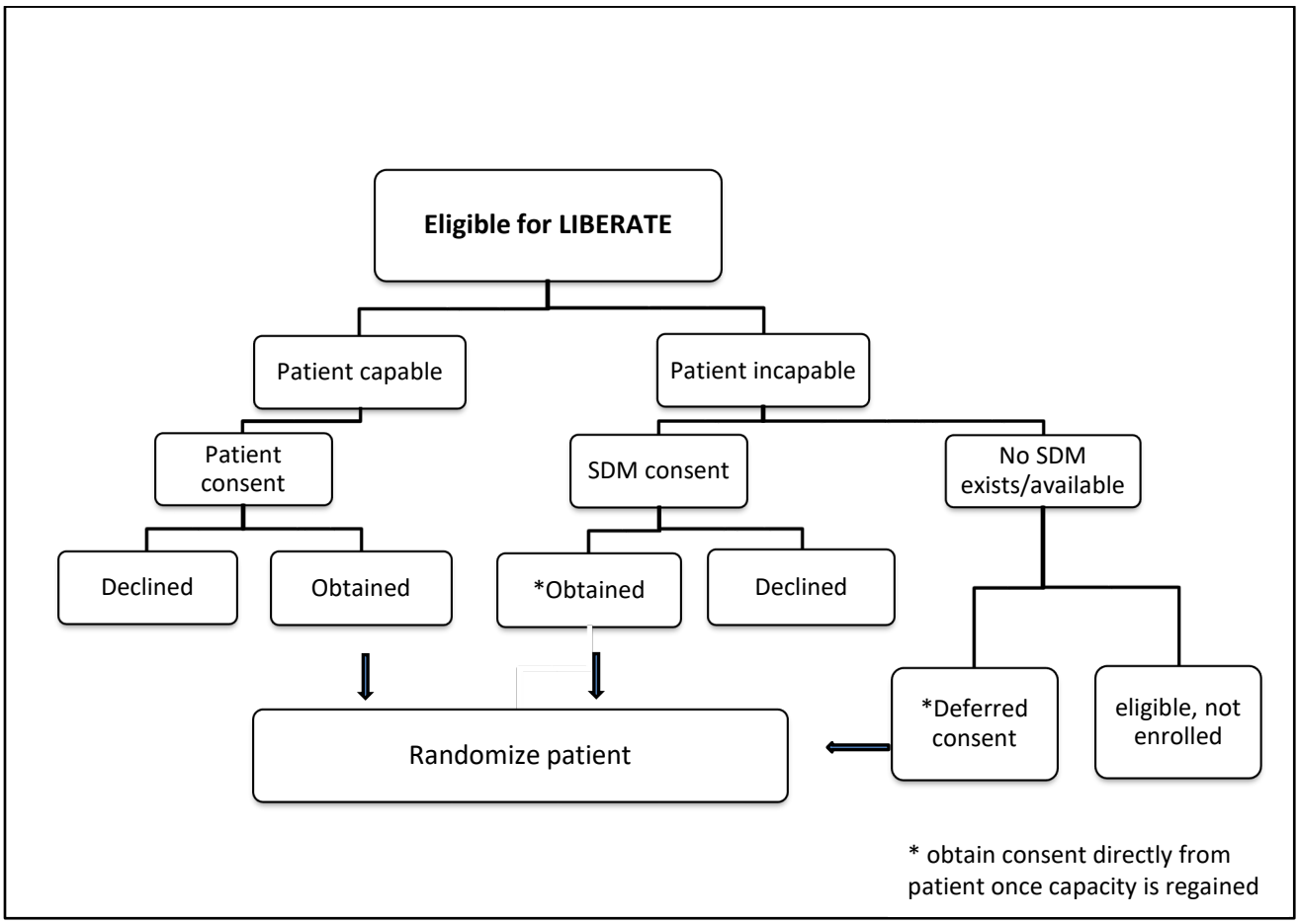
After the SDM has read the ICF, ascertain their willingness to consent to the study on behalf of the patient. If the SDM agrees, obtain their written consent. The designated study team member must also sign and date the ICF. Provide a copy to the SDM and keep the original in a separate file. Document the date and time of consent as per local site policy. Document whether the SDM declines or accepts on the Screening Log.

In situations where enrollment is based on SDM-provided consent, frequent attempts to verify the patient's capacity should be made (e.g., every 72 hours) to obtain consent from the subject once capacity is regained. If, at that time, the patient chooses to withdraw from the study, he/she will be asked to authorize retention of all data collected to date and/or completion of follow-up for detection of study outcomes at 90 days.

Patient does not have capacity and SDM not located. If the patient is incapacitated and a SDM is not found, the patient may be enrolled and randomized with deferred consent, if approved by the local REB. Deferred consent should be obtained from the MRP. However, in situations where the MRP is affiliated with the study (e.g., Co-Investigator) refer to local REB guidelines on usage of deferred

consent models. All efforts must be made by the study team to obtain consent as soon as possible from the SDM/patient once available and/or capacity is regained. Document the date and time of consent as per local site policy.

The following flow chart illustrates the possible scenarios for patient consent at most centers:



Obtaining Verbal Consent

Initial contact can be made via telephone (as per each site's policy and approved by the local REB). The following general statements may be used in the initial telephone conversation with SDMs. Please note that it is difficult to script the conversation given that it is not possible to anticipate the responses of the patient or SDM with any degree of certainty.

"Hello. My name is (insert name of research personnel) and I am the research nurse/coordinator in the ICU at (insert name of hospital). As a research facility, (insert name of hospital) participates in a number of research studies. In critical care, research is the best way we have to advance our understanding of disease and improve detection, prevention, and treatment of critical illness. As such, we feel it is important to offer opportunities for research participation to our patients and families for their consideration. When patients are in the ICU, we are usually not able to talk with them due to the severity of their illness or the treatments that they receive (mechanical ventilation, sedation). Because of this, we ask family members to act as substitute decision makers and to make decisions for the

patient based on their best knowledge of what the patient would want for themselves if they could speak.

Participation in any type of research is entirely voluntary and you have the right to refuse research or withdraw from research at any time. As (insert name of clinical team member) has explained to you, (insert patient name) is receiving medications call vasopressors because s/he has very low blood pressure. Right now the vasopressor medications are being given by IV. We are currently conducting a study that would use an oral (by mouth) medication called midodrine to try to reduce the need for IV vasopressors. Would you be willing to discuss the possibility of (insert name of patient) participating in a research study with me?"

If the SDM is willing to discuss the possibility of participation in the trial, move forward to review the content of the most recent REB approved ICF. For SDMs that are not on site, send a copy of the most recent REB approved ICF via email to assist the SDM in their decision-making process.

If the SDM agrees but is not able to provide written consent, request that the SDM provide verbal consent. Document that verbal consent has been obtained on the local REB approved verbal consent form. Document verbal consent to any additional questions, as applicable (e.g., agree to provide health care information, agree to have data used for future research, etc.).

The designated study team member and third-party witness (and interpreter, if used) must then sign and date the verbal consent form. Request that the SDM send a signed version of the ICF at their earliest convenience. Provide the SDM/subject with a complete copy of the signed ICF. Retain the original signed ICF in a separate file. Document the date and time of consent as per local site policy. Ultimately, as per Health Canada regulations and local REB policies written informed consent must be secured prior to subject discharge.

5.4 Withdrawal of Consent

The subject/SDM can withdraw their consent to participate at any time during the study. Please refer to your site's local REB policy regarding the following provisions. Please document any discussions regarding consent in the subjects research file.

Provisions of Consent

a) Subject/SDM does not wish to continue in the study but has consented to the collection of information from their medical records to complete data forms.

b) Subject/SDM does not wish to continue in the study and **does not** consent to their medical records being accessed. Ensure the subject is informed that all data collected up until the point of withdrawal will be used for study purposes. No further data is to be collected from the subject.

Chapter 6: Randomization

6.1 Subject ID/Randomization number

While all patients screened should be included on the screening log, only patients who are fully eligible and for whom consent is obtained will be entered in the study and assigned an ID#. Each time that a new patient is enrolled in the study they are assigned a unique randomization number. The way the unique randomization number is assigned is dependent on site-specific operations. For example:

- **Scenario 1** - Sites with dedicated research pharmacies that dispense IP when patients are enrolled will assign their own randomization number. The randomization number should align with the treatment assignment ID provided by the Research Pharmacy (i.e. UAH001, GNH001 etc)
- **Scenario 2** - Sites that have the IP pre-dispensed in individual containers that have been labelled with unique IDs will use the kit number on the study treatment container as the randomization number.

The patient will be identified by their unique randomization number in all correspondence with the Coordinating Centre. The format of the subject ID number is 'XXX-XXX', where the first 3 letters correspond to the site and the last 3 numbers correspond to the patient number. This randomization number is to be written on all subject CRFs and drug accountability documents.

***Sites Randomizing by Dedicated Research Pharmacies* (Scenario 1) –** Please follow local site Research Pharmacy policies.

***Sites Randomizing without Dedicated Research Pharmacies* (Scenario 2)** – Please follow instructions for dispensing IP outlined in the SIV and local site guidelines and policies.

6.2 Co-enrollment

Co-enrollment into other studies will be permitted when that investigational product or treatment has little known hemodynamic effects and will be reviewed on a case by case basis.
If a subject is being considered for multiple studies, please verify that the competing study does not prohibit the use of another investigational product. If a subject is already enrolled in another study that prohibits investigational therapies, you cannot randomize them into LIBERATE.

If co-enrollment into another study is approved by the CC, enter the name of the co-enrolled study in the Outcomes page of the REDCap case report form.

Chapter 7: Initiation and Administration of Investigational Product

Drug administration must only occur after all required screening, eligibility forms and consent are completed. The QI/Co-investigator must confirm the subject is eligible to participate in the study.

The IP should be dispensed and administered as closely to the time of randomization as possible and then every 8 hours until the end of study treatment schedule.

The administration of the IP capsules will be the responsibility of the blinded bedside nurse. If subjects are intubated and have a NG/OG tube, the contents will be removed from the study capsule, mixed with sterile water and administered through the subject's oral/nasal feeding tube.

- The IP should be administered until IV vasopressors have been discontinued for a continuous 24 hour period. **Important note: inotropic therapy should not be included in the determination of IV vasopressor termination.** i.e., vasopressors are considered discontinued even if the patient remains on IV inotropic therapy.
- If IV vasopressors are discontinued but then restarted less than 24 hours later, the IP should continue to be administered until a full 24 hours after discontinuation of IV vasopressors.
- If the patient is transferred from the ICU prior to discontinuation of the IP, the IP should be administered on the inpatient unit until the 24-hour period of administration (after IV vasopressor discontinuation) is complete.

Please refer to the LIBERATE Pharmacy Manual for information on the Investigational Product

CHAPTER 8: Data Collection

The following section will provide guidance on how to complete each element of the case report forms. Daily documentation will continue for the length of stay in the ICU, or up to study day 30 or death, whichever occurs first. Subjects will remain in the trial for 90 days from study enrollment.

8.1 REDCap Database

REDCap is a secure web-based application for managing research data. LIBERATE data will be entered and stored in the REDCap platform accessed through the following link: https://micyrn.med.ualberta.ca/

Research staff from each site will receive a unique user name and password to sign into REDCap. Research staff collecting data may enter data directly into the Redcap database or if they prefer, they may record study information on the paper CRF and then transcribe into REDCap.

8.2 Source Documents

Source documents are the first place that you collect data. Source documents may include intake notes, clinic notes, laboratory reports, phone call logs, etc. and may be paper form and/or electronic medical record. This information is then entered onto the Case Report Forms (CRFs). CRFs are study specific forms which are used to collect the data required from each subject in the study in order to obtain the primary and secondary outcomes. The data collected in the CRFs are reviewed and queried in order to ensure its accuracy and integrity prior to including it in the analysis.

8.3 Case Report Forms – data entry

Refer to the subject's hospital medical record to complete case report forms and source documentation as required by local site policy. Study days are defined as 0700hrs to 0659hrs except for Day 1 which is time of first study IP administration to 0659hrs.

Screening for Eligibility

REDCap record ID #: 5 digit number (i.e.: 1727-1) assigned to the subject by the REDCap EMR.

Randomization #: 3 letter site ID (i.e., UAH, GNH etc.) followed by sequential 3 digit study number assigned to the patient through randomization/IP label. Usually follows pattern of 001, 002, 003…

Patient initials: patient's first, middle and last initials. If the middle name is unavailable a dash may be used, i.e. George Thomas Brown – GTB or G-B.

Inclusion criteria: Review patient's inclusion criteria. All criteria should be answered 'Y' for patient to be eligible for study inclusion.

Exclusion criteria: Review patient's exclusion criteria. All criteria should be answered 'N' for patient to be eligible for study inclusion.

Eligibility: If patient has met all eligibility criteria indicate 'Y', sign and date the form and proceed to the Randomization page.

NOTE – In addition the site QI should e-sign and lock the screening form in the REDCap database.

Consent

Enter information on date and time of consent, type of consent and, if consent was obtained by an SDM or by method of deferred consent, whether consent was obtained by the subject upon regaining capacity. If consent was NOT ultimately obtained from the subject, enter the reason why.

In cases where deferred consent is used and written informed consent is not secured prior to subject discharge, the local REB must be notified and will make a decision on whether study data collected on that subject can be retained.

Randomization

After obtaining consent, an IP order should be submitted to the Research Pharmacy as soon as possible **(Scenario 1)**, or the next sequential numbered IP container should be selected and prepared for administration **(Scenario 2)**.

The time of randomization is the time the order for IP is submitted to the Pharmacy or the time the IP container is selected.

In the REDCap Randomization page, enter the date and time of randomization and the randomization code assigned to the study subject by the Pharmacy dispensing the study IP **(Scenario 1)**. Or the randomization code is the same number as the kit# on pre-dispensed IP containers in **(Scenario 2)**.

Demographics

Enter the subject's date of birth, age, sex, weight (kgs) and height (cm).

ICU Information.

Date and time of Study Eligibility – the day the subject met all inclusion/exclusion criteria

Date of ICU and Hospital admission – from subject's health record.

APACHEII score at ICU admission – calculate using the APACHE score sheet. (APPENDIX 2)

- The physiological data for calculation of the APACHE II score are derived from the **worst values in the first 24 hours after admission to the ICU.**
- If there are no laboratory values for a specific component of the APACHE II score available during the 24 hour time period (e.g., no bilirubin measured) then we consider the value missing and assign no points for that component

SOFA score at time of first IP administration – calculate using the SOFA score sheet (APPENDIX 3).

- The physiological data for calculation of the SOFA score are derived from the **worst values in the 24 hours prior to the first IP administration.**
- No exceptions for other laboratory values (e.g., data for bilirubin is restricted to that 24 hour period).
- If there are no laboratory values for a specific component of the SOFA score available during the 24 hour time period (e.g., no bilirubin measured) then the value is considered missing and no points are to be assigned for that component.
- If the study subject is on sedatives, estimate assumed GCS off sedatives.

Clinical Frailty Scale (CFS) score – If the CFS score is not documented in the subject's medical record, assign a score between 1 and 9 by referring to descriptions in the CFS tool (APPENDIX 4).

Etiology of shock – from subject's health record.

Type of ICU admission – from subject's health record.

If surgical admission provide reason – from subject's health record.

ICU admission diagnosis code - Can be identified using the embedded tool in the REDCap CRF, or by referring to the ICU Admitting Diagnosis Codes Chart. (APPENDIX 5)

Comorbid Illnesses

Comorbid illnesses can usually be found in the subject's health record. For this study, documentation of existing comorbid conditions will include: *AIDS, chronic dialysis, congestive heart failure, respiratory insufficiency (i.e., COPD, asthma etc), chronic liver failure (i.e., cirrhosis, hepatitis, etc), diabetes mellitus, acute liver failure (i.e., Tylenol overdose, alcoholic hepatitis, etc), immune suppression, leukemia, lymphoma, metastatic cancer and coronary artery disease.*

Vasopressor/Inotropic Therapy – to be collected daily.

Vasopressor/inotrope Day 1– Day 1 data collection starts from time of time of first IP administration to 0659hrs. Please note: this may not be a full 24 hours. Subsequent days are 0700hrs to 0659hrs.

Vasopressor/inotrope Type – name of vasopressor/inotrope medication infusions. (**Vasopressors: norepinephrine, epinephrine, vasopressin, phenylephrine) (Inotropes: milrinone and dobutamine)**

Highest Daily Dose – highest infusion dose within the study day with corresponding units for each vasopressor/inotropic medication.

Lowest Daily Dose – lowest infusion dose within the study day with corresponding units for each vasopressor/inotropic medication. On days the vasopressor is discontinued, the lowest dose should be recorded as 0.00 to reflect the discontinuation of the IV vasopressor. On days where the vasopressor is paused and then restarted within 24 hours (not discontinued) – the lowest dose should be the lowest dose administered that day, not 0.00.

For example: Norepinephrine is being administered at 0.02 on day 2 and then is discontinued for the rest of the day but restarted at 0.04 the morning of day 3. The highest and lowest dose entered for day 2 would be 0.02.

Please note the number of decimal places required for each vasopressor/inotrope.

Sedation – continuous IV infusions only (do not record prn sedation)

Sedation Day 1– Day 1 data collection starts from time of time of first IP administration to 0659hrs. Please note: this may not be a full 24 hours. Subsequent days are 0700hrs to 0659hrs.

Sedation Type – name of sedation medication infusion e.g., hydromorphone, morphine, fentanyl, midiazolam, propofol, and ketamine.

Highest Daily Dose – highest infusion dose within the study day with corresponding units for each sedation medication.

Lowest Daily Dose – lowest infusion dose within the study day with corresponding units for each sedation medication.

Please note the number of decimal places required for each sedation.

Co-Interventions

Study Day – Day 1 data collection starts from time of time of first IP administration to 0659hrs.

Subsequent Study Days are 0700hrs to 0659hrs

Ventilation – Worst respiratory status for the study day period.

Only choose one category, i.e., If a subject is receiving invasive mechanical ventilation and then switched to receive nasal cannula later in the study day, please only check off the "invasive" option for the study day.

Renal Replacement Therapy: Select the modality used for the study day period.

Corticosteroids: including hydrocortisone IV/PO, dexamethasone IV/PO, methylprednisone, prednisone, or other (please specify name of corticosteroid administered).

Blood products: document if the subject received any blood products during the study day period.

Total daily urine output: the total urine output for the study day period. Round up to next hour if required.

Net daily fluid balance: the net daily fluid balance during the study day period. Calculate to 2 decimal points.

Outcomes

Total duration of IV vasopressor support – start from time of first study IP administration to the time IV vasopressors have been discontinued for a continuous 24 hour period. **Important note: this calculation does not include length of inotropic support**

Please Note: if an IV vasopressor has been stopped/paused then restarted in under 24 hours, continue to calculate IV vasopressor support until they have been discontinued for a continuous 24 hour period.

Example: If first study IP dose was administered 01-JAN-2023 at 0800hrs and norepinephrine was paused on 02-JAN-2023 at 0800hrs and then restarted at 1000hrs given continuously then discontinued at 1400hrs total duration of IV vasopressor support is 28 hours.

IV vasopressors re-initiated over 24 hours after cessation – answer yes or no. If yes: provide the date and time IV vasopressors were restarted.

Please Note: IV vasopressors re-initiated over 24 hours after cessation are **NOT** to be included in *total duration of IV vasopressor support* calculations.

Echocardiogram: only report formal ECHO consultations and reporting. Do not report bedside tests.

Death/discharge from ICU: provide date/time of death or discharge from ICU.

Date/time of decision to discharge from ICU: This is the time the order is written to transfer out of the ICU.

ICU re-admission less than 48 hours after ICU discharge: Record 'Y' if subject was readmitted to the ICU within 48 hours after being discharged.

Death/discharge from hospital: provide date of death or discharge from the hospital.

Discharge location: provide the location the subject was discharged to.

90 Day Follow-up Assessment

Mortality status – alive or dead

If alive, document the use of the listed organ supports received on day 90.

Chapter 9: Adverse Events

Subjects should be closely monitored for any change to their health (including any troublesome medical occurrences) from baseline through to study completion/withdrawal.

Events can be specified as Adverse Events (AEs), Adverse Drug Reactions (ADRs), Serious Adverse Events (SAEs), Serious Adverse Drug Reactions (SADRs) and Serious Unexpected Serious Adverse Reactions (SUSARs) according to the criteria detailed in their definitions below. It is the responsibility of the QI, or delegated sub-investigator listed on the TDL, to review, assess and report all events to the LIBERATE CC according to the procedures outlined in this section.

For this study, only AEs that are determined by the QI, or delegate, to be definitely, probably, or possibly related to the IP (midodrine) will be recorded on the Adverse Event Worksheet. A list of adverse events that may be possibly related to the IP is provided on the *Adverse Events/Safety Endpoints* CRF.

Adverse events that are assessed and determined unrelated or unlikely related to the IP will not need to be recorded.

AEs and SAEs will be systematically collected for the entire duration that the subject is receiving the investigational product. Any events that occur while the subject is receiving the investigational product will be followed until either resolved or until Day 90 following randomization, whichever comes first.

Collection and evaluation of **adverse events** will include only those related to the administration of midodrine.

9.1 Definitions

Adverse Events (AE)	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment and includes an adverse drug reaction (ADR). An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product.
Adverse Drug Reaction (ADR)	An adverse drug reaction is a response to an investigational product 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. The phrase "responses to an investigational product" means that a causal relationship between an investigational product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. The expression “causal relationship” is meant to convey that in general there are facts, evidence or arguments to suggest a reasonable causal relationship.

Serious Adverse Event (SAE)	An untoward occurrence that at any dose: • Results in death, • Is life-threatening, • Requires inpatient hospitalization or prolongation of existing hospitalization, • Results in persistent or significant disability/incapacity, • Is a congenital abnormality or birth defect **NOTE:** The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Drug Reaction (SADR)	Serious adverse drug reactions are any adverse events that have a causal relationship (i.e. possibly, probably, or definitely related) with the investigational product which are serious.
Serious and Unexpected Serious Adverse Reaction (SUSAR)	Serious and Unexpected Serious Adverse Reaction are SADR that are unexpected, where severity which is not consistent with the applicable product information of each component of the paste and suspension. All SUSARs will have expedited reporting to regulatory agencies following ICH-GCP and local regulatory requirements.

9.2. Assessment

Causality Assessment	The causality assessment is the determination of a relationship between a study drug and an AE. The site QI, or delegate, should use his/her clinical judgement to determine the existence of a reasonable possibility that the study drug caused or contributed to an AE. The AE source document will allow the QI, or delegate, to select whether the study drug is definitely, probably, possibly, unlikely or unrelated to the study drug. If the site QI, or delegate, is unsure about whether or not the study drug caused or is related to the event, then the event will be handled as "related" to the study drug for reporting purposes of the trial. If the causality assessment is "unknown, but not related" this should be clearly documented in the source.
Expectedness Assessment	Events are classified as expected or unexpected based on whether the nature, severity and/or frequency is consistent with the risk information set out in the product monograph.
Seriousness Assessment	An event is classified as serious if it is associated with effects threatening the life or physiological functions of a subject. The assessment of seriousness serves as a guide for defining regulatory reporting obligations.
Severity Assessment	The term "severe" is often used to describe the intensity (severity) of a specific event (e.g. mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). It should be noted that severity is not the same as seriousness.

9.3. Adverse Event (AE) Reporting

For this study, only AEs that are determined by the QI, or delegate, to be definitely, probably, or possibly related to the IP (midodrine) will be recorded on the Adverse Event Worksheet.

Adverse events that are assessed and determined unrelated or unlikely related to the IP will not need to be recorded.

Investigations into potential AEs should be done during each contact with a subject.

Investigations may be done through specific questioning and as appropriate, by examination.

Information on all AEs should be recorded promptly in the source document (e.g. medical chart, progress notes), and assessed by the site QI or delegate in a timely manner. The AE CRFs should be completed using source documents by a delegated research team member in a timely manner/within 15 days of site awareness. All clearly related signs, symptoms, and abnormal diagnostic procedures should be recorded in the source, but should be grouped under one diagnosis in the CRF. Each diagnosed AE should then be categorized in accordance with Medical Dictionary for Regulatory Activities (MedDRA) classifications.

The QI is ultimately responsible for reviewing and assessing all AEs to determine relatedness. If the QI is unable to sign off on paper charts demonstrating review and oversight, a note can be left in the patients electronic medical record. Alternatively, sites can document their specific procedure for identifying, assessing and documenting AEs in a Note to File.

If the site investigator or delegated sub-investigator is unsure about whether or not the study drug caused or is related to the event, then the event will be handled as "related" to the study drug for recording purposes of the trial. If the causality assessment is "unknown but not related" to the study drug, this should be clearly documented in the source documents.

The following are not considered AEs and therefore do not require recording:

- Pre-existing diseases or conditions identified and recorded at screening/baseline unless, at the discretion of the investigator, the disease or condition worsens in severity or frequency.
- At the discretion of the investigator, events considered likely manifestations of the underlying disease or that commonly occur in the study population independent of treatment exposure.
- Elective medical or surgical procedures.

Use the *Adverse Event Worksheet* to complete the following:

1. Record each event separately and number each one in the "AE #" column. Enter the adverse event being reported. If 'other' is selected, provide a description of the corresponding event in the text box.
2. Record the date the site initially became aware of the event.
3. Record the date the event began.
4. Once the event has been resolved, record the date (dd-mmm-yyyy) and note the outcome of the event as it relates to the subject.
5. The coordinator can complete steps 1-4 and should initial and date the worksheet source document.
6. Provide the partially completed worksheet to the QI/delegated qualified physician to perform a review and assessment of the subject and/or event.
7. Enter the AE information into the CRF in REDCap no later than 15 calendar days from the time the QI or delegated qualified physician becomes aware of the event.
8. Maintain the Adverse Event Worksheet and any other source documents in the subject's study file.
9. Update the Adverse Event Worksheet during subsequent visits or points of contact as required.

To be completed by the QI or delegated qualified physician ONLY:

10. Once reviewed and assessed, record the medical term of the event in accordance with Medical Dictionary for Regulatory Activities (MedDRA), if applicable. All clearly related signs, symptoms, and abnormal diagnostic procedures should be grouped under one diagnosis.
11. Assess severity, causality/relatedness, seriousness and expectedness.
12. Determine the suitable course of action regarding the subject's ability to continue on the study medication and record in the "Study Treatment Administration Status" column of the *Adverse Event Worksheet*.
13. Determine and record the subject's need to discontinue the study.
14. Sign and date below the assessments and determinations in the 'investigator signature' line.

9.4. Serious Adverse Event (SAE) Reporting

Only SAEs that are assessed as related (definitely, possibly, or probably) to the assigned IP will be reported. As a reminder, a serious adverse event (SAE) or reaction is any untoward occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or in significant disability/incapacity
- Is a congenital abnormality or a birth defect

The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

9.4.1. Serious Adverse Drug Reactions (SADRs)

Expected Serious Adverse Events include:

- Clinically significant bradycardia
- Acute Coronary Syndrome
- Allergic Reaction to IP
- Hypertension
- Bowel Ischemia
- Limb Ischemia
- Stroke

9.4.2. Serious Unexpected Serious Adverse Reaction (SUSAR) Reporting

Events that are assessed to be serious and unexpected and related or cannot be ruled out as related to the investigational product are considered SUSARs. Report all SUSARs and complete the following:

1. Complete the form using the information collected on the Adverse Event Worksheet and subject's medical record. Only use the subject ID # and partial date of birth on this form. Do not include any direct patient identifiers.
2. Provide a chronologically detailed summary of the event including site, associated signs and symptoms and alternative etiologies.

3. Provide a summary of the subject's relevant past medical history.
4. List any relevant laboratory or diagnostic testing information in the tables in the form. Attach copies of available test results.
5. List concomitant medications the subject was taking prior to and at the time of onset of the event.
6. Have the QI or delegated qualified physician review the Adverse Event Worksheet form and all source documents related to the event.
7. Forward a copy of the completed Adverse Event Worksheet, summary, and de-identified Source Documents to the CC by email within 24 hours of site awareness. Report to your local REB in accordance with local reporting requirements and timelines.

Any unexpected fatal or life-threatening suspected adverse reaction related to the IP will be reported to the regulatory authority as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. If the event is not fatal or life-threatening, the safety report will be submitted within 15 calendar days after the sponsor determines that the information qualifies for reporting.

File the original copy of the completed, signed and dated SUSARs and any other source documents in the subject's study file.

Chapter 10: Protocol Deviations and Violations

A protocol deviation is a divergence from the study protocol, procedures and/or regulatory requirements that are related to the conduct of the study at the site. Deviations will be recorded using the Protocol Deviation Form.

Examples of protocol deviations include:

- Randomized but did not meet all inclusion/exclusion criteria
- Study medication dose missed
- Subject accidently unblinded
- Incorrect/unassigned intervention
- Early withdrawal of subject from study

It is the site's responsibility to determine if the Protocol Deviation requires reporting to the local REB.

10.1. Protocol Deviations (required)

If a deviation from the study protocol, procedures or regulatory requirements is required, it is best to contact the CC in advance for guidance. Email the CC with the details of the request and the CC will aim to provide guidance, within an acceptable time frame depending on the urgency for a response.

1. Complete the applicable sections of the Protocol Deviation Log in the REDCap system.
2. Notify the CC by email that you have completed the form and it is ready for review.
3. Have the Lead Investigator at the CC review the REDCap form, enter his comments, and verify the Protocol Deviation. The Lead Investigator will do this by clicking on the speech bubble in the REDCap Protocol Deviation Form, entering details in the comment box and selecting 'verify data'.
4. The CC will email the study site to confirm the protocol deviation has been reviewed.
5. If applicable the study site will submit the protocol deviation to the REB and record the date of submission to REB and REB acknowledgement.

NOTE: The approval of deviation requests are intended to facilitate required modifications to the study protocol for single events, and are not to be used repeatedly for recurring events. There are no waivers or deviations acceptable for study eligibility.

10.2. Protocol Deviations *(post-facto discovery)*

If a deviation from the study protocol, procedures or regulatory requirements has occurred, complete the *Protocol Deviation Form* in REDCap and notify the CC within five business days of site awareness.

10.3. Deliberate Action

Deliberate actions implemented to avert an immediate hazard to a subject are protocol deviations that are of the most extreme circumstances, and should be communicated to the CC immediately, specifically if the subject's safety is at risk.

Completion of the *Protocol Deviation Form* may be associated with the requirement to complete additional forms, such as Adverse Event Worksheets or Serious Adverse Event/CIOMS forms, which should be completed and sent to the CC for review promptly.

If the deviation requires notification to Health Canada, the CC will make such arrangements.

10.4. Noncompliance

Noncompliance with the study protocol, SOPs, GCP, applicable regulatory requirements, and applicable institutional policies and procedures by the site will be addressed by the CC.

Significant noncompliance that could impact the safety of the study subjects or the validity of the data will be determined by the CC using a root cause analysis (RCA). A corrective and preventative action plan (CAPA) that is appropriate to the situation may be implemented.

Chapter 11: Monitoring

This section provides details regarding study monitoring, preparing for and conducting a monitoring visit, and study close-out. Further detailed information is available in the LIBERATE Monitoring Plan as discussed at the sites SIV.

11.1. Study Monitoring

Study monitoring is conducted to verify the safety of human study subjects and to ensure the protection of their rights and well-being. Monitoring also verifies that collected study data is accurate, complete and verifiable by source documentation.

Monitoring will be done remotely and/or in person for the duration of the study. The extent and nature of monitoring conducted by the CC will be determined on a site-by-site basis to ensure that the study is being conducted and documented in a manner that is compliant with the approved protocol / amendment(s), GCP and any other applicable regulatory requirement(s).

A monitoring visit may include, but is not limited to, the following:

- Review of documents from the REB and other regulatory bodies, if applicable.
- Review of source documents including medical records.
- Review of study worksheets/logs.
- Review of signed informed consent forms.
- Review of completed case report forms.
- Review of site-specific processes related to the conduct of the study. (i.e. process for dispensing and destruction of IP, identification of potential study subjects etc.)
- Review of adverse events and protocol deviations.
- Study-specific training.
- And if able to, touring of site facilities, including the IP storage/pharmacy area, study document storage area, and the patient care area(s).

11.2. Preparing for an On-Site Monitoring Visit

1. Ensure research team members are available on the day of the visit and confirm the date and time of the visit with the CC.
2. Ensure all essential documents and case report forms are up-to-date and complete.
3. Respond to any outstanding queries in REDCap.
4. Ensure all requested medical records and charts containing source documentation are available or accessible for review.
5. Have all study binders, source documents, study-specific documents (paper or electronic) and training documentation available or accessible for review.
6. If able to, arrange for a facility tour, if requested by the monitor.
7. Log the visit in the *Study Visit Log* and file the original with the essential documents in the REDCap Regulatory Binder.

11.3. Preparing for a Remote Monitoring Visit

1. Ensure research team members are available via phone or e-mail on the day of the visit and confirm the date and time of the visit with the CC.
2. Ensure all requested essential documents and case report forms are up-to-date
3. Respond to any outstanding queries in REDCap.
4. Inform the CC of the site's remote access procedure, for instance access to EMR, screen sharing, etc.
5. If applicable, arrange for access to the requested medical records and charts containing source documentation.
6. Log the visit in the *Study Visit Log* and file the original with the essential documents in the REDCap Regulatory Binder.

11.4. Interim Monitoring Visits

The Clinical Trials Office (CTO) will conduct interim monitoring visits based on enrollment status, safety concerns, data quality, and protocol compliance at each site. Remote monitoring may also take place throughout the study on an ongoing basis. The following tasks may be performed during an interim monitoring visit:

1. Review of essential documents .
2. Review of investigator and site personnel responsibilities.
3. Informed consent review.
4. eCRF review and source document verification .
5. AE, SAE, and SUSAR review .
6. Protocol specific procedures / investigations .
7. IP accountability and pharmacy documentation .
8. Report of protocol deviations .
9. Tour of facilities.
10. Meeting or discussion with the QI and research staff to review findings and answer questions .

11.5. Close-out visit

The CC will complete a single close-out visit for each site. During this visit, the monitor will perform the following activities:

- Ensure the completion of outstanding eCRFs and queries.
- Ensure all previous monitoring corrections have been addressed.
- Ensure the return or destruction of the IP (if applicable).
- Collect outstanding subject data forms and study forms (ex. screening and monitoring logs).
- Perform a final review of the study file documents.
- Review the plans and location for record retention.
- Ensure all SAEs have been reported appropriately.
- Ensure the QI has notified the local REB of the site closure.
- Ensure Health Canada has been notified of study closure (within 15 days of closing).

The monitor will prepare the final monitoring report and send it to the site for their records and to CCTS Quality Assurance. The site will address all monitoring observations (including observations from previous monitoring reports) prior to final study closeout.

11.6. Monitoring Reports

A written report summarizing significant findings, observations and deviations detected during a monitoring visit or remote monitoring will be forwarded to the site from the CC. Upon receipt of a monitoring report, please complete the following actions:

1. Review the summary of the monitoring visit/review and clarify any questions you may have.
2. Once reviewed, the QI must sign and date the report to acknowledge receipt.
3. Respond to the report by completing each 'Required Action' and providing corrective and preventative actions where necessary. Record the completion of a required action by checking the appropriate box in the "status" column and providing the completion date in the 'Date Resolved' column of the report.
4. Implement new procedures resulting from the corrective and/or preventative actions.
5. Once all required actions have been resolved, forward the completed report, NTFs and supporting documents to the CC for review and approval.
6. A completion notice will be forwarded to the site once the responses and supporting documents provided by the site to the monitor are found to be satisfactory.
7. File the monitoring report and the completion notice in the study binder.
8. Follow up with any additional comments or actions provided by the CC in response to the proposed resolutions.
9. If a report or a communication regarding a report has not been received within 30 days of the site visit, contact the CC.

11.7. Note-to-File (NTF)

A note-to-file is a record commonly used to document an unusual occurrence during a clinical trial. When written appropriately, these notes provide clarity, establish accountability, and enable an event to be reconstructed during future review.

NTFs can be used to document:

- decisions made
- instructions from the sponsor
- unusual events that are important to remember

Each NTF should identify the issue or deviation from the protocol/SOPs/Sponsor requirement(s), provide a reason/explanation for the occurrence, include a corrective action/preventative action (CAPA) plan and be signed and dated by the responsible party within a timely manner. NTFs addressing an occurrence that affects subject safety and/or eligibility should be reviewed and signed and dated by the QI prior to the implementation or continuation of study interventions or procedures.

Chapter 12: Training and Responsibilities

12.1 Training

All site research personnel that have been delegated tasks associated with LIBERATE should be qualified by education, training, and experience to assume responsibility for the proper conduct of a randomized controlled trial in accordance with Good Clinical Practice and Health Canada Division 5 regulations. Documentation for this training must be filed and made available upon request.

12.2 Delegation of Responsibilities

The site research team must keep a completed Task Delegation Log (TDL) in their REDCap regulatory binder. The purpose of this log is to outline the key delegated tasks assigned to appropriately qualified individuals.
The Delegation Log should:

1. Identify each individual involved in the conduct of LIBERATE and to whom the Qualified Investigator has delegated key tasks.
2. Include the effective start date of their designated activities for each individual assigned to the study.
3. Be kept up-to-date over the course of the study. Copies of updated TDL must be filed in the site REDCap regulatory binder.

12.3 Qualified Investigators

The QI is ultimately responsible for the study conduct and health of the subjects at the site. They must ensure that all study team members are appropriately trained to perform the tasks defined within their role. As such, QIs must be trained in all aspects of the study. At a minimum, training on the below topics must be documented.

- Protocol
- Product Monographs
- Informed consent forms
- SOP for Management of Investigational Product
- GCP
- Health Canada Division 5
- N2 SOPs (or institutional equivalent) and TCPS2, as per institutional requirements.

12.4 Co-Investigators/ Sub-Investigators

Co-investigators and sub-investigators will provide study oversight in instances when the QI is unavailable. They may be delegated to tasks which include affirmation of eligibility criteria, medical oversight, assessment of AE/SAE criteria, and eCRF/CRF final sign off, among others. At a minimum, training on the below topics must be documented.

- Protocol
- Product Monographs
- Informed consent forms

- GCP
- Health Canada Division 5
- N2 SOPs (or institutional equivalent) and TCPS2, as per institutional requirements.

12.5 Research Coordinators

Research coordinators are important in the set up and managing the day-to-day activities of the study. They are typically responsible for maintaining essential documents throughout the study including regulatory and REB correspondence, collecting eligibility information, obtaining informed consent, completing CRFs/eCRFs, performing data entry into REDCap and possibly conducting IP accountability. At a minimum, training on the below topics must be documented.

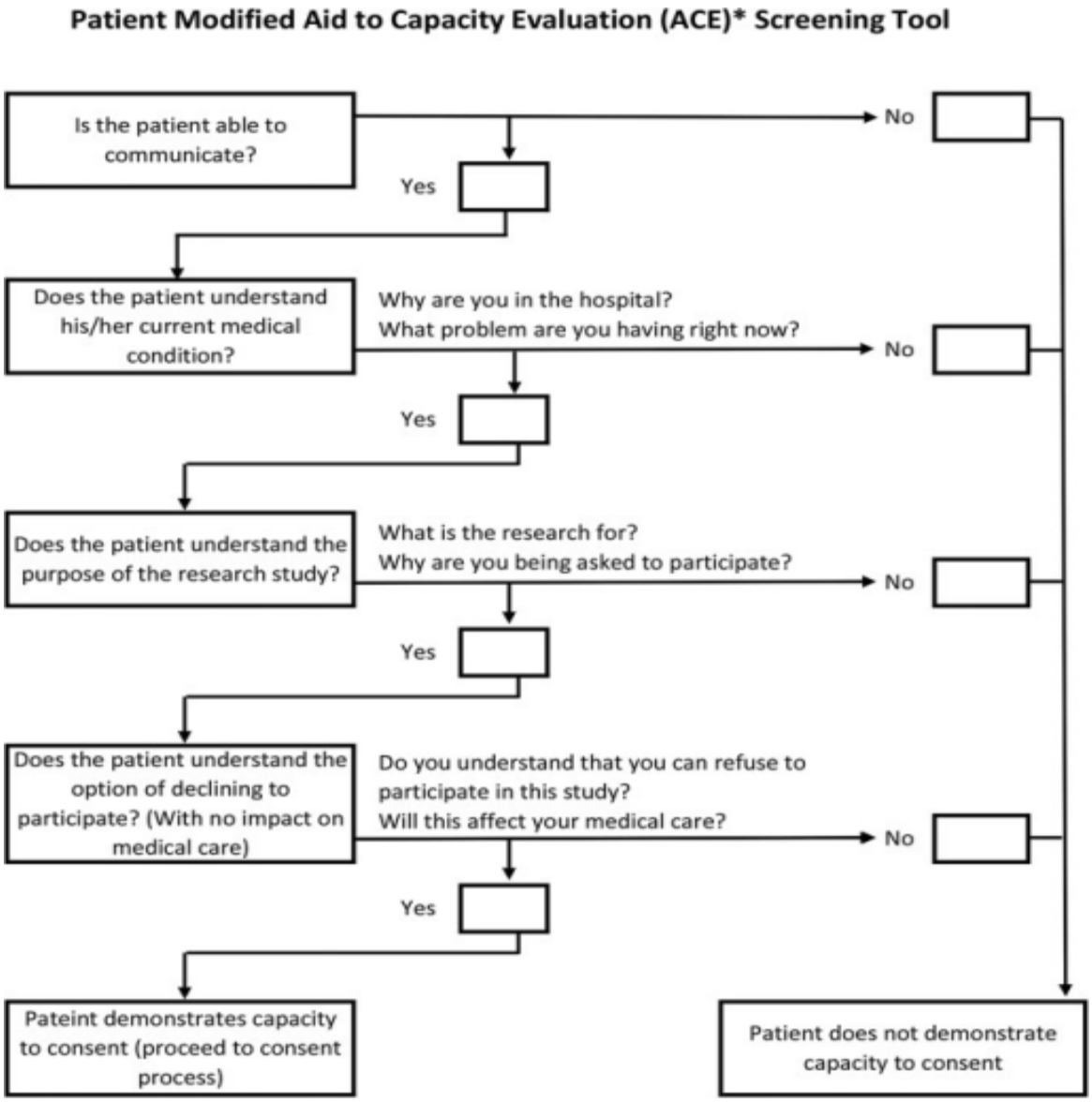
- Protocol
- Product Monographs
- Informed consent forms
- SOP for Management of Investigational Product
- GCP
- Health Canada Division 5
- N2 SOPs (or institutional equivalent) and TCPS2, as per institutional requirements.
- REDCap

12.6 Pharmacy Staff

While some sites may not require pharmacy involvement, others may need a research pharmacy for ordering, receiving, preparing/dispensing and disposing of study medications. While it is encouraged that all pharmacy team members involved in LIBERATE be listed on the TDL, at minimum, there should be at least one who will provide oversight for all pharmacy related activities and provide training to other pharmacy team personnel. The team members listed on the TDL should be fully trained in the Protocol and all Health Canada required modules. At minimum, training on the below topics must be documented.

- Protocol
- Product Monographs
- Health Canada Division 5
- GCP
- SOP for Management of Investigational Product
- Master Drug Accountability Log Instructions, if applicable.

APPENDIX 1:



Buchner DL, Bagshaw SM, Dodek P, Forster AJ, Fowler RA, Lamontagne F, Turgeon AF, Potestio M, Stelfox HT. Prospective cohort study protocol to describe the transfer of patients from intensive care units to hospital wards. BMJ Open. 2015 Jul 8;5(7):e007913. doi: 10.1136/bmjopen-2015-007913. PMID: 26155820; PMCID: PMC4499701.

APPENDIX 2: APACHE II Calculation Worksheet

Calculate using values from first 24 hours following time of ICU admission

A. Physiologic Variables Points

PHYSIOLOGIC VARIABLE	HIGH ABNORMAL RANGE						LOW ABNORMAL RANGE			PT SCORE
	4	3	2	1	0	1	2	3	4	
Temperature - rectal (°C)	≥ 41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤ 29.9	
MAP (mmHg)	≥ 160	130-159	110-129		70-109		50-69		≤ 49	
Heart Rate	≥ 180	140-179	110-139		70-109		55-69	40-54	≤ 39	
Respiratory Rate (non-ventilated or ventilated)	≥ 50	35-49		25-34	12-24	10-11	6-9		≤ 5	
Oxygenation: [A-aDO_2 = (FiO_2 x 710) – (PCO_2 x 1.25) – PO_2]					FiO_2 =		PCO_2 =		PO_2 =	
a. FiO_2 ≥ 0.5 record A-aDO_2	≥ 500	350-499	200-349		< 200					
b. FiO_2 < 0.5 record only PaO_2					PO_2 > 70	PO_2 61-70		PO_2 55-60	PO_2 < 55	
Arterial pH	≥ 7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	< 7.15	
Serum Na (mmol/L)	≥ 180	160-179	155-159	150-154	130-149		120-129	111-119	≤ 110	
Serum K (mmol/L)	≥ 7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		< 2.5	
Serum Creatinine (umol/L)	> 305	170-304	130-169		53-129		<53			
Hematocrit (%)	≥ 60		50-59.9	46-49.9	30-45.9		20-29.9		< 20	
WBC (total/mm^3)	≥ 40		20-39.9	15-19.9	3-14.9		1-2.9		< 1	
Glasgow Coma Score (GCS)	Score = 15 minus actual GCS (see below)									
Serum HCO_3 (venous mmol/L) - not preferred, use if no ABG's	≥ 52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.0	< 15	
Creatinine	ACUTE PHYSIOLOGY SCORE (APS): Sum of the 12 individual variable points =									

double points for ACUTE Renal Failure

B. Age Points - Assign points to age as follows:

AGE (yrs)	POINTS
≤ 44	0
45-54	2
55-64	3
65-74	5
≥ 75	6
AGE SCORE =	

C. Chronic Health Points

If the patient has a history of severe organ system insufficiency (see below) or is immunocompromised assign points as follows:

a. For nonoperative or emergency postoperative pt -- 5 points
b. For elective postoperative pt -- 2 points

CHRONIC HEALTH SCORE =

D. APACHE II SCORE - Sum of A + B + C

A. APS points	
B. Age points	
C. Chronic Health points	
APACHE II SCORE =	

CHRONIC HEALTH DEFINITIONS

Organ insufficiency or immuno-compromised state evident prior to this hospital admission and are consistent with the following criteria:

LIVER: Biospy-proven cirrhosis and documented portal hypertension; prior episodes of upper GI bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma

CARDIOVASCULAR: New York Heart Association Class IV

RESPIRATORY: Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction (i.e., unable to climb stairs or perform activities of daily living or household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40 mmHg), or ventilator dependency

RENAL: Receiving chronic dialysis

IMMUNO-COMPROMISED: The patient has received therapy that suppresses resistance to infection (i.e., immunosuppressive treatment, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection (i.e., leukemia, lymphoma, AIDS)

APPENDIX 2: APACHE II Calculation Worksheet (cont'd)

GLASCOW COMA SCALE		
Parameter	**Response**	**Points Assigned (please circle)**
Eyes Open	Spontaneously	4
	On spoken command	3
	On pain	2
	No response	1
Best Motor Response	To spoken command	6
	To painful stimulus:	
	Localized pain	5
	Flexion withdrawal	4
	Flexion abnormal	3
	Extension	2
	No response	1
Best Verbal Response	*(Not on ventilator)*	
	Oriented & converses	5
	Disoriented & converses	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No response	1
	(On ventilator)	
	Appears oriented	5
	Questionably oriented	3
	Generally unresponsive	1
	TOTAL GCS =	

APPENDIX 3: SOFA Score Worksheet

Calculate using values from the 24 hours prior to first dose of IP administration

	0	1	2	3	4	Score
Respiration PaO_2/FiO_2	> 400	≤ 400 (± resp. support)	≤ 300 (± resp. support)	≤ 200 (+ resp. support)	≤ 100 (+ resp. support)	
Coagulation Platelets(x 10^9/L)	>150	≤ 150	≤ 100	≤ 50	≤ 20	
Liver Bilirubin (µmol/L)	< 20	20-32	33-101	102-204	> 204	
Cardiovascular	MAP ≥ 70 mmHg	MAP < 70 mmHg	DA ≤ 5 µg/kg/min or dobutamine (any dose) or milrinone (any dose)	DA > 5 µg/kg/min or EPI ≤ 0.1 µg/kg/min or NE ≤ 0.1 µg/kg/min or VP ≤ 0.02 U/min or phenylephrine (any dose if given as infusion NOT bolus)	DA > 15 µg/kg/min or EPI > 0.1 µg/kg/min or NE > 0.1 µg/kg/min or VP >0.02 U/min	
CNS Glasgow Coma Scale	15	13-14	10-12	6-9	< 6	
Renal Creatinine (µmol /L)	≤ 106	107 – 176	177 – 308	309 – 441 or urine output ≤ 500 mL/d	≥ 442 or urine output < 200 mL/d or patient receiving RRT	
					TOTAL SCORE	

APPENDIX 4: Clinical Frailty Scale

CLINICAL FRAILTY SCALE

1 VERY FIT — People who are robust, active, energetic and motivated. They tend to exercise regularly and are among the fittest for their age.

2 FIT — People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g., seasonally.

3 MANAGING WELL — People whose **medical problems are well controlled**, even if occasionally symptomatic, but often are **not regularly active** beyond routine walking.

4 LIVING WITH VERY MILD FRAILTY — Previously "vulnerable," this category marks early transition from complete independence. While **not dependent** on others for daily help, often **symptoms limit activities**. A common complaint is being "slowed up" and/or being tired during the day.

5 LIVING WITH MILD FRAILTY — People who often have **more evident slowing**, and need help with **high order instrumental activities of daily living** (finances, transportation, heavy housework). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation, medications and begins to restrict light housework.

6 LIVING WITH MODERATE FRAILTY — People who need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 LIVING WITH SEVERE FRAILTY — **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~6 months).

8 LIVING WITH VERY SEVERE FRAILTY — Completely dependent for personal care and approaching end of life. Typically, they could not recover even from a minor illness.

9 TERMINALLY ILL — Approaching the end of life. This category applies to people with a **life expectancy <6 months**, who are **not otherwise living with severe frailty.** (Many terminally ill people can still exercise until very close to death.)

SCORING FRAILTY IN PEOPLE WITH DEMENTIA

The degree of frailty generally corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

In **very severe dementia** they are often bedfast. Many are virtually mute.

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Rockwood K et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489–495.

APPENDIX 5: ICU Diagnosis Admission Codes

MEDICAL (NON OPERATIVE CONDITIONS)	SURGICAL (POST OPERATIVE CONDITIONS)
Cardiovascular / vascular: 1. Cardiogenic shock 2. Cardiac arrest 3. Aortic aneurysm 4. Congestive heart failure 5. Peripheral vascular disease 6. Rhythm disturbance 7. Acute myocardial infarction 8. Hypertension 9. Other cardiovascular/vascular disease: _____ **Respiratory:** 10. Parasitic pneumonia (ie.pneumocystis carinii) 11. Aspiration pneumonia 12. Respiratory neoplasm (include larynx, trachea) 13. Respiratory arrest 14. Pulmonary edema (non-cardiogenic) 15. Bacterial / Viral pneumonia 16. Chronic obstructive pulmonary disease 17. Pulmonary embolism 18. Mechanical airway obstruction 19. Asthma 20. Other respiratory disease: _____ **Gastrointestinal:** 21. Hepatic failure 22. GI perforation/obstruction 23. GI bleeding due to varices 24. GI inflammatory disease (ulcerative colitis, crohn's disease) 25. GI bleeding due to ulcer/laceration 26. GI bleeding due to diverticulosis 27. Other GI disease: _____ **Neurologic:** 28. Intracerebral hemorrhage 29. Subarachnoid hemorrhage 30. Stroke 31. Neurologic infection 32. Neurologic neoplasm 33. Neuromuscular disease 34. Seizure 35. Other neurologic disease: _____ **Sepsis:** 36. Sepsis (other than urinary tract) 37. Sepsis of urinary tract origin **Trauma:** 38. Head trauma (with/without multiple trauma) 39. Multiple trauma (excluding head trauma) **Metabolic:** 40. Metabolic coma 41. Diabetic ketoacidosis 42. Drug overdose 43. Other metabolic disease:_____ **Hematologic:** 44. Coagulopathy //neutropeniathrombocytopenia 45. Other hematologic condition: _____ **Renal:** 46: Renal diseases **Other:** 47. Other medical diseases:_____	**Vascular / cardiovascular:** 48. Dissecting/ruptured aorta 49. Peripheral vascular surgery (no bypass graft) 50. Valvular heart surgery 51. Elective abdominal aneurysm repair 52. Peripheral artery bypass graft 53. Carotid endarterectomy 54. Other cardiovascular disease: _____ **Respiratory:** 55. Respiratory infection 56. Lung neoplasm 57. Respiratory neoplasm (mouth, sinus, larynx, trachea) 58. Other respiratory disease: _____ **Gastrointestinal:** 59. GI perforation/rupture 60. GI inflammatory disease 61. GI obstruction 62. GI bleeding 63. Liver transplant 64. GI neoplasm 65. GI cholecystitis / cholangitis 66. Other GI disease: _____ **Neurologic:** 67. Intracerebral hemorrhage 68. Subdural/epidural hematoma 69. Subarachnoid hemorrhage 70. Laminectomy/other spinal cord surgery 71. Craniotomy for neoplasm 72. Other neurologic disease: _____ **Trauma:** 73. Head trauma (with/without multiple trauma) 74. Multiple trauma (excluding head trauma) **Renal:** 75. Renal neoplasm 76. Other renal disease: _____ **Gynecologic:** 77. Hysterectomy **Orthopedic:** 78. Hip or extremity fracture **Other:** 79. Other surgical conditions:_____ **Cardiovascular Surgery:** 80. CABGx1 81. CABGx2 82. CABGx3 83. CABG>4 84. Valve Surgery 85 Other:_____