**PARTNERS HUMAN RESEARCH COMMITTEE**
**PROTOCOL SUMMARY**

**Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.**

**PRINCIPAL/OVERALL INVESTIGATOR**
Daniel Dante Yeh, MD

**PROTOCOL TITLE**

PEP uP Protocol**(Enhanced Protein-Energy Provision via the Enteral Route Feeding Protocol)** in Surgical Patients

**FUNDING**
Nestle HealthCare

NCT# 02459275

**VERSION DATE**
02/11/2017

**SPECIFIC AIMS**

Concisely state the objectives of the study and the hypothesis being tested.

Our hypothesis is that an aggressive feeding protocol, **PEP uP** (Enhanced **P**rotein-**E**nergy **P**rovision via the Enteral Ro**u**te Feeding **P**rotocol) will be safe, acceptable, and effectively increase protein and energy delivery to critically ill surgical patients.

**BACKGROUND AND SIGNIFICANCE**

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

Critically ill patients are often hypermetabolic and can rapidly become nutritionally compromised. Pre-existing malnutrition is prevalent in these patients and has been associated with increased morbidity and mortality, particularly in the surgical population. Consequently, the goals of nutrition therapy in critically ill patients are to attenuate the metabolic response to stress or injury by providing nutrition consistent with the patient's condition, preventing or treating nutrient deficiencies, and avoiding complications related to the route of nutrition delivery.

Gross underfeeding or iatrogenic malnutrition is prevalent in intensive care units throughout the world. Critically ill patients only receive, on average 40-50% of their prescribed nutritional requirements. Inadequate provision of nutrition to these

patients is associated with increased complications, prolonged length of stay in the ICU and hospital, and increased mortality. There are good data from large scale observational studies and randomized trials that suggest better fed patients have better clinical and economic outcomes.

There are some ICUs that consistently reach an average of 80-90% nutritional adequacy (amount of nutrition received over amount prescribed) and thus we believe that this is a feasible goal.

Historically, feeding protocols have been used to guide the delivery of enteral nutrition (EN) and they frequently utilize conservative, reactionary approaches to optimizing nutrition that are not grounded in evidence but rather, seem to have evolved over time. We propose a new, innovative approach that protocolizes an aggressive set of strategies provide EN and to shift the paradigm from reactionary to proactive followed by de-escalation if nutrition therapy is not needed: **PEP uP** (Enhanced **P**rotein-**E**nergy **P**rovision via the Enteral Ro**u**te Feeding **P**rotocol).

The key components of this new **PEP uP** protocol are the following:

1) Starting feeds at the target rate based on increasing evidence that some patients tolerate starting nutrition at a higher rate of delivery and that slow start ups are not necessary. For patients who are hemodynamically stable, we propose to shift from an hourly rate target goal to a 24 hour volume goal and give nurses guidance on how to make up this volume if there was an interruption for non-gastrointestinal reasons.

2) For patients who are deemed unsuitable for high volume intragastric feeds, we provide an option to initiate "trophic feeds" to provide a low volume of a concentrated feeding solution for 24 hours or longer, designed to maintain gastrointestinal structure and function rather than meet their protein and caloric goals.

3) To optimize tolerance in the early phase of critical illness, we propose to use a semi-elemental feeding solution instead of a standard polymeric solution. These can then be changed to more traditional polymeric solution once the patient is tolerating adequate amounts of nutrition.

4) Rather than wait for a protein debt to accumulate because of inadequate delivery of EN, protein supplements are prescribed at initiation of EN and can be discontinued if EN is well tolerated and they are receiving all their protein requirements through their standard EN.

5) Rather than wait for a problem with gastrointestinal tolerance to develop, we propose to start motility agents at the same time EN is started with a re-evaluation in the days following to see if it is necessary.

This PEP uP protocol has been previously studied in two published studies enrolling primarily medical patients. In the first study, a pilot before and after trial, the

protocol seemed to be feasible, safe, and acceptable to critical care nurses. No incidents compromising patient safety were observed. (Heyland 2010) Rates of vomiting, regurgitation, aspiration, and pneumonia were similar and the PEP uP group received significantly more energy and protein (when they were prescribed to receive full volume as opposed to "trophic"). A subsequent multi-center cluster randomized trial involving low-performing ICUs likewise demonstrated that intervention sites had improvements in energy and protein delivery as well as a decrease in average time from ICU admission to start of enteral nutrition compared to the control group. (Heyland 2013)

Heyland et al. Enhanced protein-energy provision via the enteral route in critically ill patients: a single center feasibility trial of the PEP uP protocol, *Crit Care* 2010

Heyland et al. Enhanced Protein-Energy Provision via the Enteral Route Feeding Protocol in Critically Ill Patients: Results of a Cluster Randomized Trial, *Crit Care Med* 2003

**RESEARCH DESIGN AND METHODS**

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, "Enrollment at Partners will be limited to adults although the sponsor's protocol is open to both children and adults."

This will be a prospective, randomized study which will be analyzed by "intention-to-treat." All patients admitted to the two SICUs at Massachusetts General Hospital (Blake 12 and Ellison 4) on the Trauma and Emergency General Surgery (Churchill team) service and to the SICU at Brigham and Women's Hospital on the Trauma and Emergency General Surgery service in whom initiation of tube feeds is currently planned by the intensivist will be screened for the study. Additional recruitment sites include: Jamaica Hospital Medical Center (Jamaica, NY), Carilion Clinic (Roanoke, VA) and Parkland Memorial Hospital (Dallas, TX). Those patients who are eligible and enroll will be randomized into two groups:

1) Standard of Care
2) PEP uP

The inclusion criteria are:

1) Age ≥ 18 years
2) ICU admission within past 48 hours
3) Initiation of tube feeds currently planned by the SICU team and primary surgical team
4) Admitted by a surgical service to the SICU (not a MICU or neurology patient)

5) Expected to remain mechanically ventilated for > 24 h and expected to require ICU care for > 72 h after screening

The exclusion criteria are:

1) Pregnancy
2) Attending surgeon preference (they must agree to feeding their patient according to the protocol in either arm using the goal rate determined by the SICU team and the nutritionist)
3) Contraindication to enteral nutrition (bowel obstruction, bowel discontinuity, proximal enterocutaneous fistula, and short gut syndrome)
4) DNR status or goals of care that specify limitations in medical therapies
5) Death expected within 24 hours

The primary outcome for this study is nutritional adequacy. To assess nutritional adequacy, the total amount of energy or protein received from either EN or parenteral nutrition (PN), inclusive of propofol, will be divided by the amount prescribed as per the baseline assessment and expressed as a percentage. For the purposes of evaluating these enteral feeding protocols, our primary comparison will be adequacy from EN sources between the two groups over the first seven ICU days. Categorical variables will be reported as counts and percents and compared between cohorts by the Fisher's Exact test. Length of stay variables will be described by medians and quartiles and compared by the log-rank test. Other continuous variables will be described by their means and standard deviations or medians and IQR, and compared by the Wilcoxon-Mann-Whitney or the Fisher's Exact test accordingly. Statistical analysis will be done using SAS v9.1.3 (SAS Institute Inc., Cary, NC, USA). All tests will be two-sided with statistical significance considered as a P-value <0.05

Sample Justification

From our prior work, we know the standard deviation is 31%. We aim to detect a small but clinically meaningful increase in nutritional adequacy of about 20%. For 90% power, we would need 50 patients per group. Therefore, our sample size will be 100 patients total.

Briefly describe study procedures. Include any local site restrictions, for example, "Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study." Describe study endpoints.

Once consent is obtained and necessary baseline data collected, the study co-coordinator will log on to the web-based randomization system at the Clinical Evaluation Research Unit (http://www.ceru.ca/) at Kingston General Hospital. The system will confirm eligibility prior to allowing randomization. The system will then provide the study co-coordinator with a patient study number. The randomization system, which has proven reliable in several prior RCTs, has a robust audit trail and will maintain concealment and blinding. However, due to the nature of the intervention, post-randomization concealment and blinding will not be possible.

Once a patient is randomized, tube feeds will be started through an existing naso-enteric or oro-enteric tube after proper placement is confirmed by radiograph. If a feeding tube is not already present, then it will be placed and location confirmed by radiograph. The goal rate for feeding will be set by the intensivist and SICU nutritionist to a rate that will approximate the patient's nutritional needs. This may vary significantly based on estimations of the patient's caloric and protein requirements, additional nutrition that the patient could be receiving such propofol, and restrictions in fluid such as in patients on dialysis. The intensivist may change the goal rate at any time, based on changes in the patient's nutritional demands.

For patients assigned to the **standard of care group**, feeds will be delivered as follows:

Standard formula polymeric tube feeds will be started at a rate of 20 ml/hour. Gastric residual volume (GRV) will be checked every 4 hours. GRV will be reinfused to the patient each time it is checked. If the patient is tolerating tube feeds as determined by measuring the GRV, the rate will be advanced by 20 ml/hour every 4 hours up to the goal rate.

If the GRV is:

< 200 ml
- Tube feeds will be continued to advance to goal

200 – 500 ml
- Tube feeds will be continued to advance to goal
- Metoclopramide will be started at 10 mg IV every 6 hours for 3 days (or 5mg IV q6h for renal failure)

> 500 ml
- Tube feeds will be held
- GRV will be rechecked every 4 hour and Tube feeds will be restarted at half of the previous rate (rounded up to the nearest 10 ml/hour) once GRV $\leq$ 500 ml. If the patient is tolerating tube feeds as determined by GRV$\leq$500mL, the rate will be advanced by 20 ml/hour every 4 hours back up to the goal rate.

For patients assigned to the **PEP uP group**, feeds will be delivered as follows:

Semi-elemental tube feeds (Peptamen Bariatric) will be started at the hourly goal rate (as determined by the 24 hour volume goal). For example, if the 24 hour volume goal is determined to be 1200cc, then the initial starting PEP uP feeding rate will be 50 cc/hr. Protein supplements (ProSource or Beneprotein) will be started at the initiation of tube feeds to target a daily delivery of 2 g/kg/day. A promotility agent (metoclopramide 10mg IV q6h or 5mg IV q6h for renal failure) will be started empirically concomitant with EN initiation. GRV will be checked every 4 hours and will be reinfused to the patient each time it is checked.

If the GRV is:

$\leq$ 500 ml

- Tube feeds will be continued at goal

> 500 ml

- Tube feeds will be held
- GRV will be rechecked every 4 hours feeding will be restarted at half the previous rate (rounded up to the nearest 10 ml/hour) once GRV $\leq$ 500 ml. If this half-rate is tolerated for 4 hours (as evidenced by GRV $\leq$500mL), then Tube feeds will be returned to full goal rate.

Once the patient shows tolerance of semi-elemental formula, the tube feeds will then be converted to standard polymeric formula. Daily, the patient will be reassessed for the need to continue promotility agents (metoclopramide).

In the SICU, renal failure is usually assessed according to the RIFLE criteria (Risk, Injury, Failure, Loss, ESRD). Our threshold for adjusting metoclopramide dose will be Injury, or twofold increase in the serum creatinine, or GRF decrease by 50 percent, or urine output <0.5 mL/kg per hour for 12 hours. For patients with chronic renal insufficiency, we will use an absolute cutoff of GFR <30.

Patients in both groups will be closely monitored for clinical signs of intolerance to enteral nutrition. The feeding tube will be placed to suction and feeds will be held for: witnessed aspiration, nausea (in awake patients) or emesis, or abdominal distension. After being held for these clinical signs of intolerance, tube feeds will be restarted 4 hours after resolution of the symptoms at half of the previous rate. If the intensivist, surgeon or PI does not feel that the patient cannot tolerate the full volume PEP uP feeding protocol to which they are assigned, the patient will be assigned to "trophic" rate of 20cc/hr.

The intervention will end when tube feeds are stopped and the patient is fed meals orally. At this point, the patient will not resume the intervention, even if tube feeds are restarted due to inadequate oral nutrition. The intervention will also end whenever a patient is transferred out of the SICU. Patients will be tracked until discharge from the hospital or 60 days (whichever occurs first) in order to collect follow-up data.

Within 24 hours of enrollment in the study the following data will be collected (see attached Data Collection Sheet): age, gender, APACHE 2 score, baseline SOFA score, hospital admission, ICU admission, mechanical ventilation, ICU diagnosis, operation, comorbidities, laboratory values, baseline nutritional assessment.

While receiving enteral feeds, the following data will be collected: feeding prescription (formula and goal rate), if a motility agent was given, glucose monitoring, insulin, propofol, location of feeding tube, oral nutrition, any episodes of intolerance to feeding, calories and protein received, enteral nutrition interruptions.

From the time of enrollment in the study until discharge from the hospital (or day 60), the following data will be collected: mortality, ICU length of stay, hospital length of stay, ventilator days.

As part of the data collection to assess feasibility and acceptability, nurses caring for patients randomized to the PEP uP arm will be given a survey to complete. A study investigator will distribute paper copies of the survey to the nurse and they will be asked to fill it out anonymously and return it to a collection envelope**.**

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

The standard of care protocols for both institutions are described in the above section.

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

Patients who enroll in our study will not undergo any additional diagnostic or therapeutic intervention that they would not otherwise undergo.

Furthermore, no diagnostic or therapeutic interventions will be withheld as a result of enrolling in our study.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

The most common foreseeable risk of providing a larger volume of enteral nutrition prior to confirming that a patient can tolerate a smaller volume is the risk of vomiting. However, the risk of vomiting has been described to better correlate with elevated GRVs rather than the feeding protocol TF provided. Vomiting has been described to occur in as many as 27% of the cases where GRV is continuously monitored and can reach even higher rates (39%) if no monitoring takes place.

In this study, the vomiting rate is a group phenomenon based on individual subject data blocked into 12-hour periods, where if a subject vomits once or more during a 12-hour period, this counts as one vomiting occurrence, and the vomiting rate is the incidence of such occurrences as a percentage of total 12-hour periods observed.

As stated above, patients in both groups will be closely monitored for clinical signs of intolerance to enteral nutrition. The feeding tube will be placed to suction and feeds will be held for: witnessed aspiration, nausea (in awake patients) or emesis, or abdominal distension. After being held for these clinical signs of intolerance, tube feeds will be restarted 4 hours after resolution of the symptoms at half of the previous rate. Furthermore, if either the intensivist, surgeon or PI does not feel that a patient could tolerate the feeding protocol to which they are assigned, the patient will be labeled as a protocol violation.

Additionally, the risk of refeeding syndrome could potentially be increased by our intervention. Refeeding syndrome is a rare complication that can lead to life-threatening metabolic derangements upon feeding a patient who has taken minimal nutrition for 5 days. Any patient that shows evidence of the refeeding syndrome based on a significant drop in the serum potassium, magnesium or phosphorus or other abnormalities as determined by the intensivist, surgeon or PI, the patient will be changed to the "trophic rate" feeding protocol until the electrolytes have improved enough to return to full feeding rate. This is consistent with our usual practice in the SICU. Because electrolytes are assessed frequently and aggressively replaced, we expect the actual incidence of refeeding syndrome to be very low.

We have recruited a surgeon at Partners, Dr. Janey Pratt, to act as a Medical Monitor. She is not involved in the study and will review the safety data after every 25 subjects. Stopping criteria include:

a) Vomiting in >10% of the subjects assigned to the PEPuP arm or
b) Macroaspiration in 20% of the subjects assigned to the PEPuP arm or
c) 50% more pneumonia in the PEPuP arm than the control group.

**FORESEEABLE RISKS AND DISCOMFORTS**

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

The foreseeable risks and discomforts of starting tube feeds at a greater rate before confirming that patients can tolerate a lower rate of tube feeds are abdominal pain, nausea, vomiting, and diarrhea. These events could be distressing to patients or their families and could require additional medical treatments such as pain medications, antiemetics, or antidiarrheal medications, but are likely to resolve soon after enteral feeding is held or decreased in rate. Vomiting places critically ill patients at risk for aspiration which could lead to pneumonitis and pneumonia.

In the single-center feasibility trial of the PEP uP protocol, Heyland et al. reported a 6.7% (n=2) rate of vomiting after implementation of the protocol, compared to 15% (n=3) before implementation. In the follow-up cluster randomized trial, Heyland et al. reported an average of 5.6% vomiting, which was not significantly different from 4.4% baseline rate.

Aspiration is a common event in the ICU, but it has been repeatedly shown that the majority of aspirations and aspiration pneumonia result from aspiration of oropharyngeal secretions, not gastric regurgitations. Recently it was demonstrated that despite an increased rate of vomiting episodes (39.6% vs. 27.0%) there was no significant difference in any other outcomes such as ICU-acquired infections or duration of mechanical ventilation. (Reignier et al.) Similarly, in a recent study Williams et al demonstrated that despite an increased rate of vomiting, there was no increased rate of ventilator-associated pneumonia or any other clinical outcome.

In the event of witnessed aspiration or vomiting, the decision to perform additional interventions will be left to the clinical team.

Finally, vomiting or diarrhea could place patients at risk for electrolyte abnormalities which will be counteracted by the constant assessment and replacement protocols active in the SICU.

**EXPECTED BENEFITS**

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, "It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects." Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

We expect that patients participating in our study and randomized to the PEP uP arm will receive a greater quantity of nutrition than those receiving standard of care. We believe that infectious complications, ICU length of stay, hospital length of stay and even mortality could be decreased by providing early and adequate nutrition. Starting tube feeds at the goal rate and decreasing due to intolerance has been shown to decrease infectious complications in traumatic brain injury patients. If its benefits are found to be generalizable, it could potentially benefit all surgical patients who require enteral nutrition since it takes no additional equipment to implement.

**EQUITABLE SELECTION OF SUBJECTS**

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children, and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

Pregnant women are rarely admitted to our SICUs. They have significant issues related to the effects of progesterone and the space occupying gravid uterus on the stomach and other GI organs. We could not enroll enough pregnant women to appropriately generalize our results to this population.

Children are admitted to our SICUs in only the rare occasion when their age is unknown and incorrectly estimated to be over 18 years. We would not be able to enroll enough children to appropriately generalize our results to this population.

When people who do not speak English are excluded from participation in the research, provide the scientific rationale for doing so. Individuals who do not speak English should not be denied participation in research simply because it is inconvenient to translate the consent form in different languages and to have an interpreter present.

We will not exclude patients who do not speak English. Our research does not target a non-English speaking population and we do not anticipate more than incidental cases of non-speaking subjects. In cases of unexpected encounters with non-English speakers, the Partners Human Research Committee policy on obtaining and documenting informed consent of subjects who do not speak English will be followed and we will make sure that potential subjects are provided with both; a written translation in a language understandable to them of the 'short form' and an interpreter fluent in both English and the subject's spoken language.

For guidance, refer to the following Partners policy:
Obtaining and Documenting Informed Consent of Subjects who do not Speak English
**http://healthcare.partners.org/phsirb/nonengco.htm**

**RECRUITMENT PROCEDURES**

Explain in detail the specific methodology that will be used to recruit subjects. Specifically address how, when, where and by whom subjects will be identified and approached about participation. Include any specific recruitment methods used to enhance recruitment of women and minorities.

The enrollment sites are: Massachusetts General Hospital (MGH), Brigham and Women's Hospital (BWH), and Jamaica Hospital Medical Center (JHMC). MGH and BWH are conducting the research under the Partners IRB approval and JHMC is conducting research under their own local IRB approval.
Twice daily, the Study Coordinator will screen the SICU census and identify newly admitted eligible patients (based on the inclusion and exclusion criteria) prior to initiating enteral nutrition. The patient's SICU attending will be notified to obtain approval to approach the subject for enrollment. At this point a licensed physician investigator will be introduced by a physician from the SICU team in order to obtain consent.

If the potential subject is NOT a patient of a study investigator, then the primary health care provider (attending surgeon and intensivist) will be contacted first by an investigator. That provider must then give approval for his/her patient to be contacted for research purposes, initially introduce the study to the patient, AND verbally obtain the patient's (or surrogate's) permission to be contacted by study staff.
If the potential subject is among the investigator's own patients, that investigator will reinforce with the patient (or surrogate) that participation is voluntary, that they do not have to participate, and the decision not to participate will not affect their care, now or in the future.

Hospital interpreters will be used for the enrollment of non-English speaking subjects.

Provide details of remuneration, when applicable. Even when subjects may derive medical benefit from participation, it is often the case that extra hospital visits, meals at the hospital, parking fees or other inconveniences will result in additional out-of-pocket expenses related to study participation. Investigators may wish to consider providing reimbursement for such expenses when funding is available

No remuneration will be provided

For guidance, refer to the following Partners policies:

Recruitment of Research Subjects
**http://healthcare.partners.org/phsirb/recruit.htm**

Guidelines for Advertisements for Recruiting Subjects
**http://healthcare.partners.org/phsirb/advert.htm**

Remuneration for Research Subjects
**http://healthcare.partners.org/phsirb/remun.htm**

**CONSENT PROCEDURES**

Explain in detail how, when, where, and by whom consent is obtained, and the timing of consent (i.e., how long subjects will be given to consider participation). For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician investigator must obtain informed consent. When subjects are to be enrolled from among the investigators' own patients, describe how the potential for coercion will be avoided.

Consent will be obtained by a licensed physician investigator (not a member of the clinical team) from the subject or surrogate after it is confirmed that the patient meets all eligibility criteria for the study. If the patient's physician is a member of the study staff, they will introduce another licensed physician investigator from the study staff who will obtain informed consent.

It is expected that many patients will be incapable of providing informed consent since a common indication for enteral nutrition is mechanical ventilation via endotracheal intubation, and mental status is commonly impaired in critically ill patients. If the physician investigator is unable to determine if the patient has capacity to consent for our study, a physician on the SICU team will assist in making this evaluation.

In cases where a patient is deemed incapable of providing consent, surrogate consent will be sought from legally authorized representatives.

The PHRC preferred order of surrogates will be followed and consent will be obtained accordingly:

1) Court appointed guardian with specific authority to provide consent for participation in research, or authority to make health care decisions for a class of diagnostic and therapeutic decisions inclusive of the proposed research.
2) Health care proxy/person with durable power of attorney, with specific authority to make healthcare-related decisions inclusive of the proposed research
3) Spouse, adult child, or other close family member who knows the subject well and has been involved in their care.

NOTE: When subjects are unable to give consent due to age (minors) or impaired decision-making capacity, complete the forms for Research Involving Children as Subjects of Research and/or Research Involving Individuals with Impaired Decision-making Capacity, available on the New Submissions page on the PHRC website:
**http://healthcare.partners.org/phsirb/newapp.htm#Newapp**

For guidance, refer to the following Partners policy:
Informed Consent of Research Subjects
**http://healthcare.partners.org/phsirb/infcons.htm**

**DATA AND SAFETY MONITORING**

Describe the plan for monitoring the data to ensure the safety of subjects. The plan should include a brief description of (1) the safety and/or efficacy data that will be reviewed; (2) the planned frequency of review; and (3) who will be responsible for this review and for determining whether the research should be altered or stopped. Include a brief description of any stopping rules for the study, when appropriate. Depending upon the risk, size and complexity of the study, the investigator, an expert group, an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

NOTE: Regardless of data and safety monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care.

The PI will review the data each month. If at any time, he is concerned that the study is unsafe, he may stop the study or temporarily suspend the study. Additionally an independent medical monitor, Dr. Janey Pratt, will review the data after every 25 enrolled subjects (study-wide) for safety.

Describe the plan to be followed by the Principal Investigator/study staff for review of adverse events experienced by subjects under his/her care, and when applicable, for review of sponsor safety reports and DSMB reports. Describe the plan for reporting adverse events to the sponsor

and the Partners' IRB and, when applicable, for submitting sponsor safety reports and DSMB reports to the Partners' IRBs. When the investigator is also the sponsor of the IND/IDE, include the plan for reporting of adverse events to the FDA and, when applicable, to investigators at other sites.

NOTE: In addition to the adverse event reporting requirements of the sponsor, the principal investigator must follow the Partners Human Research Committee guidelines for Adverse Event Reporting

In accordance with the Partner policy "Reporting Unanticipated Problems including Adverse Events", all unanticipated problems, adverse events, and serious adverse events will be reported electronically to the IRB within 7 calendar days of any investigator in the study becoming aware of the occurrence.

An investigator will round on the subjects daily while they are undergoing the study intervention in the SICU, and weekly thereafter until the patient is discharged from the hospital. They will meet with the PI weekly to review the data confirm that no unanticipated problems, adverse events, or serious adverse events are overlooked.

**MONITORING AND QUALITY ASSURANCE**

Describe the plan to be followed by the principal investigator/study staff to monitor and assure the validity and integrity of the data and adherence to the IRB-approved protocol. Specify who will be responsible for monitoring, and the planned frequency of monitoring. For example, specify who will review the accuracy and completeness of case report form entries, source documents, and informed consent.

NOTE: Regardless of monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for ensuring that the study is conducted at his/her investigative site in accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.

At all enrollment sites, a research fellow will maintain the data in an electronic database stored in a secure location on a password-protected computer system. The consent forms will be kept in files which will be stored in a secure location. De-identified data will be uploaded to the coordinating center (see below). The local site PI will meet with the research fellow weekly to confirm that each new patient enrolled in the study has a valid consent form. The PI will confirm the completeness of data being entered in the electronic database. For the first 2 patients in each group and every 10 patients, a patient randomly selected by the PI, the PI will review the source documents with the research fellow in order to assure that the protocol is being followed accurately and that data is being collected and reported

accurately in the electronic database. If any deviation is encountered that could place the study subjects at increased risk, an ad-hoc meeting of the Steering Committee will be convened to evaluate the problem. If only minor issues are discovered, the study staff will meet to troubleshoot and resolve the problem.

For guidance, refer to the following Partners policies:

Data and Safety Monitoring Plans and Quality Assurance
**http://healthcare.partners.org/phsirb/guidance.htm#13**

Reporting Unanticipated Problems (including Adverse Events)
**http://healthcare.partners.org/phsirb/guidance.htm#7**

**PRIVACY AND CONFIDENTIALITY**

Describe methods used to protect the privacy of subjects and maintain confidentiality of data collected. This typically includes such practices as substituting codes for names and/or medical record numbers; removing face sheets or other identifiers from completed surveys/questionnaires; proper disposal of printed computer data; limited access to study data; use of password-protected computer databases; training for research staff on the importance of confidentiality of data, and storing research records in a secure location.

NOTE: Additional measures, such as obtaining a Certificate of Confidentiality, should be considered and are strongly encouraged when the research involves the collection of sensitive data, such as sexual, criminal or illegal behaviors.

No identifiable information will be revealed to any third party. All subjects' identifiable information will be saved on Partners password protected computers with limited access to the study staff only.

**SENDING SPECIMENS/DATA TO RESEARCH COLLABORATORS OUTSIDE PARTNERS**

Specimens or data collected by Partners investigators will be sent to research collaborators outside Partners, indicate to whom specimens/data will be sent, what information will be sent, and whether the specimens/data will contain identifiers that could be used by the outside collaborators to link the specimens/data to individual subjects.

The coordinating center for this study is located at the Clinical Evaluation Research Unit (CERU) at the Kingston General Hospital, Ontario, Canada. CERU consists of a staff with experience and resources to support the successful completion of all phases of the design, conduct, monitoring, and

interpretation of multicenter clinical studies. Dr. Daren Heyland, the Director of CERU is a Professor of Medicine and Epidemiology at Queen's University, Kingston, Ontario Canada. He is trained in Internal Medicine, Critical Care Medicine, and Clinical Epidemiology. Dr. Heyland is the originator of the PEP uP protocol. The study was designed by PI Dr. Yeh under the guidance and mentorship of Dr. Heyland.

The data manager at Partners sites will be responsible for all aspects of data collection and processing, while the statistician at CERU will be responsible for all aspects of the data analysis and reporting of data. The data manager for the non-Partners sites (JHMC) will be responsible for all aspects of data collection and processing at their local site. All sites will send data directly to CERU. CERU's proprietary central randomization system (CRS) is a modular web-based tool used to monitor patient enrollment, accrual and/or randomization. CERU uses REDCap as an electronic data capture system for capturing, managing, and reporting clinical research data for trials. The REDCap system will run on the SOLARIS 10 operating system and the data will be hosted on a MySQL server database.

Accessing the servers from the CERU offices is done via Virtual Private Network. HPCVL provides an encrypted connection to their network to ensure only authorized users can access the servers. The permissions to connect to the virtual private network are granted by HPCVL at the request of CERU's IT staff.

End users will access the CRS and REDCap using a Secure Socket Layer connection (SSL) and secure passwords provided by CERU's IT staff. Access to the CRS and REDCap is only possible with previous authorization by CERU IT staff.

All data pertaining to the research participant are transmitted to CERU in an anonymized fashion. At the time of data entry participants will be identified in the CRS and REDCap with a unique identifier (i.e. enrollment or randomization number).

All these resources are compliant with Good Clinical Practice and other regulatory authorities worldwide.

Specifically address whether specimens/data will be stored at collaborating sites outside Partners for future use not described in the protocol. Include whether subjects can withdraw their specimens/data, and how they would do so. When appropriate, submit documentation of IRB approval from the recipient institution.

**RECEIVING SPECIMENS/DATA FROM RESEARCH COLLABORATORS OUTSIDE PARTNERS**

When specimens or data collected by research collaborators outside Partners will be sent to Partners investigators, indicate from where the specimens/data will be obtained and whether the specimens/data will contain identifiers that could be used by Partners investigators to link the specimens/data to individual subjects. When appropriate, submit documentation of IRB approval and a copy of the IRB-approved consent form from the institution where the specimens/data were collected.