BP Management System User Acceptance Testing

Study Protocol
NCT04688450

March 14, 2022
Version 4.1

PARTNERS HUMAN RESEARCH COMMITTEE
DETAILED PROTOCOL
March 14, 2022 Version 4.1

P.1. BACKGROUND AND SIGNIFICANCE

Historical background

Clinicians are not good at following blood pressure (BP) management guidelines. In an observational report from a California ICU by Hawryluk et al. [1 on Section P.10], 100 patients being managed with acute spinal cord injury were examined, and 42% of the documented MAP values were below the goal range, i.e., < 85mmHg. This notable failure to manage hypotension adequately after ASCI is consistent with other reports [2 on Section P.10].

Previous pre-clinical or clinical studies

Our own group studied BP patterns in ICU patients receiving continuous vasopressor infusions in two different hospitals, and found that many patients suffered episodes of sustained (>15 min) hypotension (< 60 mmHg) without any clinical event documented, nor any timely response [3 on Section P.10].

Because of this clinical need, we developed the VIGORIS system. VIGORIS is a software system that tracks BP through time and generates alerts whenever BP is forecast to drift outside of a pre-specified goal range. It is intended for use in patients receiving continuous vasopressor infusion to treat hypotension. In simulation analysis, using actual clinical data from ICUs of two different hospitals, the VIGORIS forecast algorithm predicts hypotension on average 10 min before sustained hypotension developed [3 on Section P.10].

Rationale behind the proposed research and potential benefits

However, the actual clinical value of this software system remains speculative. In the current study, we aim to run the investigational system during clinical care, and obtain user feedback about the usefulness of the decision-support functionality.

Note the conflict of interest (COI) which is also found in the consent form: “Investigators on this study invented the software that is used in this study. The hospital owns this software and therefore the investigators and the hospital may benefit financially if this study shows that the technology is valuable. The hospital’s conflict of interest policies are handled by the hospital’s owner, Partners HealthCare. In accordance with these policies, Partners has determined that the interests create no significant risk to the welfare of participants in this study or to the integrity of the research. If you want more information

about this, please contact the Partners Office for Interactions with Industry at PHSOII@partners.org, 857-282-2024."

P.2 SPECIFIC AIMS

Specify objectives and hypotheses to be tested in the research project

This is a live test of a decision-support system. The specific aim is to obtain candid user feedback about perceptions of the value of the automated decision-support.

P.3 SUBJECT SELECTION

This will be a convenience sample of 20 individual patient-subjects and also the 20 nurse-subjects who correspond to the primary nurses managing the patient-subjects. Note: patient-subjects will all be unique. Given the limits of the size of the ICU nursing staff, any nursing-subject may participate multiple times (we will seek to maximize the number of different nurse-subjects as described below).

Inclusion/exclusion criteria

Inclusion

1. Adult patient (18 years or older) receiving continuous vasopressor infusion to maintain blood pressure;
2. Clinician treating patient estimates future duration of vasopressor infusion likely at least 4 additional hours;
3. Provider order has been made that sets lower limit for mean arterial pressure;
4. Indwelling arterial catheter has been placed for continuous blood pressure monitoring.

Exclusion

1. Lack of consent or at the discretion of the patient's primary nurse;
2. The discretion of any of the patient's other clinical providers;
3. People who do not speak English will be excluded. The rationale is that this protocol involves the bedside deployment of an investigational system plus longitudinal observation. Our mitigation for psychosocial risk involves a continual observer who can monitor for any evidence of subject psychosocial discomfort, which involves the ability to effectively communicate with the subject throughout the duration of the protocol. This therefore excludes patients who do not speak English.
4. Patients who are on two simultaneous vasopressors running at maximum doses (per the ICUs own protocols) or who is on one maximum-dose vasopressor and has a contraindication to receiving a second vasopressor (e.g., insufficient vascular access).

5. Patients who are hypoxic (SpO2 < 90%) despite maximum inspired oxygen (100% for patients receiving mechanical ventilation, or 10L high-flow in patients who are not candidates for mechanical ventilation).
6. Provider order has been made that sets lower limit for SBP (because our system does not have the capability to provide decision-support for an SBP lower limit).

Source of subjects and recruitment methods

We will confer with either the active unit attending MD or the resource nurse to identify adult patients receiving continuous vasopressor infusion therapy, with a specific order to maintain mean arterial pressure (MAP) above a specific level, and that is expected to continue for at least the next 4 hours. If multiple eligible patients are identified, we will prioritize a patient whose primary nurse has previously participated in this investigation the fewest number of times.

Alternatively, we may identify potentially eligible patients by reviewing the ICU census within the electronic medical record (EMR) and, by review of the flowsheet for the current ICU patients, identify patients who are receiving continuous vasopressors and are not COVID positive. If an ICU patient is identified as receiving continuous vasopressor in the flowsheet, then we will further review that patient record for other elements of our inclusion criteria. We will keep a log of any patients whose EMR flowsheet we review to determine whether the patient is receiving vasopressors. We will not examine any other elements in the EMR (to determine further eligibility requirements) unless the patient is receiving vasopressors, and we will only review EMR elements that are necessary for determining eligibility requirements, i.e., ICU clinician notes, ICU orders, and lab results.

For an eligible patient, we will confer with the primary nurse of eligible subjects to ask whether the nurse would approve of the patient potentially being enrolled in the study. If the primary nurse approves, we will seek an in-person introduction to the patient or close family member or healthcare proxy, and proceed with the consent procedure.

P.4 SUBJECT ENROLLMENT

Methods of enrollment

Above, we described how we will identify eligible patients in the ICU and receive permission of the primary nurse to approach the patient.

Procedures for obtaining informed consent

We will ask for a determination from the patient's care team (either MD or primary RN) about whether or not the patient has capacity to consent to the investigation. If the patient is deemed consentable by the primary care team is alone in their room, the investigators

will be further attuned to ensure that the patient is able to repeat back the goal of the study demonstrating comprehension. If the patient has family members present, we will further obtain the assent of the family members, in addition to the patient's consent.

If the patient is deemed unable to consent by the primary care team, we will seek consent from the appropriate surrogate. In order of preference, this will be: healthcare proxy/person with durable power of attorney with specific authority for making health care decisions inclusive of the proposed research; or spouse, adult child, adult sibling, or parent. When surrogate consent is relied upon, the Investigators will ensure that the surrogate understands that his or her decisions should be based on "substituted judgment." This means that the decision reflects a potential subject's own views when s/he had the capacity to express them. If a potential subject did not previously express a view on the matter, the surrogate should make the decision based on the potential subject's best interests. The relationship of the surrogate signing the consent form will be documented. If surrogate consent is obtained, we will also ensure that the subject assents, unless the subject is incapable of giving assent due to his/her medical condition.

An IRB-approved member of the study staff will approach the patient (or appropriate surrogate as detailed in the preceding paragraph) and describe the study. We will provide the consent form and ask whether the patient gives permission for us to review the consent form. After reviewing the consent form, we will offer the patient the opportunity to ask any questions.

We will then ask if the patient (or surrogate) is willing to consent (or assent) to participate. If the patient would rather not participate, or if the patient needs time to consider participation. If the latter, we will ask whether the patient would prefer 30 min or 60 min or longer to consider, and return at that time.

If the patient was deemed unable to consent (which is typical for ICU patients who require vasopressor support for hemodynamic support), and the surrogate is not physically present within the MGH, then we will obtain remote (phone) consent. The reason why this is necessary is because the hospital is limiting hospital visitors due to COVID, and therefore, remote consent will be necessary for any reasonable subject recruitment accrual. We will follow the institutional policies for remote (phone) consent, as follows: study staff or the study physician will call the appropriate surrogate (surrogate to be identified as per protocol outlined above) and introduce the study via telephone. A copy of the consent form will be provided to the surrogate by email or fax. If sent by email, Partners policy on the receipt of unsecured email agreement will be followed. The study physician will obtain written consent electronically (via Partners REDCap eConsent module) after having a thorough discussion with the surrogate about study procedures and answering any questions the surrogate may have. If the surrogate decides to provide consent, a witness will be present when verbal consent is obtained from the appropriate surrogate. Study staff will record the consent date, consent time, consent place, witness name and relationship to the subject, appropriate surrogate name, and appropriate surrogate relationship to the patient.

We will also obtain the signed consent of the patient's nurse.

Treatment assignment (if applicable)
N/A

P.5 STUDY PROCEDURES

Study visits and parameters to be measured

Subjects will be enrolled during periods when the study staff are available to conduct the protocol which is anticipated to be daytime or evening hours during the routine workweek.

Parameters to be measured:

- Survey results from clinicians
- Annotation of any technical issues observed by Technical Observer
- System database archive of measured vital-signs and associated vital-sign forecasts
- Operational logs of the System software

Drugs to be used

N/A

Devices to be used

Investigational VIGORIS clinical decision support system.

Procedures/surgical interventions

a. If the patient or close family member or healthcare proxy approves, we will then provide the nurse with our staff education slides and review the content therein [see Appendix 7 of this IDE application].

b. Obtain the nurse's signed initials to indicate having received the briefing and obtain the nurse's signed consent form.

c. We will obtain the mean arterial pressure (MAP) goal from the nurse, and also any systolic blood pressure (SBP) upper limit. Specifically, we will require that each enrolled subject has a pre-enrollment MAP lower limit from the ordering provider.

We will also determine if there is a pre-enrollment ordered MAP and SBP upper limit.

d. A member of the investigative team will assist the nurse in setting the investigational software for the MAP goal. We will also assist the nurse in setting the pre-enrollment MAP upper limit (if there is no MAP upper limit, we will default to 120 mmHg, which is the accepted definition of hypertension). If there is a pre-enrollment ordered SBP upper limit, we will also assist the nurse to set this configuration into the system; if there is no pre-enrollment ordered SBP upper limit, the system will not consider SBP, at all.

e. The roll-stand will be wiped down with an antibacterial wipe, then positioned in the patient's bay and the serial port attached to the GE vital-signs monitor. We will also place a secondary remote monitor in a location outside the room that is acceptable to the primary nurse (provided that the local network configurations allow for the remote monitor to communicate with the investigational apparatus at the bedside). We will seek additional approval by the nurse that all device positioning is acceptable.

f. Begin the observational protocol. The investigational software will be launched and will begin to run.

g. Active use of the System will be observed by a Technical Observer, i.e., an IRB-approved member of the investigative team. The Observer will generally observe the system continuously, with a minimum of at least one observation every 15 minutes. These observations provide additional assurance that there is no potential interference with any other aspect of the patient's care; that the technical performance of the System is grossly consistent with its intended operation; to ensure that the patient doesn't express any concern; and to ensure that the nurse doesn't express any concern. By protocol, if the nurse, patient, or patient family member states any negative perception of the investigational system, the Technical Observer will ask whether the nurse/patient/family member prefers the protocol to stop, and will oblige if this is requested. If the protocol is stopped early by request of the nurse, patient, or family member, the Technical Observer will ask for feedback after stopping the protocol and removing the apparatus: "You requested that we stop our testing protocol. Can you tell us why, to help us ensure that this testing protocol is safe and appropriate for other ICU patients?" The protocol will also terminate early if an Exclusion criterion is met: receiving two simultaneous vasopressors running at maximum doses (per the ICUs own protocols) or who is on one maximum-dose vasopressor and has a contraindication to receiving a second vasopressor (e.g., insufficient vascular access). During the protocol, the nurse will have the option to adjust the Index Threshold per their clinical practice preferences, and the Technical Observer will provide technical support of the nurse decides to do this. Lower thresholds for the Index Threshold provide higher sensitivity and earlier warnings at the expense of reduced positive predictive value. Higher thresholds the Index Threshold provide lower sensitivity and less advanced notifications at the benefit of

higher positive predictive value. Within the second hour of the protocol session, the Technical Observer will explicitly confer with the nurse about the operation of the system, confirming whether there the nurse understands the visual display elements, whether the nurse would like to adjust the Index Threshold, and whether the nurse has any concerns about the investigational display or the protocol. This check-in will occur at a time when the nurse is not occupied with direct patient care.

h. As well the research staff member will ensure that the nurse adjusts the investigational system's MAP and SBP goals, if these are ordered to be chanced during the protocol.

i. The Technical Observer will document any identifiable interventions of events that have any effect on the patient's blood pressure or heart rate. When the Technical Observer perceives any substantial changes in the subject's hemodynamics, a time-stamped annotation will be made for the perceived cause. The goal is to have these events documented with very precise temporal resolution, i.e., down to the precise minute that the events occur. The Technical Observer may ask the nurse to clarify what intervention is occurring; by protocol, Technical Observer will not ask this clarification if there is any perception that time-sensitive interactions being delivered and/or if the nurse is discussing patient management with any other clinical team member. The Technical Observer will never suggest intervention or recommend any clinical care for the patient.

j. If the primary nurse-subject (who provided consent) takes a break and there is a temporary substitute nurse, we will turn off the display so that the investigational software cannot affect decision-making (except if the substitute nurse has been a nurse-subject for this study for a different ICU patient having completed the full protocol within the past 30 days; under that condition, we will continue the protocol during the break). If the primary nurse-subject break lasts longer than 60 min, we will terminate that enrollment.

k. The investigational software will be terminated one hour before the Technical Observer is scheduled to depart for the day, or one hour before the end of the consenting nurse's shift, or a maximum of 8 hours (whichever is shorter). After each subject enrollment, the apparatus will be removed from the care area and cleaned with an antibacterial wipe. The System hardware will be inspected to ensure there are no visible abnormalities such as evidence of spills or physical damage.

l. All ICU clinicians, including physicians, RN, NPs, and PAs, will be educated about the study by email. The "investigational protocol information" document will be sent to all clinicians in the department at least every 6 months. Before any new enrollments, we will confer with the ICU director whether there are new clinicians working since the last enrollment who need to be emailed (i.e., new staff or residents starting their ICU clinical rotation).

Data to be collected and when the data is to be collected

Subjects will be enrolled during periods when the study staff are available to conduct the protocol for a minimum of four hours of data collection (plus an extra hour for apparatus cleaning as well as conducting the post-enrollment clinician survey). The maximum duration of data collection for a given subject will be eight hours, i.e., the duration of a shift for the study staff.

During data collection, the System will automatically archive the subject's vital signs through time. The system will also auto-log any abnormal functionality.

The technical observer will annotate any clinical interventions; any technical abnormality observed in System operation; and any concerns by the clinical staff or the patient or the patient's family. The technical observer will also provide subjective descriptions of the patient's apparent state (for purposes of better understanding retrospective data analysis after the study is complete).

In the final hour of each data collection session, we will ask the nurse to complete a brief questionnaire that provides specific feedback and also indicates whether performance of the investigational system was generally acceptable (see below). This will conclude data collection.

"Thank you for participating in the clinical testing of our decision-support system. We would like your final feedback about the following topics."

- Question 1: Do you agree or disagree with the following statement:

  "*This system will make it generally easier to keep blood pressure within the goal range during continuous vasopressor infusion*?"

  1- Strongly disagree
  2- Disagree
  3- Neutral
  4- Agree
  5- Strongly agree

- Question 2: What feature(s) of the system do you think will be most useful, either to yourself or to other typical ICU caregivers?

- Question 3A: Did you identify any display output by the system that is confusing, or inaccurate?

- Question 3B (if answer "yes" to 3A): If so, what?

- Question 3C (if answer “yes” to 3A): Do you perceive that the confusing or inaccurate display output could possibly lead to any patient management error?
- Question 4A: This system provides lots of visual information, which might be distracting. At any time, did the system actually distract you from noticing something important about your patient or administering important care to your patient, such that your response to the patient was delayed?
- Question 4B (if answer “yes” to 4A): If so, what?
- Question 5: Any other ideas about what could be improved, and how?
- Question 6: If we want to hold a catered lunchtime focus group to discuss possible modifications to the system, would you be willing to join for 20 minutes, so we can get your feedback?

P.6 BIOSTATISTICAL ANALYSIS

Specific data variables being collected for the study

- Survey results from clinicians
- Annotation of any technical issues observed by Technical Observer
- System database archive of measured vital-signs and associated vital-sign forecasts
- Any error- and critical-level log statements from the server log file
- Any error- and critical-level log statements from the UI log file

Study endpoints

Subjects will be enrolled during periods when the study staff are available to conduct the protocol for a minimum of four hours of data collection (plus an extra hour for apparatus cleaning as well as conducting the post-enrollment clinician survey). The maximum duration of data collection for a given subject will be eight hours, i.e., the duration of a shift for the study staff.

Statistical methods

There will be two aspects to the data analysis: “clinician perceptions” and “technical operation”.

For the clinician perception, we will pool the feedback results from Questions 1-4. We will report quantitative responses for Questions 1, 3A, 3C, and 4A.

For Questions 2, 3B, 4B, and 5, we will employ an "exploratory sequential mixed methods design" whereby we use the results of the questionnaires to form variables that represent the most common qualitative answers, then code the questionnaire responses according to those variables, yielding quantitative results for the user perception survey data, to supplement the free-text feedback.

For assessing technical operation, we will rely on (a) real-time error surveillance by the Technical Observer who watches the system during investigational use; the Technical Observer will document any unexpected technical issues in terms of run-time issues, connectivity issues, or any other issues; (b) Retrospective data review to ensure the completeness and accuracy of electronic data collected by the research software system; and (c) Analysis of log data the server log file and UI log file to confirm an absence of error-level and critical-level log statements.

We will generate descriptive statistics associated with (a) proportion of time that the patient's BP is maintained within the goal range; and (b) descriptive statistics of the MAP prediction algorithm including mean prediction error, and also, clinical events that were associated with temporal windows with the highest prediction errors (i.e., top quartile of prediction error). The proportion of time that the patient's BP is maintained within the goal range will be used for future study design. The results about the clinical events associated with the highest prediction errors will be used for potential future enhancements to the prediction methodology. We will review log files to confirm that there are no error- nor critical-level log events (except for those that are expected to naturally occur during system shut-down, which would be after each patient-subject data collection session has been completed).

As is routine for research studies, we will also aggregate subject characteristics in our analysis. These data will be obtained from the electronic medical record (EMR). Data will include routine demographics, co-morbidities, and clinical details of the index ICU stay such as clinical pathologies and clinical interventions. As this chart review is planned to occur at a time subsequent to the main investigational protocol, we will also record two patient identifiers (MRN and name) to ensure we have the correct identity of the subject. These identifiers will be digitally erased no later than 12 months after data collection has been completed. A hardcopy of the identifier will be kept by the PI in a locked cabinet in his MGH office for long-term storage, for any unforeseen need to re-identify the subjects for purposes of obtaining additional data from the EMR.

Power analysis (e.g., sample size)

According to the FDA "Since the parameters needed to determine sample size cannot be estimated easily or cannot be at estimated at all prior to testing, a sample of 15 people to detect most of the problems in a user interface constitutes a practical minimum number of participants for human factors validation testing [4 on Section P.10].

Faulkner et al. [5 on Section P.10] estimated that a sample size of 20 users is sufficient to find an average of 98% of human use factor design failures; this is the basis of our plan to conduct 20 test sessions.

P.7 RISKS AND DISCOMFORTS

The System is only intended for use for investigational purposes. It is a secondary display and does not replace any device in current use. Therefore, risks may be accepted if they do not pose greater risk than usual care. When an identified risk is potentially worse than usual care, then reasonable risk mitigation is employed. Risk assessment and risk mitigation were developed and reviewed by a collaborative team including engineers with expertise in medical software and physicians.

Risks and discomforts are documented and assessed in detail in Section 4 of this IDE Application.

Complications of surgical and non-surgical procedures

N/A

Drug side effects and toxicities

N/A

Device complications/malfunctions

Device risks are documented and assessed in detail in Section 4 of this IDE Application.

Psychosocial (non-medical) risks

For PHI, identifiable health information will be stored on a computer on the Partners network with password protections enabled and anti-virus software or an encrypted laptop and access to identifiable data will be limited to study staff by use of password protected files or restricted shared file areas. Name and/or medical record number will be replaced with a study ID or code and the key to the code stored in a separate password RedCap project. Direct identifiers, such as name and medical record number, will be removed once all of the data is collected and analysis performed on de-identified data.

See Section 4 of this IDE Application for additional consideration of psychosocial risk.

Radiation risks

N/A

P.8 POTENTIAL BENEFITS

Potential benefits to participating individuals

We cannot guarantee there will be benefits. The investigational software system has the potential to improve BP management in the patient-subjects.

Potential benefits to society

We will use the results of the study to test that the investigational system is acceptable for clinical use by clinical users. This will help establish that the system is suitable for clinical use in a future investigation (user feedback from this trial will also be incorporated to further enhance the systems). Ultimately, this investigation will be a key step in developing a new tool with the potential to promote tight blood pressure control in critically-ill patients.

P.9 MONITORING AND QUALITY ASSURANCE

To ensure high quality protocol compliance, all study members who serve as Technical Observers will review the study protocol and sign a written acknowledgement that the protocol was reviewed. Prior to conducting the trial, Technical Observers will have had at least 250 hours working in a hospital or medical environment in a capacity that involves patient interaction, including as a medical scribe or emergency medical services.

“Protocol trainee” will refer to a study team member who has not completed protocol training. The trainee will observe a trained study team member conduct the protocol for one session (the PI will conduct the protocol for at least the first subject). Then the trainee will be considered trained. The PI will be available by text or cellphone at all times during an active data collection session.

Independent monitoring of source data

We will employ an independent monitor, Blair Parry, who is qualified as an experienced research manager and who has been an investigator and/or monitor for prior investigations that required compliance with FDA regulation.

The completeness of the following **study files** will be verified on a bi-annual basis:

A. Mass General Brigham (MGB) Human Research Committee (IRB):

1. All IRB Correspondence is on file
2. The study staff are IRB approved prior to performing any study procedures
3. Adverse events and deviations are reported to IRB per current guidelines
4. All versions of the IRB protocols and informed consent forms are on file
5. IRB is duly constituted and complies with applicable local and national laws and regulations in countries, including protections against conflicts of interest
6. Compliance with the institution's research information security office guidance has been maintained

B. FDA

1. All FDA correspondence (amendments, safety reports, annual review) is on file
2. Documentation of serious adverse events that are unexpected and related are reported to FDA within 7 calendar days
3. Annual Report is on file and completed in a timely fashion

C. Other documents / Investigator Site File (ISF):

1. CVs for all study staff are on file and updated every 2 years
2. Medical licenses for physician PI & Co-Investigators are on file and updated prior to expiration
3. Delegation Log is updated as new staff are added or removed from the study or new procedures are added
4. Financial disclosures for PI and relevant study staff are on file
5. Protocol is signed and understood by the PI
6. That information emails have been sent to Blake 12 ICU clinical staff to ensure awareness that System is limited by law to investigational use
7. Documentation exists that all software components have been tested and reviewed by users as per our specified software development procedures.
8. All other essential documents have been prepared and completed as appropriate

The completeness of the following **study documentation** will be verified after every 5 subjects or every quarter (whichever comes first):

D. Informed Consent:

1. Ensure that subject identification is on all pages of the ICF.
2. There is documentation that the subject is offered a copy of the consent form.
3. The subject and study representative signed and dated the consent form for him/herself.
4. Note to file made for any informed consent deviations.
5. Ensure a valid (current version date) copy of the consent form was used.
6. Ensure informed consent form is properly explained to and signed/dated by the study subject prior to participation.
7. Original informed consent form is retained by the investigators at the sites.

E. Protocol:

1. Confirm that the study staff is conducting the study in compliance with the protocol approved by IRB and if applicable, FDA.
2. The protocol deviations (exceptions and violations) are documented in the subject chart and reported to IRB as required.

F. Electronic Case Report Forms (REDCap):

1. Ensure the data reported on REDCap are complete.
2. Ensure that hourly BP and HR documented in REDCap by the Technical Observer are accurate, i.e., corresponds to data captured by the System within allowable tolerances (specifically, the System archive should span the documented BP and HR data in a time window +/- 5 min from the REDCap documented time of the observation).
3. Discrepancies between the source documents and REDCap are explained in a note to file or captured in a comment in REDCap.
4. Ensure that the data reported in REDCap from each nursing-subject interview are complete.
5. Ensure that the log files for each patient-subject session do not include any error- or critical-level message (except for those that are expected to naturally occur during system shut-down, which would be after each patient-subject data collection session has been completed).
6. Ensure that any event note for the patient's ICU documentation record that involved more than the primary nurse as a clinical responder was captured by the Technical Observer's annotations.

Safety monitoring

After the first 5 subjects are enrolled, the nurse-subject responses to the questionnaire will be submitted to the IRB, along with a report of any adverse events.

The following events represent possible adverse events:

(a) the Technical Observer (a member of the research team) identifies any failure of the software and terminates the session (the Technical Observer may also terminate for any subject reason related to any subjective perceived negative impact on the subject's care);
(b) if the nurse indicated that the protocol was having any negative effect on the patient's care, either during the execution of the protocol session, or in responses to the questionnaire that is conducted after every enrollment ("Question 3: Did you identify any output by the system that is dangerously confusing, or dangerously inaccurate? If so, what?"; and "Question 4: This system provides lots of visual information, which might be distracting. At any time, did the system actually distract you from noticing something important about your patient or administering important care to your patient, such that your response to the patient was delayed?");
(c) if the patient/close family member indicated any discomfort with the protocol session.
(d) Review of the software logs indicates any error-level or critical-level log statements were generated.

(e) Review of the software data archive indicates any interruption in the routine monitoring of vital-signs.

If any of these events occur, within 5 days, we will assess whether the event increased the patient-subject's risk of a serious adverse event. This assessment will include conferring with the study PI; the Blake 12 intensive care unit chief; and the Blake 12 intensive care unit nursing leader, to evaluate whether the event represented an event that is more than minimal risk to future subjects. If any of these (the study PI; the Blake 12 intensive care unit chief; and the Blake 12 intensive care unit nursing leader) judges that the event poses more than minimal risk to future subjects, we will halt the study.

Outcomes monitoring

As detailed above, the independent monitor will evaluate the outcomes data, including the completeness of all data collection instruments; the accuracy of the system software archive (based on a comparison with the Technical Observer's hourly annotation of vital signs); and the presence of time-stamped software logs for each enrolled patient-subject.

Adverse event reporting guidelines

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

We will rely on the system data archive; annotations by the Technical Observer; and interview responses by the nurses to reveal adverse events. Adverse events will include all sustained hypotension episodes (as per Section 3.2.2.1 of this IDE Application); tachyarrhythmias (HR > 150 bpm) or bradyarrhythmias (HR < 50 bpm) that persist for more than ten minutes; needs for chest compressions or defibrillation; or any unscheduled bedside response by the ICU care team involving more than the patient's primary nurse.

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of the investigator/sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

All adverse events will be recorded.

All adverse events (AEs) must have their relationship to study intervention assessed by the investigator who will evaluate the subject based on the temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The event must be p phenomenologically definitive.
- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
- Potentially Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- Unlikely to be related – A clinical event whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- Not Related – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the investigative team.

In this ICU population, expected adverse events will be episodes of hypotension (indeed, the motivation for the investigational device is a tool to reduce the frequency of observed sustained episodes of hypotension within the ICU). As well, unscheduled multiclinician responses and tachyarrhythmias are also expected in an ICU patient population receiving vasopressors.

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the Institutional Review Board (IRB) as soon as possible, but in no event later than 5 working days / 7 calendar days after the investigator first learns of the effect. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as FDA requests.

P.10 REFERENCES for this Appendix

[1] Hawryluk G, Whetstone W, Saigal R, et al. Mean Arterial Blood Pressure Correlates with Neurological Recovery after Human Spinal Cord Injury: Analysis of High Frequency Physiologic Data. J Neurotrauma. 2015 Dec 15;32(24):1958-67.

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