A Randomized Trial of Supplemental Parenteral Nutrition in

Under and Over Weight Critically Ill Patients:

The TOP UP Trial

Implementation Manual

Intended Audience: Research Coordinators & Site Investigators

This study is registered at Clinicaltrials.gov.
Identification number NCT 01206166

Funded by:

Sponsor: Dr. Daren Heyland

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Glossary

APACHE	Acute Physiology and Chronic Health Evaluation classification system for severity of disease
TOP-UP	A Randomized Trial of Supplemental Parenteral Nutrition in Under and Over Weight Critically Ill Patients
CERU	Clinical Evaluation Research Unit at Kingston General Hospital
CRS	Central Randomization System
ICU	Intensive Care Unit
IP	Investigational Product
PI	Principal Investigator (or Sponsor) of the trial
PL	Project Leader
SI	Site Investigator
SDM	Substitute Decision Maker

Methods Centre Contacts

CERU Contacts	
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Technical Support CERU Help Desk support@ceru.ca OR http://www.ceru.ca/helpdesk/open.php	

All questions related to study procedures should be directed to the Project Leader.

Participating Sites

Institution	Site Investigator
Royal Alexandra Hospital, Edmonton, Canada	Jim Kutsogiannis
University of Alberta, Edmonton, Canada	Constantine Karvellas
Grey Nuns, Edmonton, Alberta	Dan Stollery
University of Colorado Denver, USA	Paul Wischmeyer
Erasme University Hospital, Brussels, Belgium	Jean-Charles Preiser
Nouvel Hôpital Civil, Strasbourg, France	Michel Hasselmann
Oregon Health & Science University, Portland, OR	Robert Martindale
University of Texas, Houston, TX	Rosemary Kozar
Mercy Hospital St. Louis, St. Louis, MO	Rekha Lakshmanan
The Ohio State University Medical Center, Columbus, OH	Beth Besecker
Washington University School of Medicine in St. Louis, St. Louis, MO	Grant Bochicchio

Site numbers will be assigned by CERU when access to the Central Randomization System is granted

Study Synopsis

Hypothesis: Increased energy and protein delivery to underweight and overweight critically ill patients (Body Mass Index [BMI] <25 or ≥35) will result in improved 60 day survival compared to usual care.

Background: The optimal amount of energy and protein a given patient should receive to reduce morbidity and mortality is unclear and remains controversial. Our recent International multicenter observational study of 2772 ICU patients from 165 ICUs showed a significant inverse linear relationship between the odds of mortality and total daily calories received. Increased amounts of calories were most important for the BMI<20 group followed by the BMI 20-<25 group and BMI ≥35 group with no benefit of increased calorie intake for patients in the BMI 25-<35 group. Feeding an additional 1000 kcals almost halved the odds of 60-day mortality in patients with a BMI <25 or ≥35. Similar results were observed for feeding an additional 30 grams of protein per day. Thus, a prospective randomized trial is warranted to confirm our hypothesis that in patients with a BMI of <25 and those with a BMI ≥35 increasing the provision of more energy and protein can impact clinical outcomes.

Study Design: This pilot study is a multicenter, randomized trial of 160 critically ill patients. Patients will be randomized to one of 2 interventions: enteral nutrition (EN) alone or enteral nutrition plus parenteral nutrition (supplemental PN group). Patients will be stratified on the basis of admission BMI: <25 or ≥35, medical or surgical admission diagnosis, and by site.

Study Population & Setting: 160 critically ill adult patients (>18 years old) with BMI <25 or ≥35 from 8 - 9 tertiary care ICU's in Canada, United States, and Europe.

Study Intervention: Patients will be randomized to receive EN only or EN plus PN (supplemental PN group). In both groups, we suggest the following dosing standards: Guidelines for Dosing of Protein and Energy Based on BMI Category

	Minimum Energy	Minimum Protein
BMI <20	30 kcals/kg actual wt	1.5 g/kg actual wt
BMI 20 - <25	25 kcals/kg actual wt	1.5 g/kg actual wt
BMI ≥35	25 kcals/kg ABW*	1.5g/kg ABW*

* ABW=adjusted body weights. Weights in obese patients to be calculated according to the following formula: Obesity-adjusted Body weight= IBW + [(actual weight – IBW) x 0.25], where IBW is ideal body weight is based on a BMI of 25

The EN only group to receive standard enteral nutrition therapy as per our Canadian Clinical Practice Guidelines with a minimum target of calories and protein developed for each stratum. Due to variability of clinical practice around the world, the targets are minimum requirements for energy and protein; each participating site will calculate requirements based upon best-evidence for the disease process for each individual patient. Patients in the EN only group will receive no additional PN in the first 7 days following randomization unless a contraindication to EN develops.

Supplemental PN group to receive the same prescription for calories and protein (in each stratum) and will receive EN via the same protocol as in the control group but in addition, they receive additional protein/energy via the parenteral route. We propose to use a 3-in-1 parenteral admixture solution containing an olive oil/soybean oil ratio of 80:20 and 9 gms nitrogen per litre (Olimel N9 with electrolytes, BE370946 {Belgium}, NL 33592 {France} or Olimel 5.7% E DIN 02352532 {Canada}, provided by Baxter). We propose to start the PN solution immediately after randomization at 25 ml/hr and increase every 4 hours as needed and as tolerated (monitoring blood sugars and electrolytes regularly and triglycerides twice weekly until 100% of goal calories are reached). The relative amount of PN and EN will be monitored and adjusted daily to ensure that the patient receives 100% of prescribed calories daily. We will provide a feeding protocol to standardize the provision of enteral nutrition and study parenteral solutions. The study PN solution will continue for 7 days. At 7 days post randomization, if the patient is in the ICU and requires feeding via the parenteral route, Olimel will be provided to both groups, as per recommendations from recent guidelines.

Outcomes: The primary outcome for the definitive study is 60 day mortality. Secondary outcomes include 28 day mortality, hospital mortality, duration of stay (ICU and hospital), multiple organ dysfunction (SOFA and PODS), duration of mechanical ventilation, development of ICU-acquired infections, functional status at hospital discharge, and 3 and 6 month survival and health-related quality of life.

Specific Aims: The specific aim of the proposed study is to conduct a pilot study involving 160 critically-ill lean and obese patients enrolled at 8 - 9 sites in order to:

1. To confirm that we can achieve a clinically significant difference in calorie and protein intake between the two intervention groups.
2. To estimate recruitment rate i.e. number of eligible and enrolled patients per month per site.
3. To evaluate the safety, tolerance, and logistics around providing supplemental PN in the study population in the context of a multicenter trial, e.g.
    a. To ensure adequate glycemic control in both groups
    b. To ensure that the other metabolic consequences of the feeding strategies are minimized.
    c. To establish adequate compliance with study protocols and completion of case report forms.

A secondary aim of this pilot study will be:

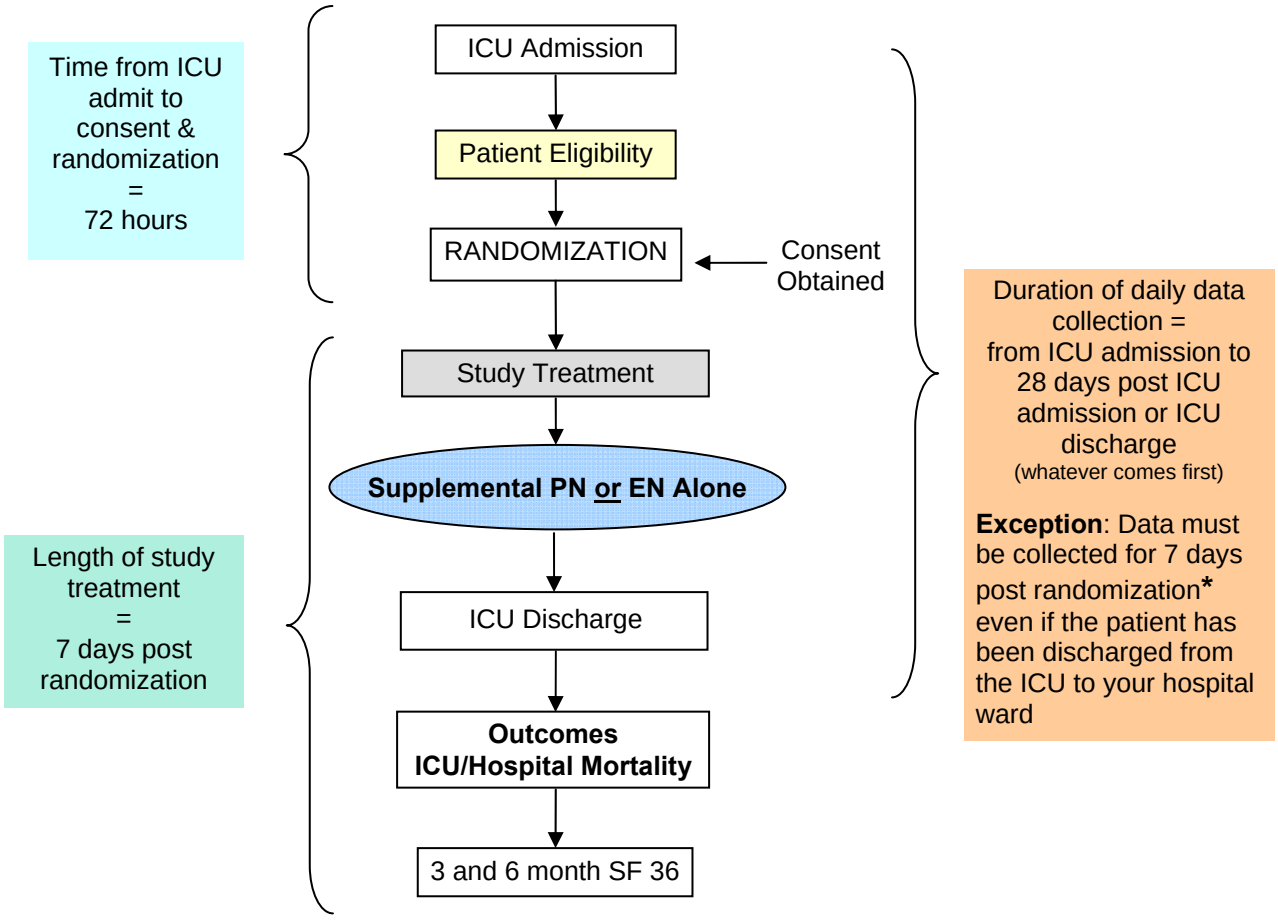
1. To explore the effect of differential rates of calorie/protein provision on muscle mass and muscle function.

Future Plans: If the results of this pilot study are positive, then we will proceed to a large scale trial of 2000 patients across approximately 40 ICUs to determine the efficacy of the proposed nutritional strategy.

Study Overview

Below is a diagrammatic representation of the TOP-UP Study. Refer to appropriate sections of the Implementation Manual for further details concerning specific activities.

Diagram 1: Overview of the TOP-UP Study



***7 days post randomization = the day of randomization PLUS an additional 7 FULL days.**

Roles & Responsibilities

Clinical Evaluation Research Unit

CERU is responsible for the following:

- Providing procedures and tools for study implementation
- Providing training on procedures and tools
- Supplying a username and password for access to the Central Randomization System (CRS) and REDCAP (electronic data capture system)
- Providing ongoing support for research site activities
- Data validation and verification
- Distribution of data queries

Research Sites

The Site Investigator and any applicable delegates at the research site are responsible for the following:

- Supplying a computer with internet access for the CRS & REDCAP
- Maintenance of local computer equipment
- Notifying CERU of any technical difficulties or malfunctions related to the CRS & REDCAP
- Allowing only authorized study personnel to access the CRS.
- Screening & enrolling eligible patients
- Informed Consent of potential research participants (or appointed substitute decision maker)
- Data collection
- Case Report Form (CRF) completion (electronic)
- Data query resolution
- Review and adjudication of all suspicions of infection

Study Preparation Activities

Coordinating Centre

Prior to the initiation of screening activities, each site must ensure the following tasks and/or documentation has been completed, and forwarded to the Project Leader:

- Signed Protocol Signature Page
- Fully-executed Site Agreement
- IRB/REB Study Submission and Approval
- IRB/REB approval of Informed Consent Form (ICF)
- Regulatory Documentation:
    - CVs & medical licenses for QIs
    - CVs for Research coordinators
    - CVs for lead Research Pharmacist
    - Delegation of Authority Log (see section below)
    - Training Logs
    - Local laboratory reference ranges
    - Local laboratory accreditation

Following completion of site start-up training, the above referenced documentation is to be sent to the Project Leader/delegate. All materials required for the implementation and conduct of the TOP-UP Study will be forwarded to the research site by the Coordinating Centre. Patient screening can commence following confirmation of receipt of necessary documentation by the Project Leader/delegate.

Delegation of Authority

The Qualified Investigator at each site must provide CERU with a completed Site Delegation of Authority Log (See **Appendix A**). The purpose of this log is to delineate the key delegated tasks assigned to appropriately qualified individuals on the TOP-UP Study research team. The Site Delegation of Authority Log should be completed as follows:

i. Identify each individual that is involved in the conduct of the TOP-UP Study and to whom the Qualified Investigator (QI) has delegated key tasks.
ii. Each individual assigned to the study should complete the log including the effective start date of their activities. (The end date will be the time when the individual no longer has any association with the study).
iii. Refer to the sample key delegated tasks below. If you are in agreement with this list of tasks you may use this to record the various responsibilities of your site personnel.
iv. Update this log during the course of the study.
v. Fax this log, including any updated versions, to the Project Leader at (613) 548-2428.

Key Delegated Tasks

Reference Number	Key Delegated Tasks
1	Screening subjects for eligibility
2	Conducting informed consent discussions for eligible patients
3	Obtaining written informed consent
4	Patient enrolment/randomization and follow-up
5	Checking eligibility criteria
6	Daily monitoring of patient health, safety and study compliance
7	Data collection, includes: ❖ Case Report Form entries ❖ Case Report Form corrections ❖ Data query resolution ❖ Hand Grip Strength tests ❖ 6 minute walk test
8	Source documentation maintenance, includes: ❖ Study worksheets, checklists, monitoring sheets ❖ Data from electronic & hard copy medical chart
9	Reporting of Protocol Violations/Unanticipated Problems involving risk
10	Identification of Serious Adverse Events and documentation
11	Maintenance of Regulatory Documents
12	REB submissions and communications
13	Perform study specific training
14	Perform Femoral Quadricep Ultrasound
15	Performing clinical assessments including burn outcomes, SAEs and ICU infection adjudication
16	Confirmation of completeness and accuracy of data collected
17	Maintenance of Product inventory
18	Checking of treatment assignment online
19	Study treatment dispensing & accountability, including maintenance of logs
20	Optimizing delivery of enteral nutrition and compliance with Guidelines for Nutrition

Training

Each member of the site research team should be qualified by education, training and experience to assume responsibility for the proper conduct of the trial. (GCP 4.1.1). For each delegated task, appropriate training documentation must be filed in your regulatory binder.

Training on the study procedures related to the TOP UP Study will be provided by the Project Leader/Principal Investigator/delegate to the site before the start of enrolment.

It is the responsibility of the qualified investigator (site investigator) to ensure that all site staff (including pharmacy staff, bedside research nurses etc) has been adequately trained

Inclusion Criteria

The following section refers to the details around the eligibility of patients for The Top Up Study. Details on how to randomize and enter data on screened patients are provided in the accompanying CRS/REDCAP Manual. In addition, when screening patients, the mock eCRFs pages 4-9 may be used as worksheets.

Patient eligibility must be confirmed by the Site Investigator/MD delegate

Patients must meet all five of the criteria at the time of screening to be eligible for the study **with the exception of criteria # 2 which is from time of ICU admission.**

#	Inclusion Criteria
1	**Critically ill adult patient (≥18 years) admitted to your ICU**
2	**Have acute respiratory failure (ARF) i.e. expected to remain mechanically ventilated > 48 hrs from ICU admission** This refers to **invasive mechanical ventilation** and is defined as intubation with mechanical ventilation or tracheostomy with mechanical ventilation. This includes **any** positive pressure delivered via an endotracheal tube or a tracheostomy. This **does not** refer to ***non-invasive*** methods of ventilation such as BI-PAP or mask-CPAP. To avoid enrolling patients that are extubated early and given current exclusion criteria # 1 i.e. >72 hours from admission to ICU to time of consent, the following clarification is provided for this revision: ***If screening is done on day 1 (day of ICU admission):*** ***ensure patient is expected to remain mechanically ventilated for 48 hrs from ICU admission*** ***If screening is done on day 2 (day after ICU admission):*** ***ensure that the patient is expected to be ventilated for an additional 24 hrs from screening (equivalent to 48 hrs from ICU admission)*** ***If screening is done on day 3:*** ***and patient was ventilated for 48 hrs but now is extubated, he/she is eligible as long as all other inclusion criteria are met. If patient remains ventilated on day 3, need to ensure that consent is still obtained within 72 hrs from ICU admission.***
3	**Expected ICU dependency of 5 or more days** (as per judgment by the Site Investigator/delegate) ICU dependency defined as need for mechanical ventilation, non invasive ventilation, renal replacement therapy, vasopressors or artificial nutrition because of their underlying illness. **N**OTE: This does **not** include patients that stay in ICU because of lack of availability of beds.

4	**On enteral nutrition or expected to initiate enteral nutrition within 7 days of ICU admission** The "expected to initiate enteral nutrition" refers to the anticipation of the start of enteral nutrition and this is an assessment that is made at the time of screening evaluation in collaboration with the Medical Team. In the event that, at time of screening, the patient was expected to start enteral nutrition within the first 7 days and the patient is randomized, but enteral nutrition does not actually get started within this time frame, the patient still remains in the study.
5	**BMI < 25 or ≥35 based on pre-ICU actual or estimated dry weight** (Refer to **Appendix B** for BMI Chart) **If using estimated weight/height, you may add a buffer of ±1 for the BMI, after rounding, In this case, ENTER THE BUFFERRED BMI into the Central Randomization System.** Example 1: If estimated BMI is 25 after rounding, use a -1 to get a BMI of 24. Record 24 into the CRS Example 2: If estimated BMI is 34 after rounding, use a +1 to get a BMI of 35. Record 35 into the CRS

Exclusion Criteria

Choose all exclusion criteria that apply. If a patient meets any of the exclusion criteria, they are not eligible to participate in the study.

#	Exclusion Criteria
1	**> 72 hrs from admission to ICU to time of consent**. The 72 hr window refers to admission to your ICU. In the event that the patient is transferred to your ICU from another ICU, the 72 hr starts from the admission to your ICU.
2	**Not expected to survive an additional 48 hours from screening evaluation**
3	**Lack of commitment to full, aggressive care (anticipated withholding or withdrawing treatments in the first week but isolated DNR acceptable)**
4	**Patients already receiving PN at screening**
5	**Absence of all risk factors for gastrointestinal intolerance, defined as:** a) High Apache II score (>20) b) On more than 1 vasopressor or increasing doses of vasopressors c) Receiving continuous infusion of narcotics d) High nasogstric/orogastric output (>500 mL over 24 hours) e) Recent surgery involving esophagus, stomach, or small bowel, OR peritoneal contamination with bowel contents f) Pancreatitis g) Multiple gastrointestinal investigations h) Recent history of diarrhea/C. difficile i) Surgical patients with future surgeries planned j) Ruptured or dissected abdominal aortic aneurysm
6	**Patients admitted with Diabetic Ketoacidosis or non-ketotic hyperosmolar coma**

7	**Pregnant or lactating patients**
8	**Patients with clinical fulminant hepatic failure.** Clinical fulminant hepatic failure is defined as: • absence of cirrhosis/chronic liver disease and • presence of coagulopathy (prothrombin time > 15 sec or INR >1.5) and • presence of any grade of hepatic encephalopathy within 26 weeks of the first symptoms in a patient with acute liver injury • **NOTE:** This criterion applies to **only** those patients who, in the opinion of the Site Investigator/delegate, are deteriorating or are at high risk of dying due to clinical fulminant hepatic failure. If the patient meets this criterion but, in the opinion of the Site Investigator/delegate, is improving significantly and is not expected to die because of the clinical fulminant hepatic failure, he/she may be eligible and this exclusion criterion would not apply. In this event, proper documentation from the Site Investigator is needed for confirmation of the patient's prognosis. Refer to Protocol Clarification memo dated May 7th, 2012
9	**Patients with Cirrhosis Child's Class C Liver Disease** (except those on a transplant list or transplantable)
10	**Dedicated port of central line not available**
11	**Known allergy to study nutrients (soy, egg or olive products)**
12	**Enrollment in another industry sponsored ICU intervention study (**co-enrollment in academic studies will be considered on a case by case basis**)**

Consent and Confidentiality

Patient Confidentiality

By definition, and in the context of a clinical trial, confidentiality refers to prevention of disclosure, to unauthorized individuals, of a Patient's identity and of records that could identify a Patient. Care and diligence in protecting confidential Patient information must be exercised throughout the duration of the TOP-UP Study.

With this in mind, prior to forwarding any documentation (i.e. as attachments to a Serious Adverse Event [SAE] report) to CERU, all patient identifiers other than the Patient's Initials, and Randomization Number should be masked.

Obtaining Consent

"Free and informed consent refers to the dialogue, information sharing and general process through which prospective subjects choose to participate in research involving themselves."

- Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans

All staff that will be involved in obtaining consent for the TOP UP Study must be trained on procedures related to informed consent and provide documentation to this effect. Refer to the Informed Consent Training Module for details.

Investigational Product Administration

Patients randomized to the TOP-UP Study will receive one of the following:

Name of Group	Intervention
Supplemental PN	**EN & Olimel N9E/5.7%E**
EN Only	**EN**

Both EN only and Supplemental PN groups

Dosing
Both the supplemental PN and the EN only group will receive the exact same prescription for calories and protein (within each BMI stratum). The proposed target dose of protein and energy based on BMI category for both groups is as follows:

Guidelines for Dosing of Protein and Energy Based on BMI Category

	Minimum Energy	Minimum Protein
BMI <20	30 kcals/kg actual wt	1.5 g/kg actual wt
BMI 20 - <25	25 kcals/kg actual wt	1.5 g/kg actual wt
BMI≥35	25 kcals/kg ABW*	1.5g/kg ABW*

* ABW=adjusted body weights. Weights in obese patients to be calculated according to the following formula: Obesity-adjusted Body weight= IBW + [(actual weight – IBW) x 0.25], where IBW is ideal body weight is based on a BMI of 25

Enteral Nutrition
Timing of initiation
Once the patient is stabilized (adequate volume status and on stable or decreasing doses of vasopressors) and there is a nasogastric tube or feeding tube in place, EN should be started within 24-48 hrs of admission to ICU in both groups.

Type of enteral formula
The enteral nutrition formula choice will be made by the site as per standard care. The type of enteral formula will be selected by the dietitian following their nutritional assessment. A standard enteral solution with 1.2 ± 0.2 kcal/ml will be used according to standard practice and the following will **not** be allowed:

- Hypercaloric entera formulas (>1.4 kcal/ml)
- Glutamine supplements (IV or EN) in the first 7 days post randomization
- Pre/probiotics in the first 7 days post randomization

The Research Coordinator/Site Investigator is to ensure that these details get communicated to all the dietitians in the ICU.

Administration of enteral formula
Enteral nutrition should be initiated at 25 ml/hr and increased by 25ml/hr increments every 4 hours as tolerated until goal rate is reached.

A bedside enteral feeding protocol to aid the nurses in initiating and progressing the rate of EN will be provided. This algorithm will include strategies to optimize delivery of EN such as monitoring gastric residual volumes, use of motility agents or small bowel feeding in patients with high gastric residual volumes and elevating the head of the bed to 45 degrees. Refer to **Appendix C** for Enteral Nutrition Algorithm.

Patients in both groups will be fed according to the Canadian Critical Care Nutrition clinical practice guidelines

Duration of administration
Patients in both groups will receive enteral nutrition until the feeding tube is removed.

Supplementation with trace elements and multivitamins
In the event that a patient does not receive enteral nutrition and is dependant on parenteral nutrition for >48 hrs, the use of intravenous trace elements and multivitamins is recommended (not to be added to the bag but to be given via IV). Standard doses of multivitamins and the following ranges of trace elements are suggested, as a guideline: 5 mg zinc, 1 mg copper, 0.5 mg manganese, 10 mg chromium and 60mcg selenium. Participating sites will use commercially available trace element solutions that are consistent with these above mentioned guidelines and their standard of care. At the end of this study period, clinicians can prescribe open label supplements as clinically indicated in both groups.

Co-Interventions
To reduce the effect of varying nutritional practices as confounding factors on the outcomes of The TOP-UP trial, it is important to standardize, *as much as possible*, nutrition practices. All sites are encouraged to follow Clinical Practice Guidelines for Nutrition Support and to follow a similar approach to weaning patients from mechanical ventilation. Implementation of daily sedation vacations, and sepsis management guidelines will be recommended. In addition, daily trials of spontaneous breathing in patients meeting the criteria specified by evidence based guidelines for weaning will be recommended. A glycemic control protocol will be used in both groups to maintain blood sugars less than 10 mmol/l (180 mg/dL) or at lower ranges specified per local protocol as long as tight glycemic control is not being practiced. The literature on early physiotherapy and mobilization is just emerging and there are no specific guidelines on this topic. Rather than standardize such practices across all participating units, we will collect data on these rehabilitation practices to be able to describe them.

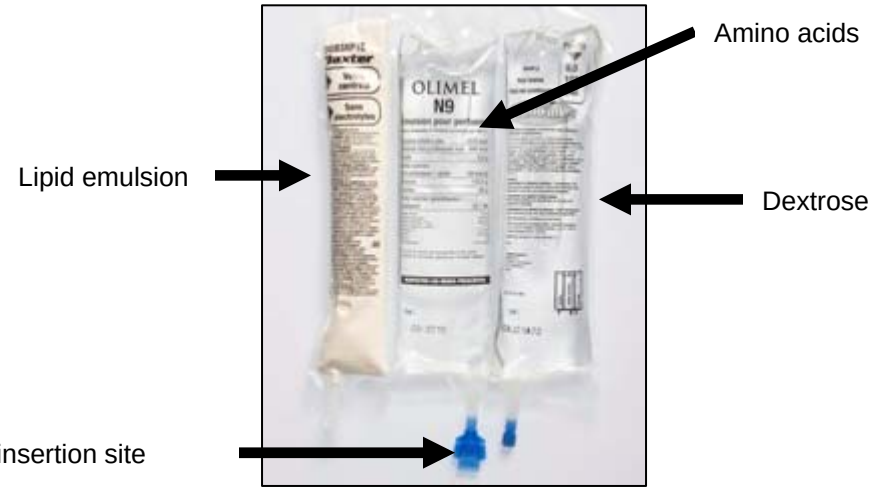
Supplemental PN group (Intervention)

In addition to receiving EN as described above, the supplemental group will also receive the study parenteral solution (ie Olimel) to achieve the target hourly prescribed rate of infusion.

Olimel
The study parenteral solution is a 3-in-1 parenteral admixture solution containing an olive oil/soybean oil ratio of 80:20 and 9 gms nitrogen per litre called Olimel 5.7% E DIN 02352532 {Canada}, IND # 112,014 in US, provided by Baxter. It is also referred to as Olimel N9 E (with electrolytes) {BE370946 in Belgium, NL 33592 in France}. This product will be similar in caloric density to the standard EN solutions (1-1.4 kcals/ml).

The olive oil contains a significant amount of alpha-tocopherol which, combined with a moderate PUFA intake, contributes to improve vitamin E status and to reduce lipid peroxidation. The amino acids solution contains 17 L series amino acids (including 8 essential amino acids), which are indispensable for protein synthesis. The protein and energy content of Olimel N9E enables the maintenance of an adequate nitrogen/energy balance in critically ill patients.

Olimel will be provided in 1 liter bags (see picture below).



Content of Olimel 5.7% E (N9E) 1000 ml bags

27.5 % Glucose solution (corresponding to 27.5 g/100 ml)	400 ml
14.2 % Amino acid solution (corresponding to 14.2 g/100 ml)	400 ml
20 % Lipid emulsion (corresponding to 20 g/100 ml)	200 ml

For more details about the composition of the reconstituted emulsion after mixing the content of the 3 compartments, refer to the Product Monograph.

After the Olimel has been reconstituted, the mixture will be a homogeneous emulsion with a milky appearance. Due to its high osmolarity, Olimel N9E can **only** be administered through a dedicated central vein. Since the compatibility issues are unknown, the infusion should not be piggybacked with other lines. Refer to Investigational Product for more details or call the project Leader for questions related to infusions with insulin etc.

Although the product monograph recommends DEHP (Di [2 ethylhexyl] phthalate) free sets and lines for use with Olimel they are not required for study purposes. Refer to memo dated Nov 30th 2011.

In accordance with the product monograph, the use of a filter is not needed for the administration of Olimel as no additions of inorganic phosphate are to be made.

The pharmacy at each site will receive an initial shipment of Olimel from Baxter before enrollment starts and after regulatory documents have been obtained by the Methods Centre. Since the study is unblinded, each site will request subsequent product by emailing the Project Leader. Additional Olimel will be provided to the sites for patients needing prolonged parenteral nutrition i.e. beyond 7 days post randomization (study intervention duration). The Methods Centre will be responsible for making arrangements for replacing expired product at the sites.

For storage of Olimel, refer to the “Product dispensing for supplemental PN group” section.

Timing of initiation

The study PN should be started as soon as central line access is available, preferably within 2 hours of randomization. Given that the sooner the PN is started, the more likely it will have a treatment effect, any delays in initiation should be minimized.

Administration of Study PN: Paired Feeding

The hourly rate of study PN to be infused is dependent upon the hourly rate of EN and should be adjusted up or down to ensure that the target hourly rate is obtained, This target rate is the rate that will provide 100% calories or protein, as determined by the dietitian/MD.
The study PN should be started at a rate of 25 ml/hr (or at a higher rate if no concerns about hyperglycemia or electrolytes) and increased by 25 ml increments at least every 4 hours (or faster if as tolerated monitoring blood glucose every 4 hours and electrolytes as needed) till 100% of goal calories/rate is reached.

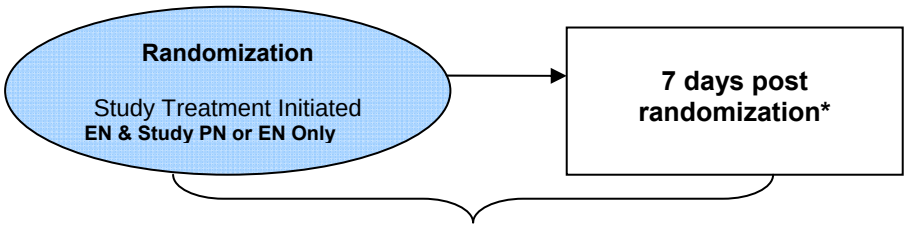
The relative amount of PN and EN received will be monitored at a minimum of every 4 hours. In the event of a change in the rate of EN delivery, PN will be adjusted accordingly to ensure that the patient receives 100% of their target goal rate on a continuous basis. If there is an interruption of EN for any reason, PN will be restarted to maintain the hourly target rate.

The target is to reach the combined rate by EN plus PN or PN alone within 24 hrs from randomization

There is no routine blood testing for the study however, blood glucose, insulin and electrolytes should be monitored frequently (whenever they are drawn for clinical reasons). **In the event that glucose, phosphate, potassium or magnesium levels are critically out of range and levels are becoming more abnormal (ranges as specified at your local site), EN or PN should not be advanced.** Refer to **Appendix F** for Paired Feeding Algorithm.

Both enteral and parenteral solutions will be provided continuously over a 24 hour period.
Do not stop parenteral study infusion for procedures or surgery. We do not encourage doubling up infusion rates to make up for missed hours.

Duration of administration
The study PN will be continued for 7 days post randomization* or until death, whichever comes first. This means that if randomization was on study day 2, the study PN should be given until 23:59 hrs on study day 9, unless central line access is an issue.



Duration of Study Intervention

In the event that the patient is discharged from ICU prior to 7 days post randomization*:
the study PN must be continued in the hospital ward at 100% goal (no hourly titration) until 7 days post randomization* regardless of whether the patient is tolerating adequate amounts of oral nutrition. In the event that the patient is discharged from ICU prior to day 7 post randomization and is still receiving EN, the study PN solution will continue to maintain 100% goal rate until 7 days post randomization*.

In the event that after 7 days post randomization*, PN is clinically indicated:

- if the patient is still in the ICU: use study PN (Olimel) until study day 28 or until PN is not needed, whatever occurs first.
- if the patient has been discharged from ICU to the hospital ward, use standard PN solution.

REMEMBER: *7 days post randomization = the day of randomization PLUS an additional 7 FULL days.

In the supplemental group, the use of non-study PN within 7 days post randomization* will be considered a protocol violation. *Please refer to the Protocol Violation section.*

Enteral Nutrition only group

The enteral nutrition only group will receive EN only as described in the section titled "Enteral Nutrition".

In the event that within 7 days post randomization*, PN is clinically indicated:

- The enteral nutrition only group MUST not receive any parenteral nutrition in the first 7 days post randomization*. If the patient develops an **absolute** contraindication to enteral nutrition, and parenteral nutrition is clinically indicated, Olimel should be used if in the ICU. However this is to be reported as a Protocol Violation (refer to protocol violation section).

In the event that after 7 days post randomization*, PN is clinically indicated:

- if the patient is still in the ICU: use study PN (Olimel) until study day 28 or until PN is not needed, whatever occurs first.
- if the patient has been discharged from ICU to the hospital ward, use standard PN solution.

Non study parenteral solutions are not recommended during the study intervention period as their use may add a confounding variable in the EN only group.

REMEMBER: *7 days post randomization = the day of randomization PLUS an additional 7 FULL days.

In the EN only group, the use of any PN (study or non-study) within 7 days post randomization* will be considered a protocol violation. *Please refer to the Protocol Violation section.*

Study Orders for EN only group

After randomization, the Research Coordinator is responsible for facilitating/writing the Physician's Orders for the TOP UP Study in the medical chart. See Sample below for patients randomized to the EN only group. Refer to **Appendix C** for Enteral Nutrition Algorithm.

Sample Medical Orders

This patient is enrolled in _____IRB study ID#, 'A Randomized Trial of Supplemental Parenteral Nutrition in Under and Over Weight Critically Ill Patients' (The TOP-UP study).

Hourly target rate of EN is __ ml/hr

- Start standard enteral solution of 1.2 ± 0.2 kcal/ml within 24-48 hrs of ICU admission at 25 ml/hr.
- Advance rate by 25 ml every 4 hrs until target rate has been achieved.
- Follow Enteral Nutrition Algorithm to minimize interruptions i.e.
    - monitor gastric residual volumes q 4 hrs
    - consider use of motility agents & small bowel feeding if gastric residual volumes repeatedly > 250 mls
    - elevate the head of the bed to 45 degrees
- Blood work: as per usual practice
- Record all hourly EN infusions in medical chart

Product Dispensing for Supplemental PN Group

After the patient has been randomized on the Central Randomization System to the supplemental PN Group, the Research Coordinator/pharmacy/delegate is to proceed with the following:

1. **For day 1**: obtain enough 1 litre bags of the investigational product (IP) to last one day, according to the dietitian/MDs determination of hourly rate.

   Example: if the dietitian has determined the hourly rate is 65 ml/hr, the total volume needed for 1 day would be 65 X 24 = 1536 mls. The Research Coordinator/pharmacy/delegate is to obtain 2 X 1 Litre bags of the product.

   In order to prevent running out of product before the bag change time, you may need to supply 2 X 1 litre bags on day 1.

   Note: To avoid wasting product, run each bag of Olimel until expiry, please avoid changing bags that are not close to expiring. Per the approved label, OLIMEL can be stored for up to 24 hours under refrigeration <u>after</u> overwrap has been removed and followed by 24 hour administration. "

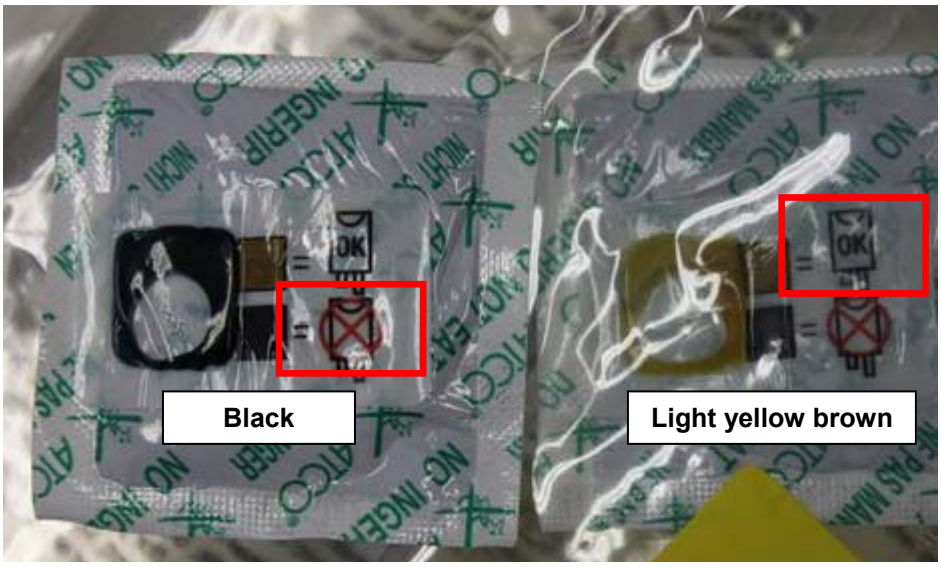
2. **For Subsequent days:** determine how much enteral nutrition the patient is anticipated to tolerate and will prepare enough IP accordingly.

   Example: if the patient is anticipated to tolerate 25 ml/hr of enteral nutrition and the goal rate is 65 ml/hr, prepare enough IP for the remaining volume i.e. 40 ml/hr X 24 = 960 mls = 1 X 1 litre bag

3. **Re-constitution of Olimel:**

To open the Olimel, remove the protective overpouch.

a. Check the oxygen absorber / oxygen indicator sachet:
   - If the tip of the indicator is **"light yellowish brown"**, this means the protective overpouch has been sealed properly and the product can be used.
   - If the indicator is **"black"**, this means the protective overpouch has **not** been sealed properly that the bag **must not** be used.



b. Confirm the integrity of the bag and of the non-permanent seals. Use only if the bag is not damaged, if the non-permanent seals are intact (i.e. no mixture of the contents of the three compartments), if the amino acids solution and the glucose solution are clear, colourless, practically free of visible particles, and if the lipid emulsion is a homogeneous liquid with a milky appearance.

   - The timing of OLIMEL administration should be considered once the product is removed from the overwrap. Per the approved label, OLIMEL can be stored for up to 24 hours under refrigeration after overwrap has been removed and followed by 24 hour administration. "

c. Ensure that the product is at room temperature when breaking the non-permanent seals.

d. Manually roll the bag onto itself, starting at the top of the bag (hanger end). The non-permanent seals will disappear from the side near the inlets. Continue to roll until the seals are open along approximately half of their length.

e. Mix by inverting the bag at least 3 times

f. After reconstitution, the mixture is a homogeneous emulsion with a milky appearance.

Refer to Training Slides for Reconstitution of Olimel for pictures

4. Generate and attach one label (appx 3 X 5") with the following patient ID details and attach to the outside of each reconstituted Olimel bag

Label Template

Study: The TOP-UP Study
ID #: NCT01206166
Olimel N9E

PARENTERAL USE ONLY

Canadian Sponsor: Dr. Daren Heyland
Clinical Evaluation Research Unit, Kingston General Hospital,
76 Stuart St, Kingston, ON K7L 2V7

Randomization #: _____
Patient ID: _____
Patient Name: _____

Directions: Run at maximum goal rate of XX ml/hr and titrate down as enteral feeds increase.

Storage: Room temperature between 15-30° C
Expiration: 24 hrs

5. Complete the Investigational Product Accountability/Dispensing Logs (amount received, destroyed, batch #, expiry, quantity dispensed, patient details, balance of product, etc) (see **Appendix D**) and keep these in the Inventory study files.

6. Repeat steps 3-7 daily for duration of intervention = 7 days post randomization, or death/discharge, whichever occurs first.

7. Destroy all expired products as per local procedures after recording this on the Investigational Accountability Log.

8. Research Coordinator/pharmacy/delegate to send the following to CERU monthly:
   Temperature logs for Olimel (unopened, unmixed bags at 15°C to 30°C).
   Refer to **Appendix E** for Sample Temperature Log.

Due to the unpredictability of EN interruptions, supplemental PN will need to be readily available for the bedside nurses, even in the absence of the Research Coordinator.
The Research Coordinator must ensure that the bedside nurses are trained on the procedures related to the reconstitution of the Olimel.

Study Orders for Supplemental PN group

After randomization, the Research Coordinator is responsible for facilitating/writing the Physician's Orders for the TOP UP Study in the medical chart. See Sample below (on next page) for patients randomized to the supplemental group (EN + Olimel). Refer to **Appendix F** for Paired Feeding Algorithm.

Sample Medical Orders

This patient is enrolled in _____IRB study ID#, 'A Randomized Trial of Supplemental Parenteral Nutrition in Under and Over Weight Critically Ill Patients' (The TOP-UP study).

Hourly target rate of EN or PN (i.e. Olimel) or combined EN + PN is 80 ml/hr

- If not on EN, start Olimel at 25 ml/hr (or higher) and advance by 25 ml (or faster) every 4 hrs until target rate has been achieved.
- If EN is started while patient is on Olimel, start standard enteral solution of 1.2 ± 0.2 kcal/ml at 25 ml/hr (or higher) and advance by 25 ml q 4 hrs (or faster) so that EN + PN = hourly target rate (80 ml/hr).
- Check PN and EN at a minimum of every 4 hours so that EN + PN = 80 mls/hr.
- Check blood glucose q4h; insulin drip to maintain blood glucose (BG) at <10 mmol/l (180 mg/dL) or according to acceptable local ranges. Do not advance EN or PN until BG within the desired range.
- Maintain EN+PN total at target rate (80 ml/hr) for 7 days from randomization.
- Follow Paired Feeding Algorithm to minimize interruptions i.e.
    - monitor gastric residual volumes q 4 hrs
    - consider use of motility agents & small bowel feeding if gastric residual volumes repeatedly > 250 mls
    - elevate the head of the bed to 45 degrees
- Record all EN and PN infusions given on the Medication Administration Record as "TOP UP supplement" as mls/hour.

Protein & Energy Dosing and Nutritional Assessment

Both groups

The Research Coordinator is to work with the dietitian/MD in the unit to ensure that she/he is trained on the type of nutrition data that needs to be collected and the timing. While the dietitian/MD will collect the data on worksheets, the Coordinator will record the data on to the Electronic Case Report Form.

Since the dose of the intervention is to be determined according to the prescribed energy, the dietitian/MD MUST determine the following asap after randomization

1. Minimum Protein and Energy needs
2. Prescribed Protein and Energy needs
3. Prescribed Volume for EN (or PN or combined EN + PN)
4. Hourly Infusion rate for EN, PN or both combined EN + PN

The following documents should be forwarded to the dietitian/MD to assist with the calculations for Protein/Energy Dosing and daily nutrition monitoring

- Protein and Energy Dosing Excel Worksheet
- Nutrition Timing mock eCRF (for instructions on data collection)
- Daily Monitoring mock eCRF (for instructions for data collection)
- Concomitant Medications mock eCRF (for instructions for data collection)

Nursing Procedures

The Research Coordinator is to train the bedside RNs in the unit on the following procedures:

- **EN group only procedures**
  - Start EN within 24-48 hrs of ICU admission is preferred but this can be delayed according to standard practice.
  - Type of enteral nutrition formula
  - Start @ 25 ml/hr and increase by 25 mls q 4 hrs as tolerated. Refer to **Appendix C** for Enteral Nutrition Algorithm.
  - Do NOT supplement with parenteral nutrition within 7 days of post randomization. If the patient develops an **absolute** contraindication to enteral nutrition, and parenteral nutrition is clinically indicated, Olimel should be used if in the ICU as described under "Enteral Nutrition only group" section.

- **Supplemental PN Group procedures:**
  - Product Dispensing (as the RN will need to reconstitute the Olimel). Refer to Training slides for Reconstitution of Olimel.
  - Administration of Study PN: Paired Feeding
    - Start Olimel @ 25 ml/hr (or higher rate) and increase by 25 mls q 4 hrs (or faster) according to blood work. Refer to **Appendix F** for Paired Feeding Algorithm.
    - Check study PN at a minimum of every 4 hours so that EN + PN = target hourly rate
    - If EN interrupted, increase PN accordingly to meet target hourly rate
    - Inform the Research Coordinator of any interruptions in the target infusion rate (if EN + PN < target rate).

- Record all hourly EN and Study PN infusions for both groups administered on the Medication Administration Record as "TOP UP supplement" in mls/hour.

Refer to the "Enteral Nutrition only group" and "Supplemental PN Group" sections for more details

Data Collection

The following information provides an overview of some of the data needed for the study. For comprehensive details on all the data and how this is to be collected, you must refer to the Mock eCRFs & Instructions.

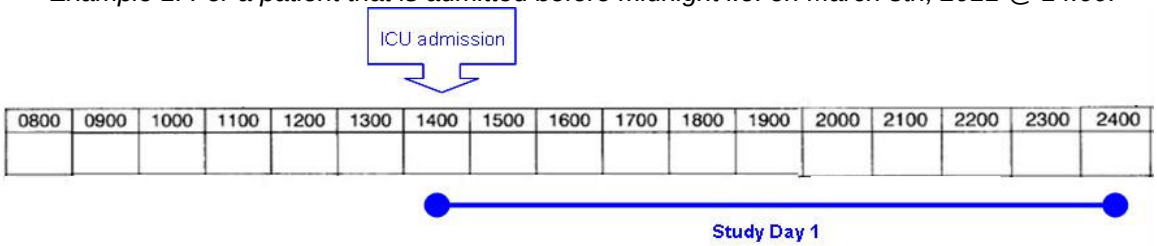
Study Days

Data for the TOP-UP Study is to be collected according to Study days. Study Days are defined according to the calendar clock as below:

Study days are defined as follows, regardless of when randomization occurs:

Study Day 1	**=**	ICU admission day i.e. from date & time of ICU admission to 23:59 of that same calendar day
Study Day 2	=	from 00:00 to 23:59 hrs the next day (24 hr period)
Study Day 3	=	from 00:00 to 23:59 hrs the next day (24 hr period) and so on…

Example 1. For a patient that is admitted before midnight i.e. on March 8th, 2011 @ 14:00:



Study Day 1= 08/Mar/2011 @ 14:00 to 08Mar/2011 @ 23:59
Study Day 2 = 09/Mar/2011 @ 00:00 to 09/Mar/2011 @ 23:59
Study Day 3 = etc...

Example 2: When a patient is admitted after midnight patient is randomized Mar 9th, 2011 @ 03:00 hrs, the study days would be:

Study Day 1= 09Mar/2011 @ 03:00 hrs to 09/Mar/2011 @ 23:59
Study Day 2 = 10/Mar/2011 @ 00:00 to 10/Mar/2011 @ 23:59
Study Day 3 = etc...

***Exception:** Daily fluid balance is collected according to flowsheet i.e. 07:00 – 07:00 hrs (Memo August 9th, 2012).

Duration & Type of Data Collection

The duration of data collection and frequency will vary depending upon each Electronic Case Report Form and is outlined below (and in the instructions in the Mock eCRF Worksheets). Refer to **Appendix G** for a reference table of the Duration of Data Collection.

Collected once:

- Protein and Energy Dosing
- Barthel Index (Baseline)
- Baseline SF 36/Nutritional Assessment
- Patient Baseline
- Nutrition Timing

- Hospitalization Overview: upon ICU/hospital discharge
- Barthel ADL Index (at hospital discharge)
- Follow-Up: at 3 and 6 months from time of admission to ICU

Collected from Study Day 1 (ICU admission) until ICU discharge or death for a maximum of 28 days from ICU admission

<u>Exception:</u> Daily data must be collected for a minimum of 7 full days post randomization even if the patient is discharged from the ICU to your hospital ward.

Daily

- Monitoring
- Organ Dysfunction
- Laboratory/Intra-Abdominal Pressure
- Rehab Practices
- Concomitant Medications
- Antibiotic, Antifungals, Antivirals
- Microbiology

Weekly/other specified intervals

- Weekly Laboratory
- Muscle Function Testing
    - Ultrasound of Femoral Muscle
    - Abdominal/Pelvis CT scans
    - Hand Grip Strength
    - 6 Minute Walk test and Weight
- Infection Adjudication (as per antibiotic and microbiology data)

Source Documentation

As per ICH GCP (1.51) source documents are original documents, data and records. The Research Coordinator must ensure source documents are available to verify all data collected for the TOP-UP study.

Electronic Case Report Form Completion

Refer to the Central Randomization System/REDCAP Manual for details on entering data into REDCAP, the electronic data capture system.

At Time of Consent

There are some data elements that the Research Coordinator must collect/obtain these from the patient's next of kin shortly after consent has been obtained. These are listed as follows.

Barthel ADL Index at Baseline

The Barthel ADL (Activities of Daily Living) Index is used to determine the level of patient independence. At baseline this index determines how independent the patient was prior to the acute episode of illness (i.e. 24-48 hrs prior). Refer to the Barthel ADL Index (Baseline) mock eCRF instructions for more details.

Baseline SF 36

The baseline SF 36 is a quality of life questionnaire that is to be completed with the patient's next of kin as soon as possible after consent has been obtained. Refer to the Baseline SF 36 mock ecrf instructions for more details.

Nutritional Assessment

This data must be obtained from the patient's next of kin after consent has been obtained. Refer to the Baseline Nutritional Assessment mock ecrf instructions for more details.

Weekly Muscle Function Tests

Weekly Ultrasounds & Abdominal/Pelvis CT Scans

In the context of this pilot study, we propose to evaluate the effect of differential amounts of protein and energy provided to study patients on muscle mass and function. Acquired weakness following prolonged critical illness is an important contributor to ongoing morbidity experienced by survivors of critical illness. Given the emerging evidence that muscle mass and muscle function predict morbidity in surviving patients and that muscle mass at ICU admission may predict length of hospital stay, we can postulate that the beneficial effect of enhanced energy and protein provision is mediated by the preservation (or attenuated deterioration) of muscle mass and increased function in these better fed patients, which would ultimately result in positive outcomes. We will evaluate muscle mass in all study patients using bedside ultrasound of the femoral muscle.

The following muscle function tests are done to determine the effect of extra protein on muscle function and the methods for conducting some of these tests are described below.

Ultrasounds

Research investigator to take ultrasound measurements at the following intervals for study patients:

1. Upon enrolment to the study

2. Weekly on day 8-14, 15-21, 22-28 (±48 hours). Refer to mock e-CRFs for more details.

Equipment Required:

1. Portable Ultrasound machine using a high frequency linear transducer.

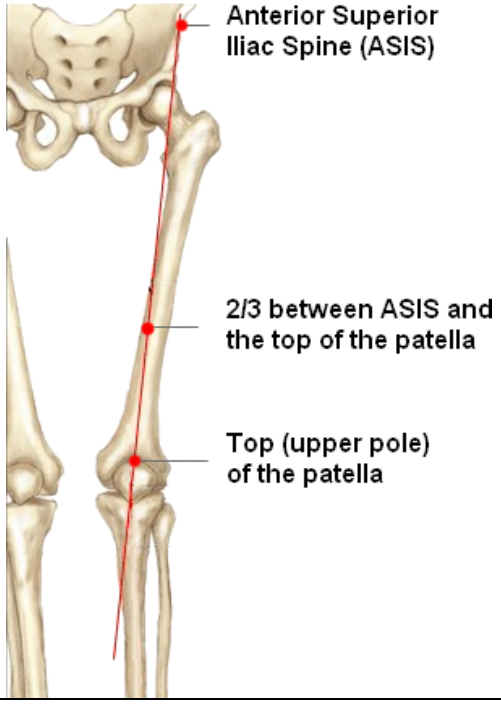
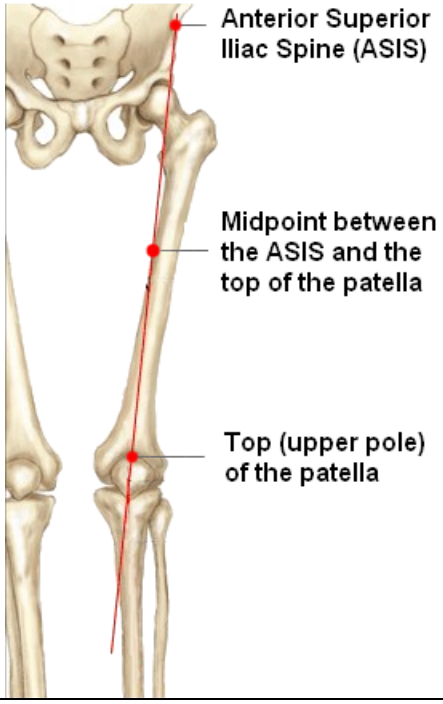
2. Tape measure

Procedure:

Please refer to the following link for a training video:
http://www.criticalcarenutrition.com/index.php?option=com_content&view=article&id=182&Itemid=79

1. Lay subject supine with knee extended and relaxed

2. Determine 2 points for measurement of quadriceps femoris muscle (see image on next page)

Reading #1	Reading # 2:
At the border between the lower third and upper two-thirds between ASIS and upper pole of the patella. 	At the midpoint between the ASIS and the upper pole of the patella. 

Note: In Obese patients, it may be very difficult to locate the ASIS. In such cases, note the distance from the upper border of the patella for all subsequent measures to be sure you are consistently coming back to the same place.

3. Provide generous amount of ultrasound gel to the thigh area that is to be assessed.

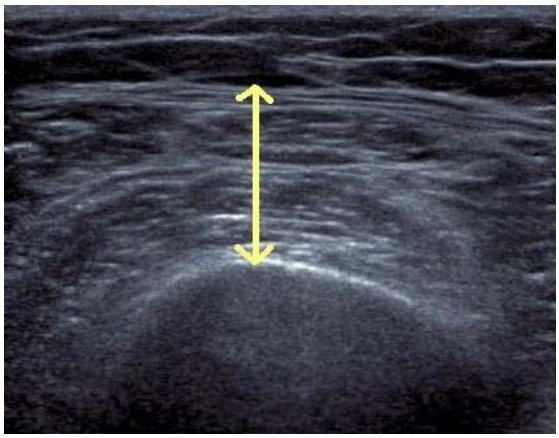
4. Hold the ultrasound probe perpendicular to the skin. Use large ultrasound probe. (i.e. 5 mHz).

5. Start at maximum depth to identify the femur. ("Depth button") Set the electronic focus depth at the shallowest depth allowable to see the femur for the purposes of measurement.

6. Set frequency (2nd button on the left) at maximum allowable frequency (13mhz on the GE machine).

7. Compress the probe maximally to measure muscle thickness directly anterior to the shaft of the femur. One of the greatest sources of variability in the measurement is how hard you push the probe down.

Muscle measurement should include the area anterior to the femur and proximal to the adipose tissue (see image on next page).



8. Take measurements at 2 points indicated above
    - Measurement (roller ball or cursor); highlight caliper on screen
    - Mark proximal depth of muscle (press Set)
    - Mark depth @ surface of femur (press Set)
        - Make sure measurement line is perpendicular.
    - Check top left of screen for measurements.
    - Repeat the measurements on the other thigh

9. Record the measurements in cms on a copy of the mock eCRF. This is to be given to the Research Coordinator who will transfer the details to the electronic data capture system.

Muscle Function Testing

Weekly Study Ultrasounds								
		Femoral Ultrasound			Repeat Femoral Ultrasound			
	Date done YYYY-MM-DD	Left Reading (cm)	Right Reading (cm)	Done by (Name)	Left Reading (cm)	Right Reading (cm)	Done by (Name)	If Not done, reason
Baseline		2/3rd midpoint	2/3rd midpoint		2/3rd midpoint	2/3rd midpoint		
Week 2 (Day 8-14)		2/3rd midpoint	2/3rd midpoint		2/3rd midpoint	2/3rd midpoint		
Week 3 (Day 15-21)		2/3rd midpoint	2/3rd midpoint		2/3rd midpoint	2/3rd midpoint		
Week 4 (Day 22-28)		2/3rd midpoint	2/3rd midpoint		2/3rd midpoint	2/3rd midpoint		

10. Avoid measurements on patients who have had recent trauma/operative procedures to leg/hip/knee. Note anything on history relating to the limbs such as previous trauma, neurological disorders, hip or knee replacements.

11. Once test is completed, wipe gel off patient with dry cloth.

12. Wipe down ultrasound machine with Virox; do not use Virox on ultrasound probe. Clean probe with damp cloth only.

References:

Gruther W et al. Muscle wasting in intensive care patients: Ultrasound observation of the M. Quadriceps Femoris Muscle Layer, J Rehabil Med 2008; 40 Campbell et al. Muscle thickness, measured with ultrasound, may be an indicator of lean tissue wasting in multiple organ failure in the presence of edema, Am J Clin Nutr 1995; 62.10/25/2010

Abdominal/Pelvis CT Scans

In order to predict lean tissue mass in patients enrolled to the TOP UP Study, all CT scans including the L3 area done for clinical reasons are to be collected. Refer to the mock eCRFs for details on the Lumber CT Scans.

Muscle Function Tests at Discharge

The following data elements MUST be collected at ICU discharge and/or, hospital discharge as follows.

Hand-Grip Strength Test

The hand grip strength determines muscle strength in the dominant hand. A hand dynamometer will be sent to you prior to the start of the study at your site. Follow these instructions to conduct this test at **ICU discharge and at hospital discharge.** If hospital discharge occurs on the same day as or the day after ICU discharge, one set of 3 hand grip strength readings is acceptable.

1. Set the adjustable handle on the dynamometer to the desired spacing. (Before moving the handle from one position to another, note that the handle clip is located at the lower post (furthest from the gauge). IF the handle is not replaced in the correct position, the reading will not be accurate).

2. Rotate the red peak-hold needle counter clockwise to 0.

3. Have the patient sit down on a chair with an arm rest. The patients elbow should be flexed at a 90°angle.

4. Place the wrist strap on the patient's dominant hand and carefully hand over the instrument. Let the patient comfortably arrange the instrument in his/her hand.

5. Have patient squeeze with their maximum strength. Sustain for 5 seconds. The peak-hold needle will automatically record the highest force exerted.

6. Record the readings **in pounds** and reset the peak—hold needle to zero.

7. Repeat this 2 more times and record all 3 readings on the mock eCRF.

8. Use an alcohol wipe to clean/sterilize the handle of the dynamometer before use on the next patient.

Refer to Hand-Grip Strength Test Module for more details.

6-Minute Walk Test (6MWT)
This test measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes. The Research Coordinator will **conduct the 6-min walk test prior to hospital discharge.**

Contraindications
Absolute contraindications for the 6MWT include the following:

1. Unstable angina during the previous month

Relative contraindications

1. Resting heart rate of more than 120
2. Systolic blood pressure of more than 180 mm Hg
3. Diastolic blood pressure of more than 100 mm Hg
4. Myocardial infarction during the previous month

Patients with any of these findings should be referred to the PI for individual clinical assessment and a decision about the conduct of the test. The results from a resting electrocardiogram done during the previous 6 months should also be reviewed before testing. Stable exertional angina is not an absolute contraindication for a 6MWT, but patients with these symptoms should perform the test after using their anti-angina medication, and rescue nitrate medication should be readily available.

Safety Issues
Reasons for immediately stopping a 6MWT include the following:

1. Chest pain
2. Intolerable dyspnea
3. Leg cramps
4. Staggering
5. Diaphoresis
6. Pale or ashen appearance

If the Research Coordinator recognizes these problems and the appropriate responses, stop the test and allow the patient to sit or lie supine as appropriate depending on the severity or the event and the Research Coordinator's assessment of the severity of the event and the risk of syncope. **The following should be obtained based on the judgment of the Research Coordinator: blood pressure, pulse rate, oxygen saturation, and a physician evaluation. Oxygen should be administered as appropriate.**

Patient Preparation

1. Comfortable clothing should be worn.
2. Appropriate shoes for walking should be worn.
3. Patients should use their usual walking aids during the test (cane, walker, etc.).
4. The patient's usual medical regimen should be continued.
5. A light meal is acceptable before early morning or early afternoon tests.
6. Patients should not have exercised vigorously within 2 hours of beginning the test.

Measurement

A long corridor (30 metres) should be marked at the start and the end (1 lap = 60 metres). The length of the corridor should be marked every 3 m. A treadmill may NOT be used as a replacement. Ensure that the patient has a source of O2 (if needed) and a chair nearby.

1. Obtain the patient's current weight and record on the worksheet on **Appendix H.**

2. A "warm-up" period before the test should NOT be performed.

3. The patient should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. As a general guideline, you may want to measure pulse and blood pressure, if needed and make sure that clothing and shoes are appropriate.

4. Set the timer to 6 minutes. Assemble all necessary equipment (timer, clipboard, worksheet) and move to the starting point.

5. Give the following instructions to the patient (as a general guideline and can be modified to meet your patient's needs):

   "The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

   You will be walking back and forth around the cones (or marked area). You should pivot briskly around the cones (or marked area) and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."

   Demonstrate by walking one lap yourself. Walk and pivot around a cone (or marked area) briskly.

   "Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog.

   Start now, or whenever you are ready."

6. Position the patient at the starting line. You should also stand near the starting line during the test. Do not walk with the patient. As soon as the patient starts to walk, start the timer.

7. Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the patient. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, mark the lap on the worksheet. Let the participant see you do it. Exaggerate the click using body language, like using a stopwatch at a race.

   After the first minute, tell the patient the following (in even tones):
   "You are doing well. You have 5 minutes to go."

   When the timer shows 4 minutes remaining, tell the patient the following:
   "Keep up the good work. You have 4 minutes to go."

   When the timer shows 3 minutes remaining, tell the patient the following:
   "You are doing well. You are halfway done."

   When the timer shows 2 minutes remaining, tell the patient the following:
   "Keep up the good work. You have only 2 minutes left."

   When the timer shows only 1 minute remaining, tell the patient:
   "You are doing well. You have only 1 minute to go."

   Do not use other words of encouragement (or body language to speed up). If the patient stops walking during the test and needs a rest, say this:

   "You can lean against the wall if you would like; then continue walking whenever you feel able."

   Do not stop the timer. If the patient stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair over for the patient to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.

   When the timer is 15 seconds from completion, say this:
   "In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you." When the timer rings (or buzzes), say this: "Stop!"

   Walk over to the patient. Consider taking the chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.

8. Post-test: Ask this:
   "What, if anything, kept you from walking farther?"

9. Record the total distance walked, rounding to the nearest meter, and record it on the worksheet on **Appendix H**.

10. Congratulate the patient on good effort and offer a drink of water.

Data Collection at discharge and Follow up (SF 36 at 3 and 6 months)

Barthel ADL Index at DIscharge
The Barthel ADL (Activities of Daily Living) Index is used to determine the level of patient independence at hospital discharge and should reflect the patient's performance over the preceding 24-48 hrs. Refer to the Baseline ADL Index (Hospital Discharge) mock eCRF instructions for more details.

SF 36 at 3 and 6 months
An SF-36 Quality of Life survey is to be done at baseline and at 3 and 6 months after **ICU admission.** If a subject cannot be reached to obtain the information, an effort must be made to determine the reasons.

- The **baseline SF-36** Quality of Life survey should be completed with the patient's family/next of kin as soon as possible **after** consent has been obtained.

- The **3 month SF-36** Follow-up survey may be done within 2 weeks before and 6 weeks after 3 months from ICU admission, i.e.: Anytime from 2.5 months to 4.5 months after ICU admission.

- The **6 month SF-36** Folllow-up survey may be done within +/- 6 weeks of 6 months after ICU admission, i.e.: Anytime from 4.5 months to 7.5 months after ICU admission.

It is encouraged to schedule reminders in your calendar for the follow up interviews.

Other Study Procedures
The Research Coordinator will follow study specific procedures related to the following:

a. Daily monitoring of patient's health and safety
b. Daily Monitoring of compliance with Investigational product (see **Appendix I** Daily Monitoring Log)
c. Identification and reporting of Protocol Violations (see **Appendix I**)
d. Identification and reporting of Unexpected Serous Adverse Events (see **Appendix I**)
e. Infection adjudication based on antibiotic and microbiology data
f. Data Collection including resolution of data queries
g. Maintenance of Regulatory Documentation
h. Ethics Board submissions, renewals and communications

Protocol Violations

A Protocol Violation is defined as non-compliance with the study protocol and/or procedures that may impact study participant safety, the integrity of study data and/or study participant willingness to participate in the study.

For the TOP-UP Study, a Protocol Violation occurs when any of the following have occurred:

Supplemental PN group only:

- **Enteral Nutrition/Parenteral Nutrition or EN + PN combined infusion rate is < 80% prescribed rate**
  - Example: if the prescribed daily volume is 1800 mls and the patient received <1440 mls in the 24 hr period, this is a protocol violation

- **Enteral Nutrition/Parenteral Nutrition or EN + PN combined rate is > 120% prescribed rate**
  - Example: if the prescribed daily volume is 1800 mls and the patient received >2160 mls in the 24 hr period, this is a protocol violation

Exceptions to < 80% prescribed volume received: Day of randomization, day of ICU discharge or death, and days subsequent to ICU discharge.

EN group only:

- **Received study parenteral nutrition before 7 days post randomization**

Both groups:

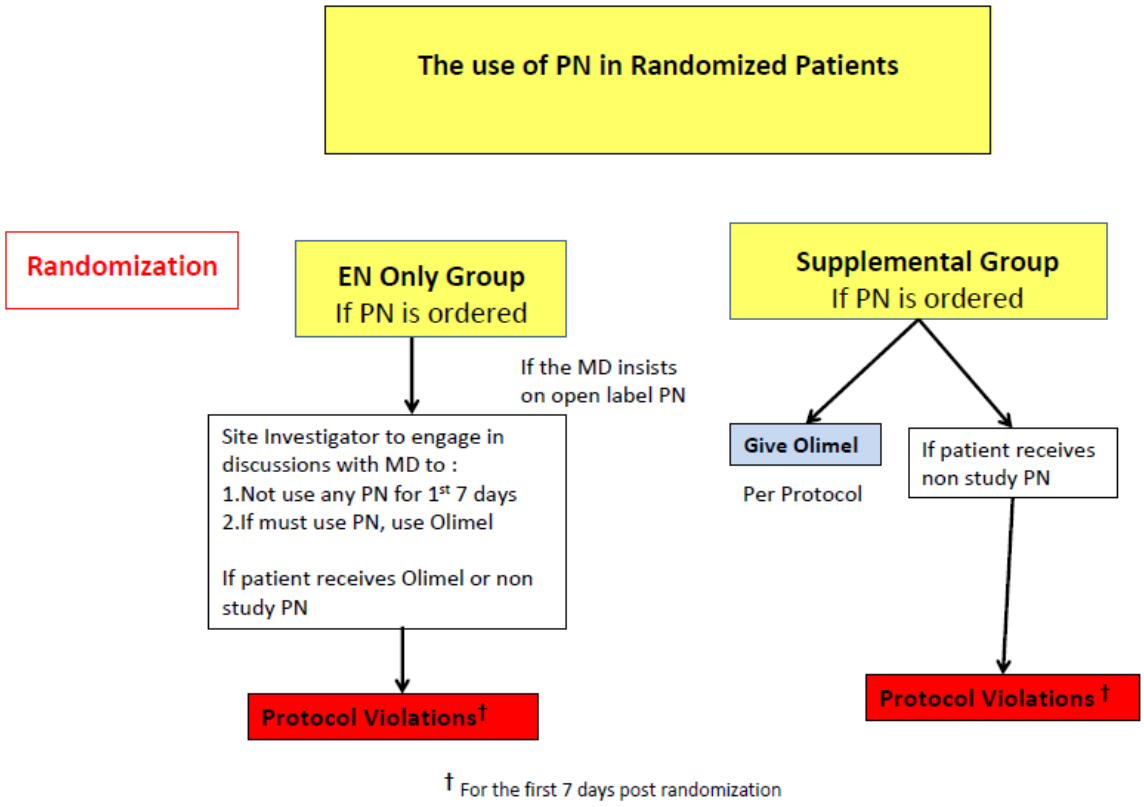
- **Dispensing/dosing error** (an incorrect dose/product was given to patient)
- **Enrollment of ineligible patient** (i.e. does not fulfill inclusion/exclusion criteria)
- **Unapproved procedures performed** (failure to obtain consent, taking blood draw on an extra day, etc)
- **Received non study parenteral nutrition before 7 days post randomization***
- **Received non study lipids before 7 days post randomization***
- **Received supplemental glutamine (EN/IV) before 7 days post randomization***
- **Received probiotics before 7 days post randomization***

REMEMBER: *7 days post randomization = the day of randomization PLUS an additional 7 FULL days.

All Protocol Violations must be reported to the Project Leader within 24 hrs of becoming aware. A protocol violation form must be completed in REDCap, printed and faxed to the Project Leader at (613) 548-2428.

A Protocol Violation form (for < 80 % volume) does not have to be completed for the day of randomization, day of ICU discharge and days subsequent to ICU discharge.

See below for diagrammatic summary of the Use of Parenteral Nutrition and Protocol Violations



Depending upon the type of the violation, the site may have to report the violation to their local Ethics Board. It is the responsibility of the site to determine this at the time of occurrence of the violation.

Refer to the Protocol Violation Form (also in mock eCRFs). See next page

TOP UP

Site Number ___ - Enrollment Number ___

Protocol Violation Report

1. **Date violation occurred** 2 0 Y Y M M D D

2. **Date violation discovered** 2 0 Y Y M M D D

3. **Is the local site investigator aware of the violation?** ☐ Yes ☐ No

4. **Was the Protocol Violation related to either < 80% or > 120% volume (Supplemental PN group only) ?**	☐ Yes, <80% Prescribed	Percent of PN/EN received: _____ % Reason for violation (check all that apply) ☐ a. No central line access ☐ b. Held for procedure/OR ☐ c. Refeeding syndrome ☐ d. Abnormal blood work ☐ e. Other, specify details or attach Note to File/Incident Report: _____ _____
	☐ Yes, >120% Prescribed	Percent of PN/EN received: _____ % Reason: _____
	☐ No	

5. **Other Types of Violations (check all that apply)**

☐ a. Dispensing/Dosing error
Details:
_____

☐ b. Enrollment of ineligible patient
Details:
_____

☐ c. Unapproved procedures performed
Details:
_____

☐ d. Received non-study PN before 7 days
Details:
_____

☐ e. Received study PN before 7 days **(EN only group)**
Details:
_____

☐ f. Received non-study IV lipids before 7 days
_____ Total time (min) _____ Volume (ml)

☐ g. Received any of the following before 7 days
☐ i. Supplemental Glutamine (EN/IV)
☐ ii. EN Probiotics
Details: _____

☐ h. Other, please specify: _____

6. **Details of protocol violation including action taken by Research Coordinator/Responsible Delegate** Study procedures reviewed, RN education, REB notification, Note To File, etc… _____

_____

_____

Serious Adverse Events

This section refers to the procedures followed by the participating site for the reporting of Serious Adverse events to the Clinical Evaluation Research Unit (CERU). CERU will forward these reports to the appropriate regulatory bodies, sites and the manufacturer, as per required timelines.

A **Serious Adverse Event (SAE**) is defined as any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (refers to an event in which the study participant was, in the opinion of the qualified investigator (QI), at risk of death from the event if medical intervention had not occurred. NOTE: This does not include an event that hypothetically had it occurred in a more serious form, might have caused death).
- Results in persistent or significant disability/incapacity (i.e. a substantial disruption in an individual's ability to conduct normal life functions).
- Requires in patient hospitalization possibly related to the use of the study materials,
- Prolongs of hospitalization.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above medically important condition

Unexpected Serious Adverse Event (SAE)

For the purposes of the TOP UP Study, an Unexpected event is defined as an event that is not identified in nature, severity, or frequency in the current investigator brochure/package insert or, in the opinion of the qualified investigator, is not consistent with the progression of the underlying disease.

All events that are serious AND unexpected MUST be reported to Clinical Evaluation Research Unit (CERU) within 24 hrs of becoming aware of the event, regardless of the relationship of the intervention to the event.

Examples of serious and unexpected SAEs and hence MUST be reported to CERU within 24 hrs of becoming aware of the event:

- Cardiac arrest in a patient without a history of cardiac disease.
- New seizure in the absence of a previous seizure disorder.
- Worsening encephalopathy in the absence of liver disease.

What about unexpected death?
All serious events that result in unexpected death MUST be reported to CERU within **24 hrs** of becoming aware of the event. For example: a patient is improving and getting better but then dies unexpectedly the next morning. This is a serious adverse event (results in death) and was unexpected and is to be reported immediately.

What about expected death?
For example, a patient develops fulminant sepsis is not improving, now has multi-organ system failure. Family has agreed to withdraw treatment and patient dies. This is a serious adverse event but death was expected due to the progression of the underlying disease (sepsis). Do not need to report to CERU.

NOTE: As a guideline, events that are captured in the Case Report Forms (CRFs) such as newly acquired infections, bleeding complications, organ dysfunction, etc are considered to be <u>expected</u> events and hence <u>do not</u> need to be captured as SAEs.

As with any study there may be other risks or side effects that we do not know about with administration of these study supplements. The Site Investigator must adhere closely to the ICH-GCP Guidelines, however when in doubt he/she can contact the Project Leader for the study.

Adverse Events
Adverse events are any untoward medical occurrences in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. Given the high acuity of diseases and morbidity related to critical illness, adverse events are NOT to be reported to CERU.

However, individual ethics boards/national regulatory bodies may require the reporting of adverse events (not serious). It is the responsibility of the site investigator to check with their respective ethics boards/regulatory bodies.

Role of Site Investigator
While the Research Coordinator may identify a Serious Adverse Event, it is the responsibility of the Site Investigator to confirm the presence of the Serious Adverse Event, to determine the relationship of the event to the underlying disease and it's relationship to the study intervention.

When reporting a SAE, the Research Coordinator MUST consult with the Site Investigator/delegate. The latter must sign both the initial and follow up SAE forms.

Time Frames for SAEs reporting by Sites to CERU

This reporting to CERU is done in 2 phases:

1. The **Serious Adverse Events Initial Report *must*** be completed in REDCap and faxed to CERU **within 24 hrs** of becoming aware of each event.

2. The **Serious Adverse Events Follow-up/Final Report *must*** be completed and faxed to CERU **within 10 days** from becoming aware of the event. The Project Leader will collaborate with the Site Investigator to assess the need for additional details and further follow-up reporting.

Events must be Serious Adverse Events and unexpected

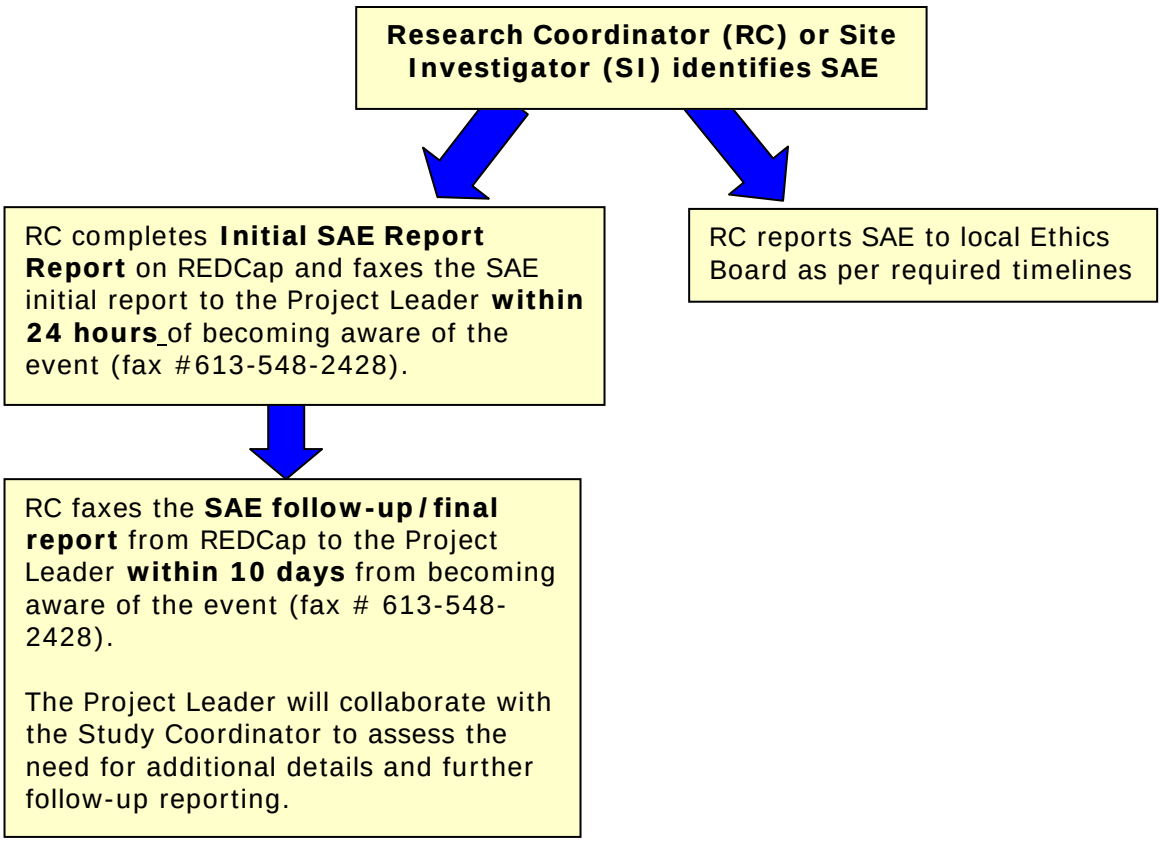
A **serious adverse event** (experience) or reaction is any untoward medical occurrence that at any dose,

- Results in **death**
- Is **life threatening**
- Requires or prolongs **in-patient hospitalization**
- Results in persistent or significant **disability/incapacity**
- May require **medical or surgical intervention** to prevent one of the other outcomes to defining serious
- Is a **congenital anomaly/birth defect**

An **unexpected** adverse event is that event that is NOT expected due to the progression of the underlying disease or co-morbid illnesses.

Examples of unexpected events:

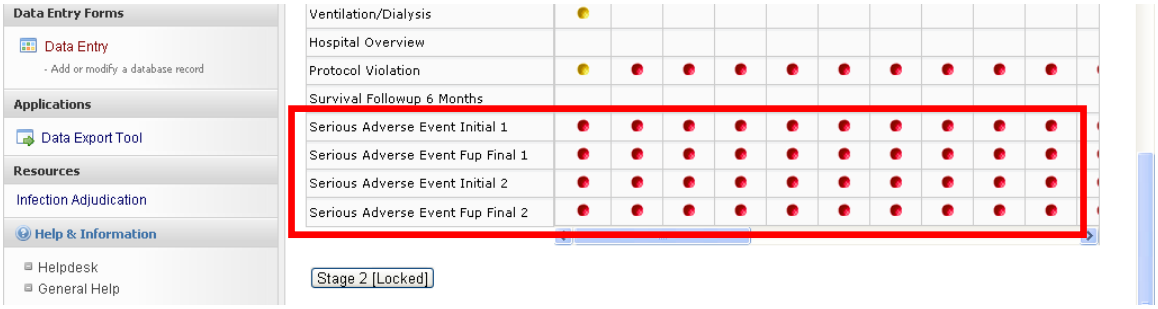
- Patient without a history of cardiac disease that has a cardiac arrest.
- Patient with new seizure in the absence previous seizure disorder
- Patient with worsening encephalopathy in the absence of liver disease
- Patient that develops an ischemic bowel in the absence of massive fluid resuscitation or increased abdominal pressure/abdominal compartment syndrome



SAEs on REDCap

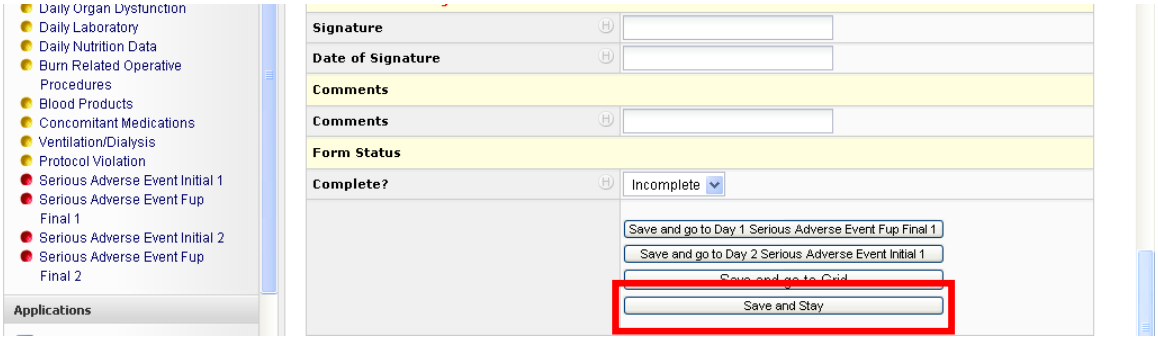
SAE forms must be completed on REDCap, the web-based system that will be used for the TOP-UP Study. REDCap may be accessed via http://www.criticalcarenutrition.com or directly at: https://ceru.hpcvl.queensu.ca/EDC/redcap/

The SAE forms are listed at the bottom of the Event Grid.

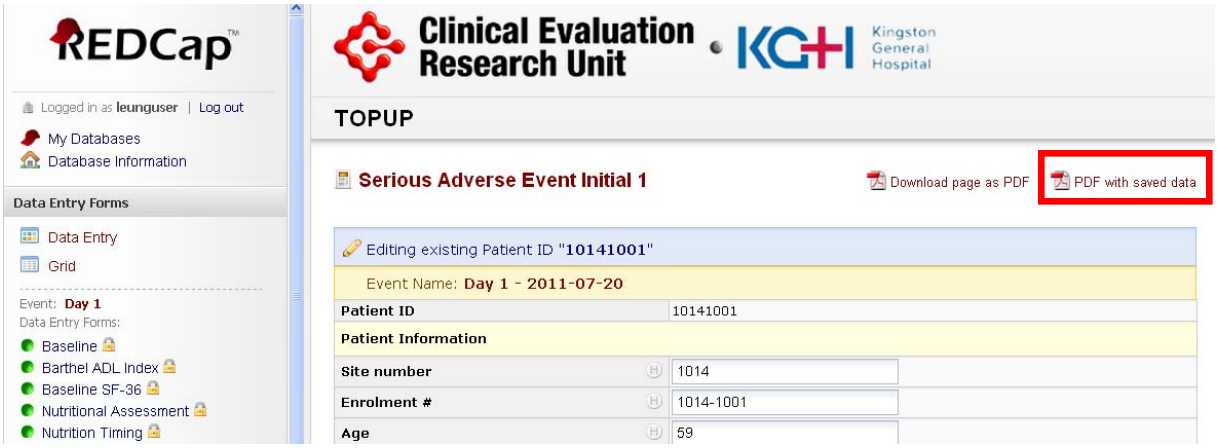


Refer to the worksheets provided for the data elements required. All SAEs must be entered in real time into REDCap.

Upon completing the form, save the form.



After saving the form, save as a PDF using the button shown below onto your desktop. **Print the PDF copy.**



The Site Investigator must sign the hard copy and the form. Fax the signed form to CERU at 613-548-2428. Include all additional documents indicated on the SAE form with the fax.

Initial SAE Report

All Serious Adverse Events that are unexpected must be reported to CERU **within 24 hrs** of becoming aware of the event by filling out the **Serious Adverse Events Initial Report on REDCap** (see worksheet on next page).

This form must be completed by the Site Investigator/delegate in consultation with the Research Coordinator and requires the signature of the Site Investigator.

Only include those SAEs that occur during the study period. This includes the period from the time of randomization to the end of the study period (28 days post ICU admission). For a SAE that occurred during the study period and is still not resolved by the end of the study period, refer to section on SAE follow up.

All known data elements on the form must be completed within 24 hrs of discovery of the event. It may be that certain aspects of the form may change (for example, the date of recovery may not be known at the time of reporting) and this should be made clear in the narrative form that will follow at a later date.

The following fields of the Initial form must be completed:

- Patient identification
  - Your TOP UP **site number**
  - TOP UP **enrollment number**
  - Patient's **initials**
  - **DOB** (date format dd/mmm/yyyy)
  - Gender, select **male** or **female**
  - **Height** (cm)
  - **Weight** (kg)
- **Name of Site Investigator**
- **Name of person reporting the SAE**
- **SAE #:** Record the sequential SAE # for the patient; i.e. for the first SAE for the patient, enter 01. For the second SAE for the patient, enter 02.
- **Serious Adverse Event Reported (only one per form):**
  Record the event that you are reporting (must be serious and unexpected).

  Do NOT record death (outcome) as a SAE but the underlying cause of death.

  Do not record respiratory failure as a SAE but what was felt to cause the respiratory failure i.e. sepsis.

- **Date SAE reported**
- **Date became aware of SAE**
- **Seriousness of the SAE:** (select all that apply):
  - patient died (if so, record this date in the Outcomes section)
  - life threatening
  - requires or prolongs hospitalization
  - results in persistent or significant disability/incapacity
  - may require medical or surgical intervention to prevent one of the other outcomes.
  - congenital anomaly/birth defect
  - other serious medical event
- **Outcomes:** Select **the most** appropriate at the time of the initial report:
  - complete recovery/return to baseline (include date of recovery)
  - alive with sequelae
  - death (include date of death)

- SAE persisting
- unknown/lost to follow up

- **Record the date (dd/mmm/yyyy format) and time (hh:mm) for the following:**
  - Onset of SAE
  - ICU admission
  - Start of study supplement
  - Stop of study supplement (if available at the time of this report)

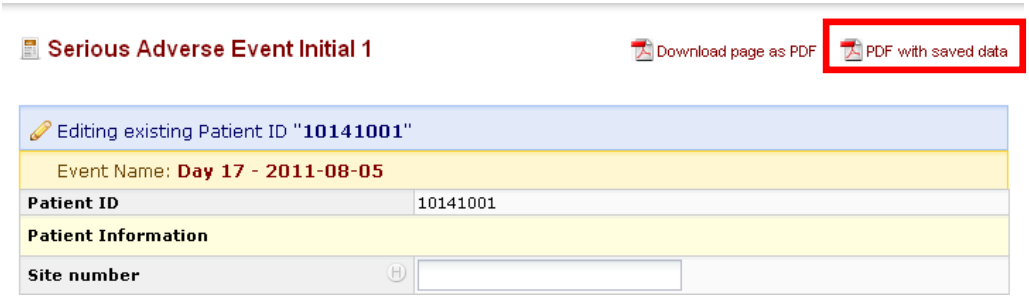
- **Action taken:** Select **all** that apply from the following
  - none
  - uncertain
  - procedure or physical therapy
  - blood or blood products
  - prescription drug therapy
  - non-prescription drug therapy
  - hospitalization
  - IV fluids
  - Other

- **Action taken with Study Supplements:** Select **only one** of the following:
  - none (including not on study supplements)
  - dose reduced, interrupted or therapy delayed (include date/time)
  - study supplements stopped permanently due to SAE (include date/time).

- **Relationship of SAE to the study supplements:** The determination of the relationship of the event to the supplements is to be done by the Site Investigator/delegate in collaboration with the Research Coordinator. To assist the Investigator in making this assessment, the following definitions have been provided (select **only** one):
  - **Not related:** A serious adverse event that is clearly due to extraneous causes (disease, environment, etc.) and does not meet the criteria for drug relationship listed under "Possibly" or "Probably".
  - **Unlikely related:** A serious adverse event that is more likely due to other causes than the study supplements
  - **Possibly related***:* Suggests that the association of this SAE with the study supplements is unknown and the event is not reasonably supported by other conditions.
  - **Probably related***:* Suggests that a reasonable temporal sequence of this SAE with study supplement administration exists and the association of the event with the study supplement seems likely.

Once SAE form completed, save by clicking "PDF with saved data", print and fax to CERU along with the SAE Cover Sheet (**Appendix J**) at

 # 613-548-2428
Attention: Project Leader TOP UP



See the following page for the Initial Report Worksheet.

The TOP-UP© Study

Serious Adverse Events (SAE) - Initial Report Worksheet

Go to the REDCap SAE forms and complete the the INITIAL SAE report. Save, print off and fax to CERU at 613 548 2428 attention: Project Leader within **24 hours** of becoming aware of the event.

Complete one form for **EVERY** adverse event that is Serious and Unexpected. Report only those SAEs that occur from the time of intervention to 28 days.

Patient Information

Site number | Initials | ◯ Male | Height (cm) | Name of Site Investigator | SAE #

Enrolment # | DOB (Date (yyyy-mm-ddy)) | ◯ Female | Weight (kg) | Person Reporting SAE

Record the sequential SAE # for the patient i.e. for 1st SAE for this patient, write 01; For 2nd SAE for this patient, write 02.

Description of Serious Adverse Event Reported (only one per form)

Date SAE reported (Date (yyyy-mm-ddy))

Date became aware of SAE (Date (yyyy-mm-ddy))

Seriousness (select all that apply)

- ◯ Patient died --> please document date in Outcomes
- ◯ Life threatening
- ◯ Requires or prolongs hospitalization
- ◯ Results in persistent or significant disability/incapacity
- ◯ May require medical or surgical intervention to prevent one of other outcomes.
- ◯ Congenital anomoly/birth defect
- ◯ Other serious medical event

Outcomes (at the time of initial report) - select only one

- ◯ Complete recovery/return to baseline - Date of recovery (Date (yyyy-mm-ddy))
- ◯ Alive with sequelae
- ◯ Death - death date (Date (yyyy-mm-ddy))
- ◯ SAE persisting
- ◯ Unknown/lost to follow-up

	Date (yyyy-mm-ddy)	Time(hh:mm)
Onset of SAE		
ICU admission		
Start of study supplement		
Stop of study supplement		

Signature of Site Investigator

Date (yyyy/mm/dd)

Action taken (select all that apply)

- ◯ None
- ◯ Uncertain
- ◯ Procedure or physical therapy
- ◯ Blood or blood products
- ◯ Prescription drug therapy
- ◯ Non-prescription drug therapy
- ◯ Hospitalization
- ◯ IV fluids
- ◯ Other (Specify in box)

Action taken with Study Supplement (select only one)

- ◯ None (including not on study supplement)
- ◯ Dose reduced, interrupted or therapy delayed (Date (yyyy-mm-dd) | Time(hh:mm))
- ◯ Study Supplement stopped permanently due to SAE (Date (yyyy-mm-dd) | Time(hh:mm))

Relationship of SAE to Study Supplement

- ◯ Not related
- ◯ Possibly related
- ◯ Unlikely related
- ◯ Probably related

Version: Oct 17, 2011

Follow-up Final SAE Report

For every SAE that was reported, a **Serious Adverse Events Follow-up/Final Report (see worksheet on the next page)** must be completed on REDCap and faxed to CERU within the following time frame:

- within 10 days from becoming aware of the event.

In the event that the event has not resolved, been explained or stabilized, the Project Leader will collaborate with the Research Coordinator for additional details and further follow-up reporting.

The Follow Up/Final SAE report **must be completed by the Site Investigator/designate** by reviewing the Serious Adverse Events Report (Initial) and the patient's medical chart. To make this process easier, it is strongly recommended that this be done as close to the event as possible.

Since the information in the Follow-up/Final Report will be reviewed by the Steering Committee, regulatory bodies and manufacturer, it **must** include details on the patients admitting diagnosis, co-morbidities, a chronological complete narration of the events leading to the SAE, the nature of the SAE, action taken with the study supplements, the outcome and the relationship of the event to the study supplements.

The following additional documentation is required and is to be attached to the follow-up/final report:

- Medication the patient received in the 48 hours before the onset of the SAE
- Laboratory results related to the SAE must also be provided.
    - Examples: if the event is cardiac arrest, provide cardiac enzymes; if the event is cholestasis/pancreatitis, provide liver function tests & amylases. For further clarification about which lab tests are relevant, the Research Coordinator is encouraged to ask the Site Investigator.

All data fields in the Follow-up/Final form must be completed:

- **Patient identification: Site #, Initials, enrollment #** and **SAE** # can be copied from the initial reporting form.
- **Patient medical history, co-morbid illness and reason for admission to hospital:** provide a detailed narrative of this information.
- **Admitting diagnosis to ICU and chronological events leading to the SAE:** provide a detailed narrative of this information
- **Chronological events proceeding the SAE until time of report:** provide a detailed narrative of this information and attach other reports/details as needed.
- **Concomitant Medications:** list all medications given within 48 hrs before the onset of the SAE.
- **Laboratory Results and Investigations:** record all lab results and investigations done that are pertinent to the SAE. For example, cardiac enzymes, ECG results in the event of a cardiac arrest.
- **Confirmation of Unexpected nature of the SAE:** record the pertinent clinical features that, in the opinion of the Site Investigator, made him/her think that the event was unexpected vs. due to the progression of underlying disease.
- **Relationship of SAE to the Study supplements:** The determination of the relationship of the event to the supplements is to be done by the Site Investigator/delegate in collaboration with the Research Coordinator. To assist the Investigator in making this assessment, the following definitions have been provided:
    - **Not related:** A serious adverse event that is clearly due to extraneous causes (disease, environment, etc.) and does not meet the criteria for drug relationship listed under "Possibly" or "Probably".

- **Unlikely related:** A serious adverse event that is more likely due to other causes than study supplement.
- **Possibly related***:* Suggests that the association of this SAE with the study supplement is unknown and the event is not reasonably supported by other conditions.
- **Probably related***:* Suggests that a reasonable temporal sequence of this SAE with study drug administration exists and the association of the event with the study supplement seems likely.

- **Rationale for relationship of the SAE to the study supplements vs. progression of underlying disease:** If the event is considered to be related to the study supplement, record the pertinent clinical features that, in the opinion of the Site Investigator, made him/her think that the event was related to the study supplements vs. the progression of underlying disease. Refer to the definitions of degree of relationship to the study supplements (not related, unlikely related, possibly related, probably related).

- **Outcomes:** Select **the most** appropriate at the time of the FOLLOW-UP report
  - complete recovery/return to baseline (include date of recovery)
  - alive with sequelae
  - death (include date of death)
  - SAE persisting
  - unknown/lost to followup

- **Action taken:** Select **all** actions taken from the onset of SAE, including those that occurred between the initial report and the follow-up report:
  - none
  - uncertain
  - procedure or physical therapy
  - blood or blood products
  - prescription drug therapy
  - non-prescription drug therapy
  - hospitalization
  - IV fluids
  - Other

- **Action taken with Study Supplements:**
  - none (including not on study supplements)
  - dose reduced, interrupted or therapy delayed (include date/time)
  - study supplements stopped permanently due to SAE (include date/time).

- **Event reported to IRB (Institutional Review Board) / REB (Research Ethics Board):** indicate whether this event was reported to your IRB/REB.

- **Further Details:** add any further details concerning the SAE.

The completed-**Follow-up/Final Report must** be entered and printed on REDCap, signed by the Site Investigator and **faxed to CERU with copies of the relevant medication and lab documentation** along with the SAE Cover Sheet (**Appendix J**) to:

 # 613-548-2428
Attention: Project Leader, TOP UP

See the following page for the Follow-up/Final Report Worksheet.

The TOP-UP© Study

Serious Adverse Events (SAE) - Follow-up/Final Report Worksheet

Patient Identification

Site # | Enrol. # | Initials | SAE #

Admitting diagnosis to ICU and chronological events leading to the SAE

Past medical history, allergies, co-morbid illness and reason for admission to hospital

Chronological events proceeding SAE until time of this report ☐ Further details attached

Concomitant Medications (List all concomitant medications given within 48 hours preceding the onset of the event)

Laboratory Results and Investigations (Related to the SAE) ☐ No relevant results to report

Serious Adverse Events (SAE) - Follow-up/Final Report Worksheet

Confirmation of unexpected nature of SAE (why not due to progression of underlying disease

Relationship of SAE to study supplement

- ◯ Not related
- ◯ Possibly related
- ◯ Unlikely related
- ◯ Probably related

Rationale for relationship of SAE to study supplements vs. progression of underlying illness (based on timing of supplement, SAE, etc...)

Outcomes (at time of fnal report)

- ◯ Complete recovery/return to baseline - Date or recovery yyyy-mm-dd
- ◯ Alive with sequelae
- ◯ Death - death date yyyy-mm-dd
- ◯ SAE persisting
- ◯ Unknown/lost to follow-up

Action taken

- ◯ None
- ◯ Uncertain
- ◯ Procedure or physical therapy
- ◯ Blood or blood products
- ◯ Prescritption drug therapy
- ◯ Non-prescription drug therapy
- ◯ Hospitalization
- ◯ IV fluids
- ◯ Other, specify below

Action taken with Study supplement

- ◯ None (including not on study supplement)
- ◯ Dose reduced, interrupted or therapy delayed yyyy-mm-dd Time(hh:mm)
- ◯ Study Supplment stopped permanently due to SAE yyyy-mm-dd Time(hh:mm)

Event Reported to IRB

- ☐ Yes
- ☐ No
- ☐ N/A

Further Details Concerning the SAE ☐ No further details to report

Signature of Site Investigator

Date

Version: Oct 17, 2011

SAE Follow up

Any subject who experiences a serious adverse event during the study period, should be followed by the Research Coordinator until the event:

- resolves
- an outcome is reached, or
- the event is otherwise explained or stabilized.

The Project Leader will follow up with the Research Coordinator at the site to obtain documentation regarding the status of the subject. This information will be forwarded to the Sponsor.

If follow-up information reveals that the event no longer meets the serious, unexpected, or drug related criteria, this information will be provided to the appropriate stakeholders.

Infection Adjudication

In order to determine the incidence of infections in patients enrolled to the TOP-UP study, the Site investigator/MD delegate is to determine the presence/absence of a newly acquired infection and the certainty of this.

A suspicion of infection is determined by the antibiotics received by the patient and the data on positive cultures. All antibiotics and cultures that lead to a suspicion of infection will be recorded on the appropriate electronic case report form (i.e. REDCAP).

Once a clinical suspicion of an infection has been identified, the Site Investigator/MD delegate MUST adjudicate the data to determine the following:

- Is there an infection or not
- Degree of certainty of the infection
- Category of Infection

Since the data related to the Infection Adjudication process is generated electronically and the adjudication is to be conducted on REDCAP, please refer to the CRS/REDCAP Manual for detailed instructions.

Appendices

A Delegation of Authority Log

B BMI Chart

C Enteral Nutrition Algorithm

D Product accountability/dispensing log

E Sample Temperature Log

F Paired Feeding Algorithm

G Duration of Data Collection

H Daily Monitoring Log

I 6-Minute Walk Test Worksheet

J SAE Cover Sheet

Delegation of Authority Log

This log is used by the Qualified Investigator (i.e. Site Investigator) to indicate the Site Staff that have a material effect on the conduct of the Study and to whom the Investigator has delegated significant Study related duties/tasks. The signatures and details on this log will also facilitate tracking of edits/changes of the Site records. This log is to be kept by the Qualified Investigator and the Sponsor.

Name of Qualified Investigator: _____ Signature of Qualified Investigator: _____

Print Name	Signature	Initials	Study Role (Qualified Investigator*, sub-QI*, Research Coordinator (RC), Pharmacist, Technician, Dietitian	Key Delegated Tasks Reference numbers (see next page)	Dates	
					Start	End

*Qualified Investigator: the Site Investigator responsible for the conduct of the TOP UP Study at your site
*Sub QI: Investigator other than the Qualified Investigator that is responsible for tasks related to the TOP UP Study at your site.

February 18th 2011 ICH GCP sections 4.1.5 and 8.3.24

Delegation of Authority Log

Key Delegated Tasks

Reference Number	Key Delegated Tasks
1	Screening subjects for eligibility
2	Conducting informed consent discussions for eligible patients
3	Obtaining written informed consent
4	Patient enrolment/randomization and follow-up
5	Checking eligibility criteria
6	Daily monitoring of patient health, safety and study compliance
7	Data collection, includes: ❖ Case Report Form entries ❖ Case Report Form corrections ❖ Data query resolution ❖ Hand Grip Strength tests ❖ 6 minute walk test
8	Source documentation maintenance, includes: ❖ Study worksheets, checklists, monitoring sheets ❖ Data from electronic & hard copy medical chart
9	Reporting of Protocol Violations/Unanticipated Problems involving risk
10	Identification of Serious Adverse Events and documentation
11	Maintenance of Regulatory Documents
12	REB submissions and communications
13	Perform study specific training
14	Perform Femoral Quadricep Ultrasound
15	Performing clinical assessments including burn outcomes, SAEs and ICU infection adjudication
16	Confirmation of completeness and accuracy of data collected
17	Maintenance of Product inventory
18	Checking of treatment assignment online
19	Study treatment dispensing & accountability, including maintenance of logs
20	Optimizing delivery of enteral nutrition and compliance with Guidelines for Nutrition

Appendix B: BMI Chart

WEIGHT lbs	100	105	110	115	120	125	130	135	140	145	150	155	160	165	170	175	180	185	190	195	200	205	210	215
kgs	45.5	47.7	50.0	52.3	54.5	56.8	59.1	61.4	63.6	65.9	68.2	70.5	72.7	75.0	77.3	79.5	81.8	84.1	86.4	88.6	90.9	93.2	95.5	97.7
HEIGHT in/cm																								
5'0" - 152.4	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
5'1" - 154.9	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	36	37	38	39	40
5'2" - 157.4	18	19	20	21	22	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	36	37	38	39
5'3" - 160.0	17	18	19	20	21	22	23	24	24	25	26	27	28	29	30	31	32	33	34	35	36	37	37	38
5'4" - 162.5	17	18	18	19	20	21	22	23	24	24	25	26	27	28	29	30	31	32	33	34	35	36	36	37
5'5" - 165.1	16	17	18	19	20	20	21	22	23	24	25	25	26	27	28	29	30	31	32	33	34	35	35	36
5'6" - 167.6	16	17	17	18	19	20	21	21	22	23	24	25	25	26	27	28	29	30	31	32	33	34	35	35
5'7" - 170.1	15	16	17	18	18	19	20	21	22	22	23	24	25	25	26	27	28	29	30	31	32	33	34	35
5'8" - 172.7	15	16	16	17	18	19	19	20	21	22	22	23	24	25	25	26	27	28	29	30	31	32	33	34
5'9" - 175.2	14	15	16	17	17	18	19	20	20	21	22	22	23	24	25	25	26	27	28	29	30	31	32	33
5'10" - 177.8	14	15	15	16	17	18	18	19	20	20	21	22	23	23	24	25	25	26	27	28	28	29	30	31
5'11" - 180.3	14	14	15	16	16	17	18	18	19	20	21	21	22	23	23	24	25	25	26	27	28	28	29	30
6'0" - 182.8	13	14	14	15	16	17	17	18	19	19	20	21	21	22	23	23	24	25	25	26	27	27	28	29
6'1" - 185.4	13	13	14	15	15	16	17	17	18	19	19	20	21	21	22	23	23	24	25	25	26	27	27	28
6'2" - 187.9	12	13	14	14	15	16	16	17	18	18	19	19	20	21	21	22	23	23	24	25	25	26	27	27
6'3" - 190.5	12	13	13	14	15	15	16	16	17	18	18	19	20	20	21	21	22	23	23	24	25	25	26	26
6'4" - 193.0	12	12	13	14	14	15	15	16	17	17	18	18	19	20	20	21	22	22	23	23	24	25	25	26

Appendix C: Enteral Nutrition Algorithm

TOP UP Enteral Nutrition Algorithm (for EN only group)

Nutrition Target = _____ml/hr (EN only)

STOP ENTERAL NUTRITION IF PATIENT DEVELOPS:
bowel obstruction
bowel perforation
paralytic ileus

Start Enteral Nutrition
preferably within 24-48 hrs of ICU admission
Use a standard formula 1.2 0.2 kcal/ml
Start at 25 ml/hr and ↑ by 25 mls q 4 hrs as tolerated

↓

Elevate HOB to 45 degrees where possible

↓

Check GRV q 4 hrs
(only if gastric feeding)
Is the GRV > 250 mls?

Yes → **If this is the 1st GRV > 250 ml:**
1) Refeed GRV to 400ml max and discard rest
2) Start motility agent (maxeran 10mg IV q 6 hrs)
3) Continue with Enteral Nutrition
4) Continue with checking GRV q 4hrs

No → 1) Refeed gastric residual
2) Continue with Enteral Nutrition

Yes ↓

Is this a rechecked residual that is > 250 mls?

No → 2) Continue with Enteral Nutrition

Yes ↓

1) Discard the residual
2) Continue with Motility agents
3) Switch to SMALL BOWEL FEEDING
4) Restart Enteral Nutrition

WATER FLUSHES:
Flush tube with at least 10 mls of sterile water:
- q4hrs during feedings
- after aspiration for GRVs
- before and after meds

BLOCKED TUBE:
Pancrealipase 8000 units mixed with crushed Na Bicarb 500mg in 5ml warm water prn

Blood work: as needed, according to usual practice at your ICU

Version: Oct 17, 2011

Investigational Product Dispensing/Accountability Log

Olimel 9E (Supplemental PN Group)

Site:

Page ____ of ____

The Investigational Product Accountability Log should be completed by the Research Coordinator/Pharmacist/delegate

Date IP received at site	# Olimel 1000ml bags received	#Olimel 1000ml bags destroyed	Lot #	Lot Expiration date	Subject number and initials	# 1000 ml bags dispensed	Date dispensed	Initials*	# 1000 ml bags returned	Initials†

*of site staff dispensing the investigational product – signature must be on delegation log

†of site staff acknowledging return of investigational product – signature must be on delegation log

Monthly Site Temperature Log

Store unmixed Olimel in overpouch between 15-30° C. Do not freeze.

Name of Site: _____ Research Coordinator/Pharmacist:_____ Month: _____Year: 20_____

Date	Temperature Low	Temperature Current	Temperature High	Date	Temperature Low	Temperature Current	Temperature High
01				16			
02				17			
03				18			
04				19			
05				20			
06				21			
07				22			
08				23			
09				24			
10				25			
11				26			
12				27			
13				28			
14				29			
15				30			
				31			

Signature of person submitting log: _____

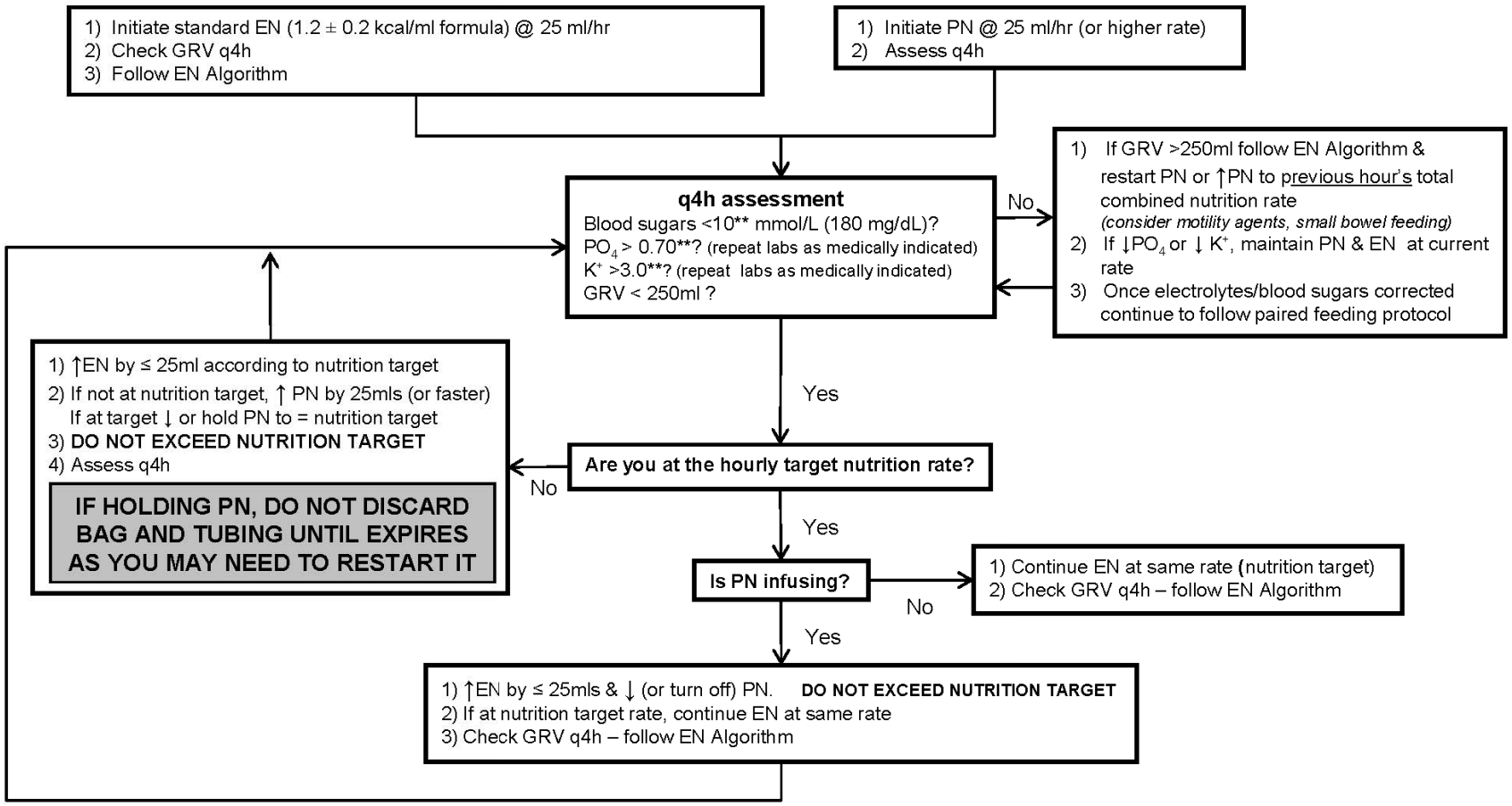
Fax completed form to: (613) 548-2428
Attention: CERU TOP UP Study (613) 549-6666 ext 3830

To be filled out by Site daily and faxed to Clinical Evaluation Research Unit (CERU) monthly.

TOP UP Paired Feeding Algorithm (for supplemental PN* group only)

Nutrition Target = _____ml/hr (EN/PN total)

Elevate HOB >45° where possible



If EN is held for any reason (ie OR, procedure, no gastric tube) then ↑ or restart PN at previous hrs nutrition rate. When restarting EN, start at previous rate and ↓ or hold the PN. For questions, please call the project leader at 613-549-6666 ext 3830

***PN refers to Olimel**

****or according to local ranges***

Version: Oct 17, 2011

Appendix F: Paired Feeding Algorithm

Version: August 7th 2013

Appendix G: Duration of Data Collection

Data/Test	STUDY DAY											
	ICU Admission (Study Day 1)	2	3	4	5	6	7	8-14	15-21	22-28	ICU Discharge, Hospital Discharge or Death	3 & 6 Month Follow-up
Barthel ADL Index	•										•	
SF-36 / Nutritional Assessment	•											•
Baseline	•											
Nutrition Timing	•											
Ventilation/Dialysis	•	•	•	•	•	•	•	•	•	•		
Daily Monitoring	•	•	•	•	•	•	•	•	•	•		
Daily Organ Dysfunction	•	•	•	•	•	•	•	•	•	•		
Daily Lab and IAP	•	•	•	•	•	•	•	•	•	•		
Weekly Lab	•							•	•	•		
Muscle Function Testing • Ultrasound	•							•	•	•		
• Hand Grip Strength											• ICU Discharge • Hospital Discharge	
• 6-min Walk test											• Hospital Discharge	
• Abdominal/Pelvis CT Scans/ Accompanying Ultrasounds	As Clinically Indicated (Including 1-2 days prior to ICU admission)											
Rehabilitation Practices	•	•	•	•	•	•	•	•	•	•		
Concomitant Medications	•	•	•	•	•	•	•	•	•	•		
Antibiotic, Antifungal, Antivirals	•	•	•	•	•	•	•	•	•	•		
Microbiology	•	•	•	•	•	•	•	•	•	•		
Infection Adjudication	According to Antibiotic and Microbiology Data											
Hospitalization Overview											•	
Protocol Violations	•	•	•	•	•	•	•	•	•	•		
SAE	•	•	•	•	•	•	•	•	•	•		

Appendix H: 6-Minute Walk Test Worksheet

6-Minute Walk Test Worksheet

The following elements should be present on the 6MWT worksheet and report:

Patient ID# _____

Research Coordinator Name: _____ Date: _____

Weight: _____ kg

Stopped or paused before 6 minutes? No Yes, reason: _____

Other symptoms at end of exercise: angina dizziness hip, leg, or calf pain

Total distance walked in 6 minutes: _____ meter

Other comments: _____

Appendix I: Daily Monitoring Log

Patient ID #:_____

Daily Monitoring Log

This data must be collected daily in real time. Please initial data entry at bottom of page.

Study Day		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
DD/MMM/YYYY								
Prescribed Volume of EN or EN + PN or PN (mL)								
Violations	Volume received (mL)	____	____	____	____	____	____	____
	Protocol Violation: > 80% OR	❐	❐	❐	❐	❐	❐	❐
	Protocol Violation: > 120%	❐	❐	❐	❐	❐	❐	❐
	Other Violation Type	❐	❐	❐	❐	❐	❐	❐
Was there a Protocol Violation today? If yes, fax to CERU within 24 hrs		Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
SAE	**Is there an SAE today that is SERIOUS and UNEXPECTED?** If yes, fax to CERU within 24 hrs	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N

AFTER 72 HOURS FROM ICU ADMISSION

Study Day		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
DD/MMM/YYYY								
MICRO	*If positive, is culture: (1) A manifestation of an infection that occurred within 72 hrs of ICU admission? **Consult with SI before answering**	N/A	N/A	N/A	Y** / N	Y** / N	Y** / N	Y** / N
ANTIBIOTICS	* If an antibiotic was administered today, was it prescribed: (1) For prophylaxis? (2) As a substitution? **Consult with SI before answering**	N/A	N/A	N/A	Y** / N Y** / N	Y** / N Y **/ N	Y** / N Y **/ N	Y** / N Y **/ N

***If NO to the micro question or NO to both antibiotic questions (or NO to all three questions),** flag this as a suspicion for a newly acquired infection that must be adjudicated by the Site Investigator. The infection adjudication can only be entered on to REDCAP after all daily data and ICU outcomes have been added, but you may ask the Site Investigator to adjudicate in real time. Refer to Implementation Manual for details.

If YES to micro question: ask Site Investigator if relapse/recurrent **or** persistent infection (see mock eCRFs)

Initials							

Appendix J: SAE Cover Sheet

Attention:	Rupinder Dhaliwal, Project Leader
Date:	
Fax Number:	613 548 2428
# Pages	____ (including coversheet)

FAX TRANSMISSION

Serious Adverse Event Information

Site Name: _____ Site Investigator:_____

Name of person sending fax:_____

REMINDER:

1. Please DO NOT submit hospital records/source documents unless requested.
2. If submitting REQUESTED source documentation, please ensure patient confidentiality by obscuring any reference to the patient's name and placing their subject ID and initials on the page.
3. If submitting answers to queries, all information needs to be recorded in English in clear and legible handwriting, including signatures.