THE RE-*ENERGIZE* STUDY

A RandomizEd Trial of ENtERal Glutamine to minimIZE Thermal Injury

Dietitian Manual

Intended Audience: Dietitians

This study is registered at Clinicaltrials.gov.
Identification number NCT00985205

Critical Care Nutrition

CIHR IRSC
Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

Clinical Evaluation Research Unit

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Document History

Version: Date	Superseded Version (Date)
Version 1: 10 December 2015	Original version
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Study Contacts

Name	Role	Contact Details
Dr. Daren Heyland	Principal Investigator, Coordinating Investigator	dkh2@ queensu.ca Cell: +1403-915-5573 Fax: +1613-548-2428
Maureen Dansereau	Project Leader	danserem@kgh.kari.net office: +1613-549-6666 ext. 6686 cell: +1613-888-4320 ***For urgent issues, if unable to reach PL or PI:*** Janet Overvelde CERU Operations Manager overvelj@kgh.kari.net office: +1613-549-6666 ext. 6241
IT Help Desk	http://www.ceru.ca/helpdesk/open.php	

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

In the event you are unable to reach the Project Leader, please contact the Principal Investigator (PI). If you are unable to reach either the PL or PI, please contact the CERU Operations Manager.

Glossary

ACU	Acute Care Unit (ICU or Burn Unit)
CERU	Clinical Evaluation Research Unit at Kingston General Hospital (Methods Centre)
CRF/eCRF	Case Report Form/electronic Case Report Form
CV	Curriculum Vitae
DAL	Delegation of Authority Log
EDCS	Electronic Data Capture System
EN	Enteral Nutrition
FDA	Food and Drug Administration (USA)
GCP	Good Clinical Practice
HC	Health Canada
hCG	Human Chorionic Gonadotropin (pregnancy indicator)
HOB	Head of Bed
IP	Investigational Product
PL	Project Leader or delegate
PN	Parenteral Nutrition
RC	Research Coordinator
REDCap™	Research Electronic Data Capture system
SAE	Serious Adverse Event
SD	Study Day
SI	Site Investigator
Sub-I	Sub-Investigator
po	per os (by mouth)

Study Synopsis

Overview
The primary purpose of this study is to determine the overall treatment effect and safety of enteral glutamine administration to severely burn injured patients in acute care units (ACUs). We assert that glutamine administration will decrease 6 month mortality, decrease hospital-acquired blood stream infections from Gram negative organisms, reduce acute care unit and hospital length of stay, and improve the physical function of surviving burn injured patients.

Study Design
A large, multicenter, double-blind, pragmatic, randomized controlled trial of 2700 patients with severe burns randomly allocated to receive enteral glutamine or placebo.

Setting
Approximately 60 tertiary acute care burn centres in Canada, the United States, Australia and Europe.

Study Population
2700 adult patients with deep 2nd and/or 3rd degree burns requiring skin grafting. For patients age 18 – 59 years we require a TBSA (Total Burn Surface Area) ≥ 20%, or in the presence of an inhalation injury, a minimum of 15 % TBSA is acceptable. For patients aged 60 years or older we require a TBSA ≥ 10%.

Study Intervention
Patients will receive glutamine or maltodextrin (placebo/control) through their feeding tube every 4 hours, or orally 3 – 4 times a day, for a total of 0.5 g/kg/day until 7 days after their last grafting operation, or discharge from the acute care unit, or 3 months after admission to the acute care unit, whatever comes first.

Outcomes

Primary outcome:	6-month mortality
Secondary outcome:	Time to discharge alive
Tertiary outcomes:	Health-related quality of life with particular focus on physical function Incidence of acquired bacteremia due to Gram negative organisms Hospital mortality Duration of mechanical ventilation Acute care unit length of stay Hospital length of stay

Trial Duration

Study Recruitment Period

4 years - based on approximately 1 patient per site per month, as demonstrated in the pilot study.

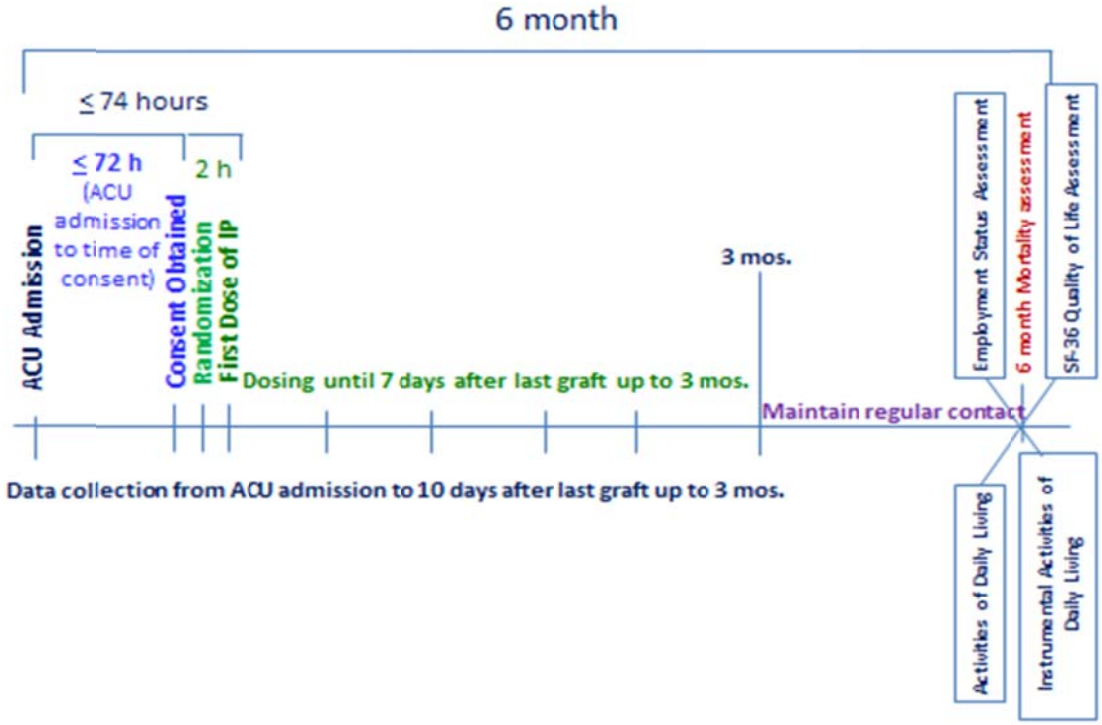
Estimated Total Study Duration

We anticipate the total study duration to be 5 years, broken down as follows:

6 month Start-up period
4 year recruitment period
6 month follow-up period

Diagram of Study Overview

Below is a diagrammatic representation of the RE-ENERGIZE Study. Refer to appropriate sections of the Study Procedures Manual for comprehensive instructions for study activities.



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. The Site Investigator is responsible for ensuring that s/he and the local staff are adequately trained in GCP (GCP 4.1.1).

Each **Dietitian** must have documented training on the RE-ENERGIZE study. Study specific training will be provided by CERU Staff and conducted either in person or via webinar.

Patient Population

Inclusion Criteria

1) **Deep 2nd and/or deep 3rd degree burns requiring grafting**
   The presence of deep 2nd degree and/or deep 3rd degree burns requiring grafting is an assessment that must be made by the surgeon/physician.

2) **Patient meets one of the following 3 criteria:**
   a. Patients 18 – 59 years of age with TBSA ≥ 20%
   b. Patients 18 – 59 years of age with TBSA ≥ 15% WITH inhalation injury
   c. Patients ≥ 60 years of age with TBSA ≥ 10%

Exclusion Criteria

1) > 72 hours from admission to Acute Care Unit (ACU) to time of consent
   This refers to admission to your ACU. If a patient is transferred from another facility, the clock starts form the time of admission to your unit. An exception would be a patient who has been an extended period of time at another facility post burn prior to admission to your unit.

2) Patients younger than 18 years of age

3) In patients **without known renal disease**, renal dysfunction defined as a serum creatinine >171 mmol/L or a urine output of less than 500 ml/last 24 hours (or 80 ml/last 4 hours if a 24 hour period of observation is not available).

   In patients **with acute on chronic renal failure** (pre-dialysis), an absolute increase of >80 mmol/L from baseline or pre-admission creatinine or a urine output of <500 ml/last 24 hours (or 80 ml/last 4 hours) will be required.

   Patients with **chronic renal failure on dialysis** will be excluded.

4) Liver cirrhosis -Child's class C liver disease

5) Pregnancy (urine/blood tests for pregnancy will be done on all women of childbearing age by each site as part of standard of ACU practice)

6) Contra-indication for EN: intestinal occlusion or perforation, intra-abdominal injury. (Being NPO is not considered a contraindication for Enteral Nutrition).

7) Patients with injuries from high voltage electrical contact.

8) Patients who are moribund (not expected to survive the next 72 hours in the judgement of the Site Investigator or delegated doctor in charge).
Note that an isolated DNR does not fulfil this criteria.

9) Patients with extreme body sizes: BMI < 18 or > 50 kg/m^2
Ideally BMI should be calculated using the patient's pre-burn dry weight. Given that there may be some subjectivity involved in the determination of BMI, err on the side of including the patient.

10) Enrollment in another industry sponsored ICU intervention study *(co-enrollment in all non-randomized academic studies will be approved. For academic RCTs, forward a synopsis or abstract of the study to the project leader to obtain pre-approval of the study to which you would like to co-enroll.*

11) Received glutamine supplement for > 24 hours prior to randomization.
This refers to consistent administration of glutamine over the 24 hr period prior to randomization. If the patient received random or intermittent doses of open label glutamine, discontinue the glutamine prior to randomization.

12) Known allergy to maltodextrin, corn starch, corn, corn products or glutamine.

Investigational Product

The active and control products will both be supplied in pre-packaged 5g packets. The active and control have the same visual appearance and taste.

Nutrestore™ (L Glutamine)
Nutrestore is an amino acid (L Glutamine) powder that is approved for oral use in short bowel syndrome by the FDA. L Glutamine is produced normally by the body and has important functions in regulation of gastrointestinal cell growth, function, and regeneration. Under normal conditions, glutamine concentration is maintained in the body by dietary intake and synthesis from endogenous glutamate. Data from clinical studies indicate that the role of and nutritional requirements for glutamine during burns, catabolic illness, trauma, and infection may differ significantly from the role of and nutritional requirements for glutamine in healthy individuals. Glutamine concentrations decrease and tissue glutamine metabolism increases during many catabolic disease states, and thus glutamine is often considered a "conditionally essential" amino acid.

Maltrin® M100 Maltodextrin (control)
The MALTRIN® M100 maltodextrin is produced by Grain Processing Corporation (GPC) and then packaged by Anderson Packaging for the trial. Maltodextrins are bland, low sweetness, pharmaceutical grade, white carbohydrate powders that are Generally Recognized As Safe (GRAS) as direct human food ingredients at levels consistent with current good manufacturing practices. They are prepared as a white powder by partial hydrolysis of corn starch with safe and suitable acids and/or enzymes. Patients will receive an iso-calorically delivered amount of maltodextrin (control) mixed with water or other liquids. Maltodextrin is a source of carbohydrate commonly found in standard enteral nutrition and has no metabolic effects other than serving as

a source of additional energy. The maltodextrin used in this study contains approximately 19 calories per 5g packet.

Dosing
Study intervention will be dosed in accordance with the patient's pre-burn dry weight and recorded in the eCRF. By dry weight, we mean prior to resuscitation and it is likely consistent with the usual weight recorded on a prior chart or obtained from a family member.

Patients will receive glutamine or maltodextrin through their feeding tube, every 4 hours enterally or TID to QID if po, for a total of 0.5 g/kg/day.

a) Patients with a BMI <35 will receive 0.5 g/kg/day of either glutamine or maltodextrin based on pre-burn dry weight (actual or estimated).
b) Patients with a BMI ≥35 will receive 0.5 g/kg/day of either glutamine or placebo (maltodextrin) based on the adjusted body weight, as per calculation below.

Adjusted Body Weight (ABW) = Ideal Body Weight (IBW) based on a BMI of 25 + [(pre-burn dry weight – IBW) x 0.25]

The patient's IP dosing weight should only be changed IF the clinical team changes the weight used for drug dosing. If the clinical team changes the weight used for drug dosing due to a clinically significant change in the patient's weight, the pharmacy will be notified and the study intervention dose adjusted in accordance with the patient's current drug dosing weight. Associated data will be recorded in the eCRF.

Duration

Patients will receive the study intervention from randomization until 7 days post last successful grafting operation, or until acute care unit discharge, or until 3 months after acute care unit admission, whatever comes first.

We recognize that defining the end of study treatment phase by 7 days post last successful graft may not be very exact or precise. There may be unique features to some patients that make it difficult to define. As guidance, we generally mean when the patient is over the acute phase of their illness and either discharged from the acute care unit or entering in their rehabilitation phase.

Standardization of Nutrition Practices

We recommend all study patients be fed in accordance with the Standardization of Nutrition Practices.

Given the metabolic complications and increased nutritional requirements in burns patients, the provision of nutrition support is a challenging task and variability in nutrition practices across burn units exists[1]. To reduce the effect of varying nutritional practices as confounding factors on the outcomes of The RE-ENERGIZE study, it is important to standardize, *as much as possible*,

the prescription of enteral and parenteral nutrition, micronutrient delivery and practices related to withholding feeds for high gastric residual volumes and use of motility agents in these patients.

Based on the literature and providing for some flexibility for current practices across the participating sites, we are recommending compliance with the following nutritional practices for all patients enrolled in the study. After reviewing the practices at all the participating sites, these ranges below will allow for most current practices to continue.

1) **Prescribed Energy needs are to be calculated using** Indirect Calorimetry, a predictive equation, or a simple weight-based formula but on average, should not lead to a prescription of less than 30 kcal/kg.

   Use pre-burn dry weight. For Obese patients, if your standard practice is to adjust for obesity, follow your standard practice. If you do not have an obesity adjustment practice, use the formula below.

   Adjusted Body Weight (ABW) = Ideal Body Weight (IBW) based on a BMI of 25 + [(pre-burn dry weight – IBW) x 0.25]

2) **Prescribed Protein needs are to be calculated using the following:**

   According to % burn surface area

   i. If > 50% burns, use 1.5 g/kg*/day to 2.5g/kg*/day
   ii. If < 50% burns, use 1.2 g/kg*/day to 2 g/kg*/day

   Pre-burn dry weight* should be used when calculating protein needs. For Obese patients, if your standard practice is to adjust for obesity, follow your standard practice. If you do not have an obesity adjustment practice, use the formula below.

   Adjusted Body Weight (ABW) = Ideal Body Weight (IBW) based on a BMI of 25 + [(pre-burn dry weight – IBW) x 0.25]

3) **Vitamin & Mineral Prescription should be given as follows or depending upon blood levels (if blood testing is done as part of routine practice) :**
   - Vitamin C: 0-1000 mg/day
   - Vitamin A: 0-10,000 IU/day
   - Vitamin D: according to serum levels
   - Vitamin E: 0-420 mg/day
   - Zinc (not elemental): 0-220 mg/day
   - Copper Sulfate: 0-4.5 mg/day
   - Selenium: 0-500 micrograms/day
   - Magnesium:0-600 mg/day
   - Folate: 0-1500 mg/day
   - Thiamin: 0-110 mg/day

Early supplementation by high dose IV Vitamin C (66 mg/kg/hr) within the first 48 hrs is allowed [2]. Standard multivitamin/mineral preparations are allowed (IV, NG or po).

These ranges of vitamins/minerals/trace elements may be provided as supplementation over and beyond what is present in the standard enteral/parenteral nutrition.

OR

These ranges of vitamins/minerals/trace elements may be provided as the total amounts. This means that the amounts received from enteral/parenteral nutrition are to be subtracted from the total ranges and the remainder is given as supplements.

4) Specialized nutritional formulas are not allowed such as:

i. Arginine enriched formulas (formulas that contain arginine > 6 g/L), eg:
- Pivot® (13 g/L)
- Perative (8 g/L)

ii. Glutamine supplements or formulas enriched with glutamine, eg:
- Impact® Glutamine (15 g/L)
- VIVONEX® Plus (13.5 g/L)
- GLUTASOLVE® (15 g/L)/other glutamine powders
- Juven® (7 g/L)

Formulas with glutamic acid inherently present are allowed

To minimize any potential contamination, patients that have received glutamine for >24 hrs before randomization, should NOT be included.

5) Optimization of the Delivery of Enteral Nutrition:
The use of enteral nutrition is preferred over parenteral nutrition in burn patients. Interruptions to the delivery of enteral nutrition should be minimized while adopting strategies to optimize the delivery of EN such as elevating the head of the bed to a minimum of 45 degrees (unless otherwise contraindicated), using a minimum gastric residual volume threshold of 250 ml (if you use a larger GRV threshold, that is acceptable), and the use of motility agents and small bowel feeding tubes as clinically indicated. Refer to Enteral Feeding Protocol in the Appendix A for more details.

Ongoing monitoring of the volumes of delivery of enteral nutrition and an action plan to ensure that the recommended prescribed needs are being met is recommended as part of the study protocol.

6) Glycemic control:
The use of a glycemic control protocol (or the use of insulin) to control blood sugars between the ranges of at least 80 mg/dL to a maximum of 180 mg/dL (4.4-10 mmol/L) is recommended in order to avoid hyperglycemia, while minimizing the risk of both iatrogenic hypoglycemia and other harms associated with a lower blood glucose target.

Data Collection

Data for the RE-ENERGIZE study are to be collected from ACU admission through 10 days post last successful graft, ACU discharge, or 3 months from ACU admission, whichever comes first.

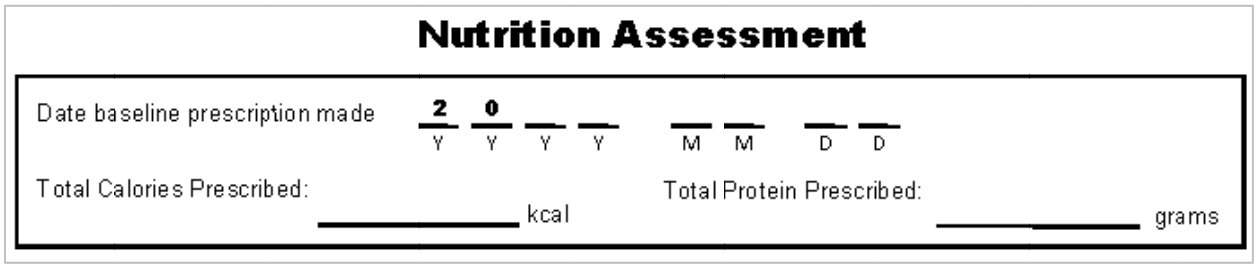
Worksheets for collecting data related to nutritional assessment and adequacy are provided for convenience. Whether recording data on the worksheet or completing the data in the patient's chart, please ensure the research coordinator has access to the information for entry into the EDCS.

Nutrition Assessment/Timing (see Appendix B)
Prescribed Energy and Protein Needs
Record the date in the Baseline Assessment box that the initial energy and protein needs were assessed by the dietitian, or physisican if no dietitian available, after the patient was admitted to the ACU. If prescription information is not available, we will use the following:

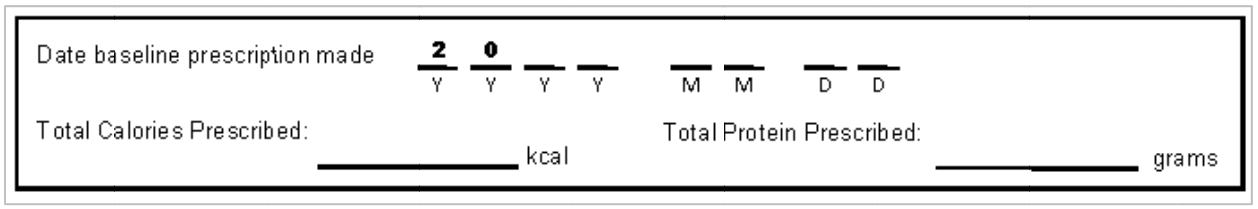
- Calories = 25 kcal/kg/day
- Protein = 1.2 g/kg/day

Record the energy prescribed in kcals
Record the protein prescribed in grams

If the energy and protein prescription changes during the study period, record the date and the new prescription for calories and protein on the Nutrition Assessment/Timing form (example below).

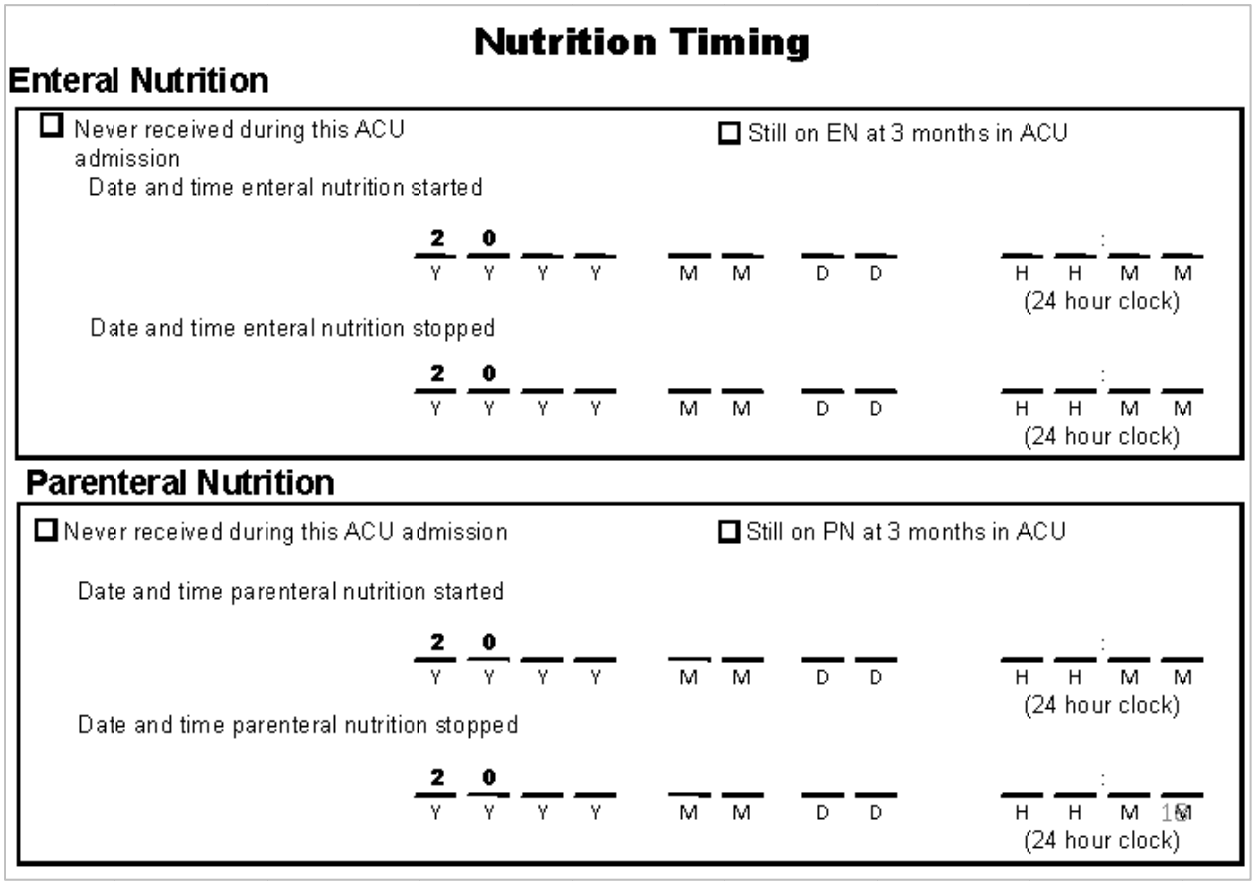


IF THE PRESCRIPTION CHANGES FOR THIS PATIENT, ENTER THE DATE AND NEW PRESCRIPTION:
NOTE: ENERGY AND PROTEIN REQUIREMENTS ARE INDEPENDENT OF FORMULA PRESCRIBED.
DO NOT CHANGE PRESCRIPTION TO ACCOMMODATE FORMULA CHANGE.



Enteral and Parenteral Start and Stop Dates and Times
Record the start and stop date and time of both Enteral and Parenteral Nutrition. Only record the date and time EN and PN were stopped permanently on the Nutrition Assessment / Timing form (example below). Do not record temporary interruptions.

- Indicate if the patient **received EN/PN** during this ACU admission, by marking the appropriate box.
- If **EN/PN is continued beyond ACU discharge**, record ACU discharge as the EN/PN stop date and time.
- If the patient is **still receiving EN/PN in the ACU at 3 months**, indicate by marking the appropriate box.



Daily Nutrition Received (see Appendix C)
Enteral Nutrition (EN)
Record the date.
Indicate whether or not the patient received EN that day by marking Yes or No.

If EN was **not** received, using the list below, indicate all the reasons the patient did not receive EN on the specified day:

- NPO for endotracheal extubation or intubation or other bedside procedure
- NPO for operating procedure
- NPO for radiology procedure
- High NG drainage
- Increased abdominal girth, abdominal distention, or patient discomfort
- Vomiting, emesis, or nausea
- Diarrhea

- No enteral access available/enteral access lost, displaced, or malfunctioning
- Inotropes, vasopressor requirement
- Patient deemed too sick for enteral feeding
- On oral feeds
- Reason not known
- Other, please specify: _____

If EN was received:

- Enter the name(s) of the formula(s) (up to 3 formulas)
- Enter the total kcals received from EN
- Enter the total grams of protein received from EN

Protein Supplements

Indicate whether or not the patient received a protein supplement that day by marking Yes or No in the PROTEIN SUPPLEMENT row. If a protein supplement was received:

- Enter the name of the supplement
- Enter the total kcals received from the protein supplement
- Enter the total grams of protein received from the protein supplement

Parenteral Nutrition (PN)

Indicate whether or not the patient received PN that day by marking Yes or No.

If PN was received:

- Enter the total kcals received from PN
- Enter the total grams of protein received from PN

IV Fluids containing Glucose

Indicate whether or not the patient received IV fluids containing glucose that day by marking Yes or No.

If IV fluid containing glucose was received:

- Enter the total kcals received from IV fluids

Oral Intake

Indicate whether or not the patient received oral nutrition that day by marking Yes or No.

Propofol

Indicate whether or not the patient received a continuous infusion of Propofol for $\geq$ 6 hours that day by marking Yes or No.

If a continuous infusion of Propofol for $\geq$ 6 hours was received:

- Enter the volume of Propofol received in mL.

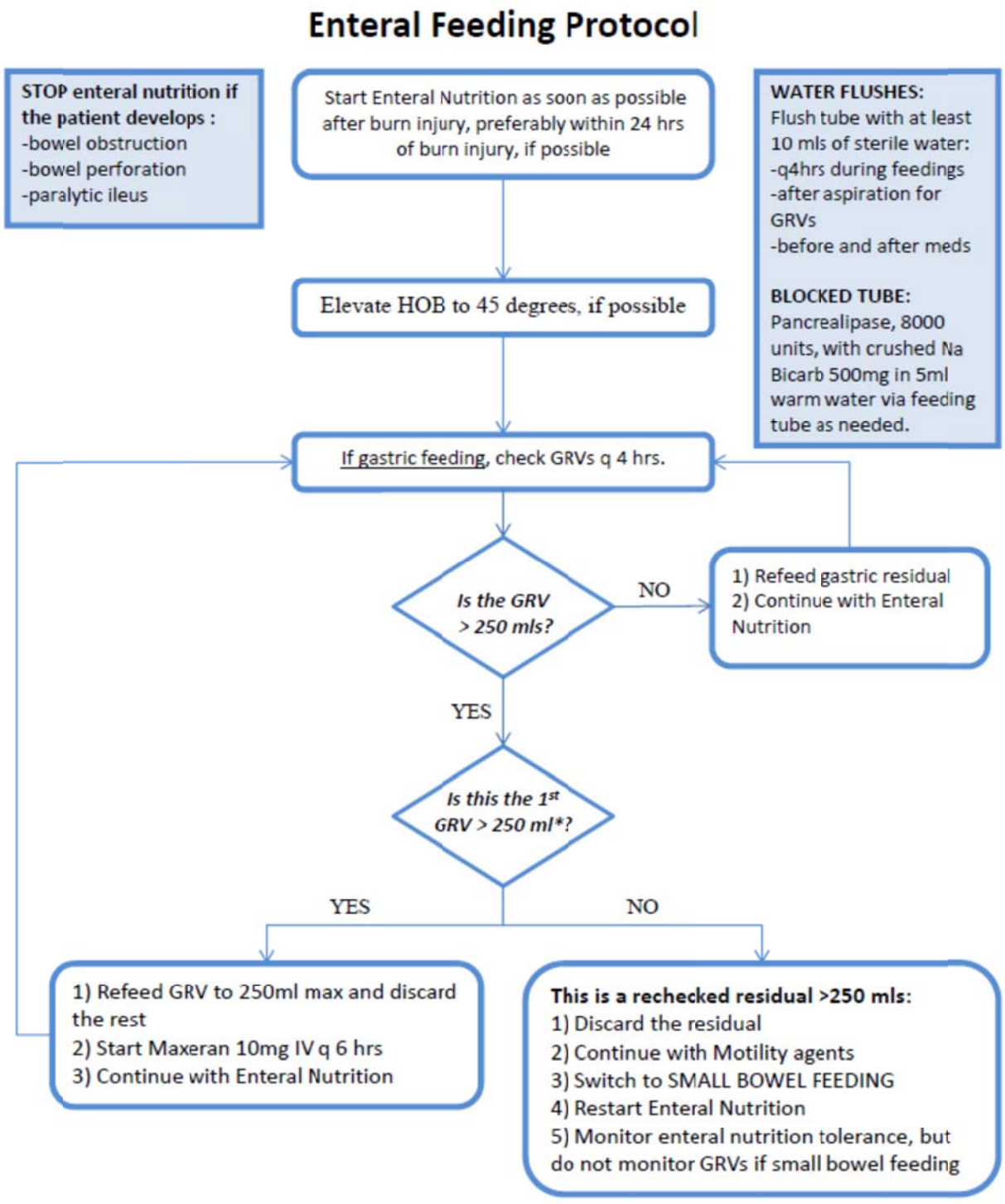
Appendices

Appendix A: Enteral Feeding Protocol

Appendix B: Nutritional Assessment/Timing form

Appendix C: Daily Nutrition form

Appendix A: Enteral Feeding Protocol



* Gastric residual volume (GRV) of 250 mls is the minimum threshold volume. Volumes higher than 250 mls are acceptable if allowed at the individual site.

Appendix B: Nutrition Assessment/Timing Form

RE-ENERGIZE

Enrollment Number _____

Nutrition Assessment

Date baseline prescription made 2 0 __ __ (Y Y Y Y) __ __ (M M) __ __ (D D)

Total Calories Prescribed: _____ kcal

Total Protein Prescribed: _____ grams

If the prescription changes for this patient, enter the date and new prescription below:
Note: Energy and protein requirements are independent of the formula prescribed.
Do NOT change prescription to accommodate a formula change.

Date baseline prescription made 2 0 __ __ (Y Y Y Y) __ __ (M M) __ __ (D D)

Total Calories Prescribed: _____ kcal

Total Protein Prescribed: _____ grams

Date baseline prescription made 2 0 __ __ (Y Y Y Y) __ __ (M M) __ __ (D D)

Total Calories Prescribed: _____ kcal

Total Protein Prescribed: _____ grams

Nutrition Timing

Enteral Nutrition

☐ Never received during this ACU admission

☐ Still on EN at 3 months in ACU

Date and time enteral nutrition started

2 0 __ __ (Y Y Y Y) __ __ (M M) __ __ (D D) __ __ : __ __ (H H M M) (24 hour clock)

Date and time enteral nutrition stopped

2 0 __ __ (Y Y Y Y) __ __ (M M) __ __ (D D) __ __ : __ __ (H H M M) (24 hour clock)

Parenteral Nutrition

☐ Never received during this ACU admission

☐ Still on PN at 3 months in ACU

Date and time parenteral nutrition started

2 0 __ __ (Y Y Y Y) __ __ (M M) __ __ (D D) __ __ : __ __ (H H M M) (24 hour clock)

Date and time parenteral nutrition stopped

2 0 __ __ (Y Y Y Y) __ __ (M M) __ __ (D D) __ __ : __ __ (H H M M) (24 hour clock)

Appendix C: Daily Nutrition Form

Daily Nutrition

Page #:_____

Date (yyyy-mm-dd)					
EN Received	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
If EN NOT received (Select all that apply)					
NPO for endotracheal extubation or intubation or other bedside procedure	☐	☐	☐	☐	☐
NPO for operating procedure	☐	☐	☐	☐	☐
NPO for radiology procedure	☐	☐	☐	☐	☐
High NG drainage	☐	☐	☐	☐	☐
Increased abdominal girth, abdominal distension or pt. discomfort	☐	☐	☐	☐	☐
Vomiting or emesis	☐	☐	☐	☐	☐
Diarrhea	☐	☐	☐	☐	☐
No enteral access available / enteral access lost, displaced or malfunctioning	☐	☐	☐	☐	☐
Inotropes, vasopressor requirement	☐	☐	☐	☐	☐
Patient deemed too sick for enteral feeding	☐	☐	☐	☐	☐
On oral feeds	☐	☐	☐	☐	☐
Reason not known	☐	☐	☐	☐	☐
Other (Please specify)					
If EN received (complete below)					
Formula 1 (Name or Number)					
Formula 2 (Name or Number)					
Formula 3 (Name or Number)					
Total Kilocalories from EN					
Total Protein from EN					
Protein Supplement	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Protein Supplement Name					
Total Calories from Protein Supplement					
Total Protein from Protein Supplement					
PN Received	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Total Calories from PN					
Total Protein from PN					
IV Fluids containing Glucose	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Total Calories from IV Fluids					
Oral Intake	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Propofol ≥ 6 hours					
Volume of propofol received (mL)					

References

[1] Masters B, Wood F. Nutrition support in burns--is there consistency in practice? J Burn Care Res. 2008 Jul-Aug;29(4):561-71.

[2] Tanaka H, Matsuda T, Miyagantani Y, et al.Reduction of Resuscitation Fluid Volumes in Severely Burned
Patients Using Ascorbic Acid Administration. A Randomized, Prospective Study. Arch Surg. 2000;135:326-331