SECTION 4: RECRUIT PARTICIPANTS

Contents

Participant Eligibility & Enrollment

Screening

Beginning on the first day your site is approved for screening, you will screen consecutive patients (mechanically ventilated, adults) in the study. Consecutive means the very next patient admitted to your ICU, instead of picking and choosing patients. Repeat screening daily. Remember to document your screening in the Screening Log described in Section 3: Prepare and Promote.

Study ID Numbers

Please enter data on all patients screened that meet the inclusion criteria. Patients, with their data entered into REDCap will be assigned a unique study number by the system. For patients that are randomized, this study number will never change and will be used for the entire duration of the patient's participation in the study and should be used to label all patient CRFs, worksheets and records.

Inclusion Criteria

If eligible, they must be randomized to the trial within ***96h of admission to your ICU***.

1. **≥18 years old.**

2. **Requiring mechanical ventilation with actual or expected total duration > 48 hours from time of screening.**
   This includes ***any*** positive inspiratory pressure (excluding PEEP only) delivered via an endotracheal tube or a tracheostomy. ***Non-invasive*** methods of ventilation, such as high flow oxygen nasal cannula (OPTIFLOW), BI-PAP or mask-CPAP, are not permitted.

   The 48h window should be measured from the time of initiation of mechanical ventilation (i.e. intubation). A patient should either have ***already achieved*** at least 48h of mechanical ventilation or they are ***expected*** to achieve at least 48h from point of screening.

   Also, if the patient received $\geq$ 48h of mechanical ventilation, but is extubated at the time of screening or been actively weaned, please do not enroll the patient. We want patients that will remain in ICU requiring artificial nutrition for another 3-4 days minimum from the point of screening.

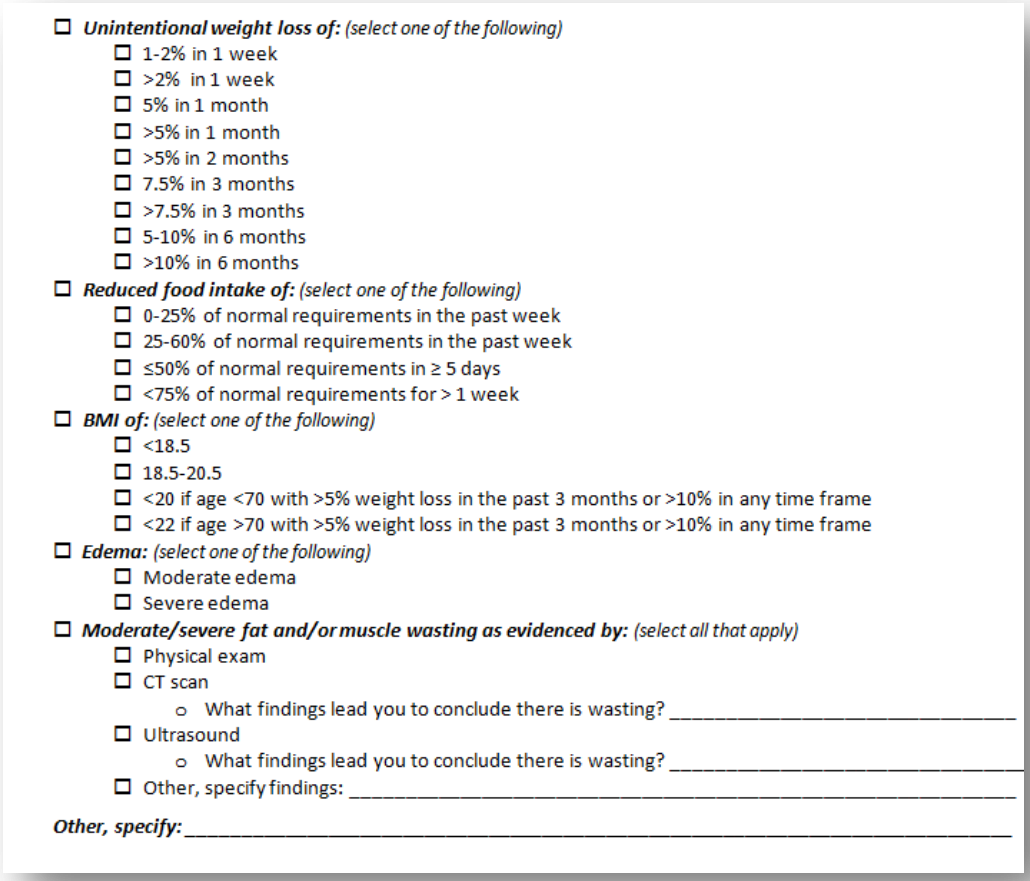
   If the patient was intubated outside of the hospital setting (e.g. by paramedics in the field or at another hospital), use the precise time of intubation from the medical notes. However, if such a time is not available, use the time of your hospital's admission to determine this criterion.

3. **Have <u>one or more</u> of the following risk factors that make them a high nutritional risk.**
   NOTE: Each patient will need to be assessed for the presence of 5. a-d of these nutritional risk criteria at some point. If the patient is eligible on one of the criteria, say for example BMI, the rest of the data points can be deferred till later. Only one criterion of the following is required to meet these inclusion criteria:

a. **Low (≤25) or high BMI (≥35)**

b. **Moderate to severe malnutrition (as defined by local assessments).**

We are not trying to be prescriptive as to how you document mod-severe malnutrition. But rather, we will document the means by which sites are making this determination and capture the elements of the assessment (history of weight loss, history of reduced oral intake, etc.). For example, the data collection worksheet in REDCAP looks like this and you will be required to indicate yes or no to all the following criteria:



- ☐ ***Unintentional weight loss of:*** *(select one of the following)*
  - ☐ 1-2% in 1 week
  - ☐ >2% in 1 week
  - ☐ 5% in 1 month
  - ☐ >5% in 1 month
  - ☐ >5% in 2 months
  - ☐ 7.5% in 3 months
  - ☐ >7.5% in 3 months
  - ☐ 5-10% in 6 months
  - ☐ >10% in 6 months
- ☐ ***Reduced food intake of:*** *(select one of the following)*
  - ☐ 0-25% of normal requirements in the past week
  - ☐ 25-60% of normal requirements in the past week
  - ☐ ≤50% of normal requirements in ≥ 5 days
  - ☐ <75% of normal requirements for > 1 week
- ☐ ***BMI of:*** *(select one of the following)*
  - ☐ <18.5
  - ☐ 18.5-20.5
  - ☐ <20 if age <70 with >5% weight loss in the past 3 months or >10% in any time frame
  - ☐ <22 if age >70 with >5% weight loss in the past 3 months or >10% in any time frame
- ☐ ***Edema:*** *(select one of the following)*
  - ☐ Moderate edema
  - ☐ Severe edema
- ☐ ***Moderate/severe fat and/or muscle wasting as evidenced by:*** *(select all that apply)*
  - ☐ Physical exam
  - ☐ CT scan
    - o What findings lead you to conclude there is wasting? _____
  - ☐ Ultrasound
    - o What findings lead you to conclude there is wasting? _____
  - ☐ Other, specify findings: _____

Other, specify: _____

c. **Frailty (Clinical Frailty Scale of 5 or more from proxy).**

The Clinical Frailty Scale assessment tool, including instructions for use, are found in the ***Patient CRF and Instructions*** (found in Section 5), and can be downloaded from this website.

d. **Sarcopenia (SARC-F score of 4 or more from proxy).**

The SARC-F assessment tool, including instructions for use, are found in the ***Patient CRF and Instructions*** (found in Section 5), and can be downloaded from this website.

e. From point of screening, projected duration of mechanical ventilation >4 days.

To aid the attending physician in making this determination, ask them what the probability (i.e. high, medium, low) of the patient being in the ICU for an additional 4 days (or 3 days if the study intervention can start on the day of screening).

- If the physician assessment is medium or high, they fulfill this particular high risk criteria.
- If the patient is considered low probability, then the patient does not fulfill this particular high risk criteria

NOTE: All randomized patients will have documented assessments completed for nutrition risk factors 5a-d. If these are not required to be completed at the time of screening, they will be completed when the patient is confirmed to be eligible for the study and have been randomized. See Section 5 and Patient CRF & Instructions for data collection details.

Exclusion Criteria

1. **> 96 continuous hours of mechanical ventilation before screening.**
   We want the study intervention to begin as early as possible and if more than 96 hours have transpired, they likely have received significant amount of nutrition already. If the patient was intubated outside of the hospital setting (e.g. by paramedics in the field or at another hospital), use the precise time in the notes. However, if such a time is not available, use the time of your hospital's admission to determine this criterion.

2. **Expected death or withdrawal of life-sustaining treatments within 7 days from screening.**
   Patients who die or receive palliative therapy (have nutrition stopped) within days of randomization are not good study patients. They won't help us answer the study question. By this criterion, we mean a very high likelihood or death or withdrawal of life-sustaining treatments (If the patient has an isolated DNR, they can still be included). It may be difficult for some clinicians to make this judgment. Therefore, only patients with a 'high' probability (>50%) of not surviving the next 7 days should be excluded.

3. **Pregnant.**
   We don't know the safety of high protein on the fetus. Post-partum and lactating patients are permitted.

4. **The responsible clinician feels that the patient either needs low or high protein**
   If this is the case, we require an understanding of the clinician's reasons. From the options below, check all that apply.

   - ❒ No longer critically ill
   - ❒ New onset of ARDS
   - ❒ Worsening renal function
   - ❒ Improved renal function
   - ❒ Starting dialysis
   - ❒ New wound (non-surgical)
   - ❒ New surgical wound
   - ❒ Negative nitrogen balance
   - ❒ Increased protein losses (eg. increased ostomy output, pleural fluid drainage, etc)
   - ❒ BMI ≥30
   - ❒ Improving hepatic failure
   - ❒ Worsening hepatic failure
   - ❒ Other, please specify: _____

5. **Patient requires parenteral nutrition only and site does not have products to reach the high protein dose group.**

Note: These exclusion criteria are assessed at the time of screening. If a patient is eligible for the trial and randomized, if then subsequently and unexpectedly meet an exclusion criteria (e.g. patient starts on dialysis or life-sustaining treatment is withdrawn), the patient is to continue in the trial and the nutrition should be managed as per clinical standards.

Co-Enrollment

We are supportive of co-enrollment in non-industry sponsored or academic randomized trials and observational studies. However, patients should not be co-enrolled in any other nutrition-related trials. If there are questions about the suitability of co-enrollment, please contact the Central Project Leader.

Informed Consent Procedures

Following the confirmation of participant eligibility with the site investigator, the site should proceed with consent procedures. The consent procedures to be followed will differ across participating regions. Sites must ***adhere to consent procedures as approved by their ethics committee*** (i.e. IEC, IRB, REB).

Sites will either have ethics clearance to use waived consent or standard consent (i.e. written consent obtained from substitute decision maker).

Substitute-decision maker (SDM): *is someone who has the responsibility for making decisions for a patient, who is not able to make his/her own health care decisions. You will see this term used in the information below.*

Consent Type: Waiver of Consent

- ☑ This must be pre-approved by your ethics board before registering for this trial.

- ☑ For enrolled patients, the family member or a substitute-decision maker (SDM) should be contacted where and when available to advise them regarding the fact that the patient is enrolled in a clinical trial.
- ☑ The information sheet is to be given to the family member/SDM and, once appropriate, the patient.
- ☑ Administer the Clinical Frailty Scale and SARC-F assessments to the family member/SDM at this time.

Consent Type: Standard Consent

- ☑ For sites that need to obtain consent, the ICF must be pre-approved by your ethics board before registering for the trial.
- ☑ Written consent from the family member/SDM must be obtained within the first 96h of ICU admission, in order to ensure the participant is randomized to the trial within the 96h timeframe.
- ☑ Administer the Clinical Frailty Scale and SARC-F assessments to the family member/SDM after written consent is obtained.
- ☑ If during the trial period (first 60 days from ICU admission) the patient regains the capacity to provide informed consent, the patient should be consented using the same ICF the family member/SDM signed. Refer to local policies for further details regarding capacity and re-consent procedures.

Randomization

Once the applicable consent process has been completed, the site study team should proceed to randomize the participant.

 Download a detailed instruction guide ***How to Randomize a Participant Using REDCap*** from the website.

High Protein Dose	Low Protein Dose
Participants randomized to the *high protein dose* treatment arm of the study will have a prescribed protein intake of *≥ 2.2g/kg/d*.	Participants randomized to the *low protein dose* treatment arm of the study will have a prescribed protein intake of *≤ 1.2g/kg/d*.

Participant Procedures

The following Schedule of Events table will give you a high level look at how to progress an enrolled participant through the study from the time of randomization until the Day 60 Follow-up.

Schedule of Events

Procedures	Screening/ Enrollment	Day 1 (ICU Adm)	ICU Days 1-12*	ICU days 13-28†	Day 60 from ICU admission
Review of Inclusion/Exclusion criteria	☑				
Randomization	☑				
Participant Characteristics Admission category, diagnosis, comorbidities, sex, age, height, weight, APACHE II, SOFA.		☑			
Enrollment Conditions present at the time of enrollment.		☑			
Nutrition Assessment Recent weight loss or food intake changes.		☑			
Nutrition Goals Protein and calorie goals.		☑			
Laboratory Measures Blood sugar levels, lowest phosphate level, urea (BUN) and creatinine.			☑		
Daily Nutrition Data Type and amount of nutrition received (EN, PN), use of pro-kinetics, use of supplements.			☑	☑ *Protein intake only*	
Other Daily Data Vasopressors/inotropes received and renal replacement therapy.		☑	☑		
Outcomes information Duration of mechanical ventilation, renal replacement therapy, vasopressor use, length of ICU and hospital stay, ICU readmissions, and hospital mortality.					☑
Study Participation Complete					☑

*Collected daily until the first of ICU discharge, death or day 12.

†Collected daily until the first of ICU discharge, death, transition to oral feeds or day 28.Baseline

Nutrition Procedures

Nutrition Prescription

Protein and energy targets will be achieved through any combination of EN, protein supplements, and PN or amino acids. The only difference between the nutrition prescriptions between the 2 study groups is that the protein goals are set.

Protein Target

In accordance with the study group the participant has been randomized to, the participant should be prescribed one of the two (2) following protein targets:

Lower Protein Dose	Higher Protein Dose
≤ 1.2 g/kg/day	≥ 2.2 g/kg/day

In both groups:

- Targets will be set using pre-ICU dry actual weight.
- For patients with BMI <20 or >30, ideal body weight based on a BMI of 25 will be used.

   Refer to the website to access a table that will help you calculate this body weight based on a BMI of 25.

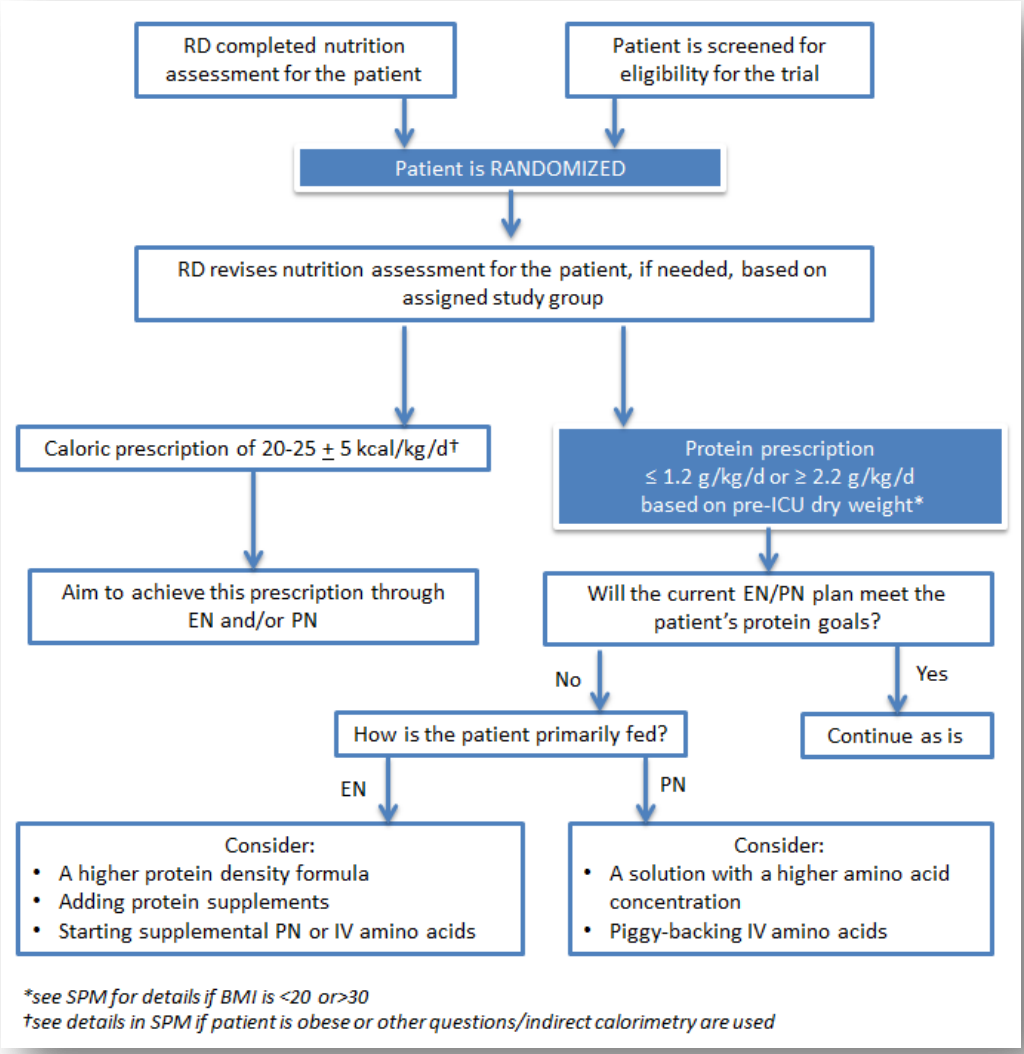
Calorie Target

Although this trial is not about caloric dose, we want to encourage participating clinicians to be conservative in meeting energy targets and avoid overfeeding. Caloric goals should be the same in both groups and we recommend sites follow the SCCM/ASPEN clinical practice guidelines (McClave JPEN 2016).

- For non-obese patients, we suggest that their caloric prescription be around 20-25 kcal/kg/day.
  - If the site choses to use more sophisticated equations or indirect calorimetry, that is permissible.

- For obese patients, if indirect calorimetry is used, the goal of the nutritional prescription should be to provide energy not to exceed 65%–70% of measured requirements.
  - If indirect calorimetry is unavailable or not used, we suggest using the weight-based equation 11–14 kcal/kg actual body weight per day for patients with BMI in the range of 30–50 and 22–25 kcal/kg ideal body weight per day for patients with BMI > 50.

Figure 4: Overview of Nutrition Procedures



Throughout the study the site should be monitoring compliance with the study protein target on a daily basis. Refer to the REDCap section for details on how to use the nutritional adequacy calculator built into REDCap.

Feasibility of Meeting Goals

Similar efforts should be used in both study groups to achieve at least 80% of the protein and calorie targets.

Refer below for several scenarios that have been developed to help the dietitians and study team members optimize nutrition delivery in study patients.

BMI = 20; Weight = 67kg

Meeting Goals with Enteral Formulas

	Lower Protein Dose (≤ 1.2 g/kg/day) Energy 25kcal/kg actual weight/day	**Higher Protein Dose** (≥ 2.2 g/kg/day) Energy 25 kcal/kg actual weight/day
Protein Goal (g/day)	≤ 80	≥ 147
Energy Goal (kcal/day)	1675	1675
Suggested Enteral Nutrition Products to Achieve Goals	**Peptamen 1.5** ➢ 1.1 L (75g protein, 1650 kcal) **Osmolite 1.0 + Juven** ➢ 1.5L + 1 packet (81g protein, 1670 kcal)	**Peptamen Intense** ➢ 1.7L (156g protein, 1700 kcal) **Vital AF 1.2 + Juven** ➢ 1L + 6 packets (159g protein, 1680 kcal)

Meeting Goals with Parenteral Formulas

	Lower Protein Dose (≤ 1.2 g/kg/day) Energy 25kcal/kg actual weight/day	**Higher Protein Dose** (≥ 2.2 g/kg/day) Energy 25 kcal/kg actual weight/day
Protein Goal (g/day)	≤ 80 (75)	≥ 147 (150)
Energy Goal (kcal/day)	1675	1675
Suggested Parenteral Nutrition Products to Achieve Goals	**Clinimix 5.0/25** ➢ 1.5 L (75g amino acids, 1575 kcal) **Kabiven** ➢ 2.0 L (68g amino acids, 1740 kcal)	**Clinimix 5.0/20 + Clinimix 15.0** ➢ 1.5 L + 0.5 L (150g amino acids, 1620 kcal) **Kabiven + Clinimix 15.0** ➢ 1.5L + 700 mL (156g amino acids, 1725 kcal)

BMI = 35; Weight = 100kg, weight at BMI 25=84kg

Meeting Goals with Enteral Formulas

	Lower Protein Dose (≤ 1.2 g/kg/day) Energy 11-14kcal/kg actual weight/day	**Higher Protein Dose** (≥ 2.2 g/kg/day) Energy 11-14 kcal/kg actual weight/day
Protein Goal (g/day)	≤ 100	≥ 185
Energy Goal (kcal/day)	1100-1400	1100-1400
Suggested Enteral Nutrition Products to Achieve Goals	**Peptamen Intense VHP** ➢ 1.0 L (92g protein, 1000 kcal) **Peptamen AF** ➢ 1.2L (91g protein, 1440 kcal) **Vital AF 1.2 + Juven** ➢ 1.0 L + 1 packet (89g protein, 1280 kcal)	**Peptamen Intense VHP + Prosource NoCarb** ➢ 1.2L + 150mL (185g protein, 1500 kcal) **Vital High Protein + Prosource NoCarb** ➢ 1L + 210mL (193g protein, 1420 kcal)

Meeting Goals with Parenteral Formulas

	Lower Protein Dose (≤ 1.2 g/kg/day) Energy 11-14 kcal/kg actual weight/day	**Higher Protein Dose** (≥ 2.2 g/kg/day) Energy 11-14 kcal/kg actual weight/day
Protein Goal (g/day)	≤ 100	≥ 185
Energy Goal (kcal/day)	1100-1400	1100-1400
Suggested Parenteral Nutrition Products to Achieve Goals	**Clinimix 4.25/10** ➢ 2.25 L (95g amino acids, 1148 kcal) **Kabiven + Clinimix 15** ➢ 1.5 L + 0.25 L (98g amino acids, 1455 kcal)	**Clinimix 4.25/10 + Clinimix 15.0** ➢ 1.0 L + 1.0 L (193g amino acids, 1110 kcal) **Kabiven + Clinimix 15.0** ➢ 1.0L + 1.05 L (192g amino acids, 1500 kcal)

BMI = 45; Weight = 134kg, weight at BMI 25=84kg

Meeting Goals with Enteral Formulas

	Lower Protein Dose (≤ 1.2 g/kg/day) Energy 22-25kcal/kg actual weight/day	**Higher Protein Dose** (≥ 2.2 g/kg/day) Energy 22-25 kcal/kg actual weight/day
Protein Goal (g/day)	≤ 100	≥ 185
Energy Goal (kcal/day)	1848-2100	1848-2100
Suggested Enteral Nutrition Products to Achieve Goals	**Peptamen 1.5 + Prosource NoCarb** ➢ 1.2 L + 30 mL (96g protein, 1880 kcal) **Perative** ➢ 1.4 L (93g protein, 1820 kcal)	**Peptamen Intense VHP** ➢ 2.1 L (193g protein, 2100 kcal) **Peptamen AF 1.2 + Prosource NoCarb** ➢ 1.2 L + 150 mL (189 protein, 2100 kcal) **Promote + Juven** ➢ 1.7 L + 6 packets (190g, 2180 kcal)

Meeting Goals with Parenteral Formulas

	Lower Protein Dose (≤ 1.2 g/kg/day) Energy 20-25 kcal/kg actual weight/day	**Higher Protein Dose** (≥ 2.2 g/kg/day) Energy 20-25 kcal/kg actual weight/day
Protein Goal (g/day)	≤ 100	≥ 185
Energy Goal (kcal/day)	1848-2100	1848-2100
Suggested Parenteral Nutrition Products to Achieve Goals	**Clinimix 4.25/20** ➢ 2.25 L (96g amino acids, 1913 kcal) **Kabiven + Clinimix 15** ➢ 2.0 L + 200 m L (98g amino acids, 1860 kcal)	**Clinimix 4.25/20 + Clinimix 15.0** ➢ 2.0 L + 700 mL (190g amino acids, 2120 kcal) **Kabiven + Clinimix 15.0** ➢ 1.5 L + 1.0 L (201g amino acids, 1905 kcal)