

# Supplementary Online Content

Doig GS, Simpson F, Sweetman EA, et al. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a randomized controlled trial. JAMA. doi:10.1001/jama.2013.5124.

## Table of Contents

Table of Contents .....	2
Early PN Trial Conduct and Management: .....	3
eTable 1: Complete Eligibility Criteria: .....	4
Inclusion Criteria (All YES answers for enrolment).....	4
Exclusion Criteria (All NO answers for enrolment, YES to any for exclusion) .....	4
Contraindications to Kabiven G19% based on TGA Licensing Indications. ....	5
eTable 2: PN Protocols.....	6
eTable 2 continued: PN Protocols .....	7
Study PN Protocol B: <b>MALNOURISHED Early PN PATIENTS (Ex. BMI ≤ 17)</b> :.....	7
eTable 3: Harris-Benedict equations and adjustment factors used by study web site .....	8
eTable 4: Nutritional therapy received during ICU stay, Standard Care and Early PN patients.....	9
eTable 5: Clinically Significant Organ Failure and Concomitant Interventions, crude event rates, not adjusted for time at risk (ICU stay).....	10
eFigure 1. Energy intake from enteral nutrition and/or parenteral nutrition during ICU stay .....	11
eFigure 2: Subjective Global Assessment of muscle wasting during ICU stay.....	12
eFigure 3: Subjective Global Assessment of fat loss during ICU stay.....	13

*Note: Additional information may be found at the study web site:  
[www.EvidenceBased.net/EarlyPN](http://www.EvidenceBased.net/EarlyPN).*

This supplementary material has been provided by the authors to give readers additional information about their work.

### **Early PN Trial Conduct and Management:**

**Study Management Committee:** Gordon S. Doig (Chair), Fiona Simpson, Elizabeth A. Sweetman, Simon R. Finfer, D. Jamie Cooper, Philippa T. Heighes, Andrew R. Davies, Michael O’Leary, Tom Solano and Sandra Peake. **PN protocol sub-committee:** Gordon S. Doig (Chair), Fiona Simpson, Michael O’Leary. **Infectious complications sub-committee:** Gordon S. Doig (Chair), Tom Solano, Fiona Simpson. **Data Quality and Management:** Jennifer L. Hannam (Northern Clinical School Intensive Care Research Unit, University of Sydney, Australia). **Statistical analysis:** Gordon S. Doig. **Independent Data Safety and Monitoring Committee:** John Moran (Chair, Dept of Intensive Care, The Queen Elizabeth Hospital, Adelaide, Australia), Petra Graham (Dept of Statistics, Macquarie University, Sydney, Australia) and Andrew Bersten (Dept of Critical Care Medicine, Flinders University, Adelaide, Australia).

### **eTable 1: Complete Eligibility Criteria:**

#### **Inclusion Criteria (All YES answers for enrolment)**

1. Is the patient expected to remain in ICU today and tomorrow?
2. Is the patient 18 years of age or older?
3. Has the patient been admitted to the study ICU less than 24 hours?
4. Does the patient have a central venous access line through which parenteral nutrition could be delivered?
5. Is this patient **not** expected to receive enteral, parenteral or oral nutrition today or tomorrow?

#### **Exclusion Criteria (All NO answers for enrolment, YES to any for exclusion)**

1. Known pregnancy or currently breastfeeding.
2. Has the patient previously been enrolled and randomised into this study?
3. Is the patient to receive palliative care only and is not expected to survive ICU or hospital discharge?
4. Was the patient admitted to this, or another, ICU during this current hospitalisation?
5. Was the patient admitted to the study ICU directly from another ICU?
6. Is the patient moribund and not expected to survive 24 hours?
7. Is the patient brain dead or suspected to be brain dead?
8. Are there long term contraindications to enteral or oral nutrition such that the patient would normally be supported with parenteral nutrition (Ex. Home TPN patient)?
9. Does the patient require treatment of thermal injury to greater than 20% of total body surface area?
10. Is the primary reason for admission to the ICU for the treatment of a condition that requires timely nutritional support (Ex. Anorexia nervosa.)?
11. Body weight < 35 Kg
12. Height < 140 cm (Demi armspan < 59 cm)
13. Is there a contraindication to treatment with Kabiven G19%?

**NB - see next page for contraindications to Kabiven G19% based on TGA licensing indications.**

### Contraindications to Kabiven G19% based on TGA Licensing Indications.

- c1. Known hypersensitivity to egg or soya protein or to any of the ingredients of the study PN (for full ingredients see Product Information, MIMS TGA Document Appendix 1).
- c2. Severe hyperlipidaemia (Documented serum total cholesterol >7mmol/L and/or triglycerides >3 mmol/L).
- c3. Severe liver insufficiency (Biopsy proven cirrhosis, or documented portal hypertension with a known past history of either upper GI bleeding attributed to portal hypertension or of hepatic failure leading to encephalopathy / coma.)
- c4. Severe blood coagulation disorders (Documented INR > 3.0 not due to coumarin therapy, platelet count <15,000).
- c5. Inborn errors of amino acid metabolism (Ex. PKU etc)
- c6. Severe renal insufficiency without access to haemofiltration or dialysis.
- c7. Acute shock as defined by arterial systolic blood pressure  $\leq$  90mmHg or mean arterial pressure  $\leq$  70mmHg despite adequate fluid resuscitation (i.e. following rapid infusion of  $\geq$  500mL crystalloid or 200mL colloid solution and /or PAOP  $\geq$  12mmHg, CVP  $\geq$  8mmHg) **or** increasing need for noradrenaline / adrenaline / dopamine to maintain blood pressure where the infusion rate has **increased by more than 50%** over the previous hour **to greater than 0.6mg/hour (10 mcg/min)** norad / adrenaline or **30mg** dopamine.

*Patients are **not excluded** if their initial shock responds to fluid therapy or if the catecholamine infusion rate has not increased by more than 50% over the previous one hour period or if the current infusion rate is less than 0.6mg norad / adrenaline per hour .*

- c8. Hyperglycaemia (blood sugar > 10 mmol/L) that currently requires the administration of more than 6 units of insulin/hour **at the time of enrolment.**
- c9. Pathologically elevated serum levels of any of the electrolytes included in Kabiven G19% **at the time of enrolment. Documented** Sodium >155 mmol/L, potassium > 6.2 mmol/L, magnesium > 2.0 mmol/L, ionised calcium > 1.5 mmol/L, phosphate >2.0 mmol/L, chloride > 120 mmol/L.

*The patient may become eligible if these pathologically elevated electrolyte levels can be corrected within 24 hours of admission to the study ICU.*

- c10. General contraindications of infusion therapy: acute pulmonary oedema, hyperhydration, decompensated cardiac insufficiency and hypotonic dehydration

*The patient may become eligible if these general contraindications to fluid therapy can be corrected within 24 hours of admission to the study ICU.*

- c11. Haemophagocytic syndrome
- c12. Severe trauma with acute shock (see **Exclusion Criteria c7** for definition of acute shock).
- c13. Diabetes mellitus with ketoacidosis or non-ketotic hyperosmolar state.
- c14. Acute myocardial infarction with acute shock (see **Exclusion Criteria c7** for definition of acute shock) or pulmonary oedema.
- c15. (Metabolic acidosis or severe sepsis) with acute shock (see Exclusion Criteria c7 for definition of acute shock. Use Bone Criteria for definition of Severe Sepsis).
- c16. Coma (GCS  $\leq$ 8) in association with hyperosmolarity of the blood ( $\geq$ 320mOs/kg) from any cause.

## eTable 2: PN Protocols

### Study PN Protocol A: ALL Early PN PATIENTS EXCEPT MALNOURISHED

#### Feeding Day 1 (first 24 hours of PN)

- Commence Kabiven G19% at **60ml/hr** (or goal rate, whichever is lower).
- **Consider** trace element, mineral and vitamin needs as clinically appropriate.

#### Feeding Day 2 (second 24 hours of PN)

- Increase Kabiven G19% to **80ml/hr** (or goal rate, whichever is lower).
- **Consider** trace element, mineral and vitamin needs as clinically appropriate.

#### Feeding Day 3 (next 24 hours)

- Increase Kabiven G19% to **goal rate**, as appropriate.
- **Consider** trace element, mineral and vitamin needs, as clinically appropriate.
- **Recommend** trialing enteral/oral nutrition, if clinically appropriate.
- Once the patient tolerates  $\geq 475$  kcal/day EN, complete remainder of 24 hour Kabiven infusion and do not hang another bag.
- If patient tolerates any oral caloric intake from food, complete remainder of 24 hour Kabiven infusion and do not hang another bag.

#### Feeding Day 4 (next 24 hours) *plus all additional days after Day 4*

- **May switch** to parenteral nutrition solution tailored to patient's specific clinical needs. Goals not to exceed 25–35 kcal/kg and 1.0–1.5 g protein/kg.
- **Consider** long term needs regarding trace element, mineral and vitamins as clinically appropriate.
- **Recommend** trialing enteral/oral nutrition, if clinically appropriate.
- Once the patient tolerates  $\geq 475$  kcal/day EN, complete remainder of 24 hour Kabiven infusion and do not hang another bag.
- If patient tolerates any oral caloric intake from food, complete remainder of 24 hour Kabiven infusion and do not hang another bag.

### INSULIN / GLUCOSE PROTOCOL: Early PN Patients

If glucose levels exceed **10 mmol/L** an insulin infusion should be commenced and titrated to achieve peak serum glucose levels of **< 10 mmol/L**. Frequent monitoring of the patient's blood glucose should be initiated as per your ICU's usual practice for patients receiving an insulin infusion.

If insulin infusion is required at  $\geq 6$  **units/hr** to maintain glucose target:

- Reduce Kabiven G19% to 40ml/hr for 24 hours.
- At the end of 24 hours, if insulin needs are reduced below 6 units/hr, increase Kabiven G19% to 80mls (or original goal rate, whichever is lower) for 24 hours.
- At the end of this second 24 hour period, if insulin needs remain below 6 units/hr, increase Kabiven G19% to goal rate.
- If insulin requirements exceed 6 units/hr at any time during the above process, reduce PN to previously tolerated rate, or 40 ml/hr (whichever is higher), for 24 hours. Begin increasing rate every 24 hours as above, if tolerated.

## eTable 2 continued: PN Protocols

### Study PN Protocol B: **MALNOURISHED Early PN PATIENTS (Ex. BMI ≤ 17):**

#### **Feeding Day 1 (first 24 h of PN)**

- Commence Kabiven G19% at **40ml/hr** (or goal rate, whichever lower).
- **Strongly recommend** administering 100mg thiamine, commencing at least 30 minutes prior to initiation of Kabiven G19% infusion, as clinically indicated as per product licensing indications.
- **Recommend** daily administration of other vitamins, minerals and trace elements, as clinically appropriate.

#### **Feeding Day 2 (second 24 hours of PN)**

- Increase Kabiven G19% to **60ml/hr** (or goal rate, whichever is lower).
- **Recommend** daily administration of vitamins, minerals and trace elements, as clinically appropriate.

#### **Feeding Day 3 (next 24 hours)**

- Increase Kabiven G19% to **goal rate**, as appropriate.
- **Recommend** daily administration of vitamins, minerals and trace elements, as clinically appropriate.
- **Recommend** trialing enteral/oral nutrition, if clinically appropriate.
- Once the patient tolerates  $\geq 475$  kcal/day EN, complete remainder of 24 hour Kabiven infusion and do not hang another bag.
- If patient tolerates any oral caloric intake from food, complete remainder of 24 hour Kabiven infusion and do not hang another bag.

#### **Feeding Day 4 (next 24 hours) plus all additional days after Day 4**

- **May switch** to parenteral nutrition solution tailored to patient's specific clinical needs. Goals not to exceed 25–35 kcal/kg and 1.0–1.5 g protein/kg.
- **Strongly recommend** addressing long term needs regarding trace elements, minerals and vitamins as clinically appropriate.
- **Recommend** trialing enteral/oral nutrition, if clinically appropriate.
- Once the patient tolerates  $\geq 475$  kcal/day EN, complete remainder of 24 hour Kabiven infusion and do not hang another bag.
- If patient tolerates any oral caloric intake from food, complete remainder of 24 hour Kabiven infusion and do not hang another bag.

### **INSULIN / GLUCOSE PROTOCOL: Early PN Patients**

If glucose levels exceed **10 mmol/L** an insulin infusion should be commenced and titrated to achieve peak serum glucose levels of **< 10 mmol/L**. Frequent monitoring of the patient's blood glucose should be initiated as per your ICU's usual practice for patients receiving an insulin infusion.

If insulin infusion is required at  $\geq 6$  units/hr to maintain glucose target:

- Reduce Kabiven G19% to 40ml/hr for 24 hours.
- At the end of 24 hours, if insulin needs are reduced below 6 units/hr, increase Kabiven G19% to 80mls (or original goal rate, whichever is lower) for 24 hours.
- At the end of this second 24 hour period, if insulin needs remain below 6 units/hr, increase Kabiven G19% to goal rate.
- If insulin requirements exceed 6 units/hr at any time during the above process, reduce PN to previously tolerated rate, or 40 ml/hr (whichever is higher), for 24 hours. Begin increasing rate every 24 hours as above, if tolerated.

**eTable 3: Harris-Benedict equations and adjustment factors used by study web site**

**For males:**

Target metabolic needs (kcal/day) =  $(66.5 + (13.75 \times \text{Wt}) + (5.003 \times \text{Ht}) - (6.775 \times \text{Age})) \times \text{adjustment factor}$

**For females:**

Target metabolic needs (kcal/day) =  $(655.1 + (9.563 \times \text{Wt}) + (1.85 \times \text{Ht}) - (4.676 \times \text{Age})) \times \text{adjustment factor}$

Wt = weight in Kg

Ht = height in cm

Age = Age in years

**Adjustment Factors** (most severe was selected).

**Other, not listed below** <value="1.2">

- Any other problem, not listed below.

**Infection, mild** <value="1.3">

- Ex. mild skin, line or surgical wound infection. Local redness, heat and swelling but no systemic signs.

**Operation, minor** <value="1.3">

- Any surgical procedure that does not require general anaesthesia or respiratory support.

**Operation, major** <value="1.35">

- Any surgical procedure that **does** require general anaesthesia or respiratory support.

**Infection, peritonitis (non-septic)** <value="1.35">

- Peritonitis based on visual inspection or culture. Patient does not have systemic signs of sepsis.

**Cancer** <value="1.35">

- Patient is known to have an active tumour. May or may not be undergoing active or palliative treatment.

**Trauma, single fracture (skeletal)** <value="1.4">

- Patient has trauma resulting in a single skeletal fracture of any bone except long bones.

**Infection, moderate** <value="1.45">

- Infections that would normally require ICU admission for treatment. Ex. Community acquired pneumonia, Ventilator Associated Pneumonia.

**Trauma, single long-bone fracture** <value="1.45">

- Trauma with a fracture to a long bone (femur, humerus, tibia, fibula, radius and ulna).

**Trauma, multiple fractures** <value="1.5">

- Trauma with multiple fractures to any bones, including at least one long bone.

**Trauma, blunt with or without fractures** <value="1.6">

- Blunt trauma, such as a motor vehicle crash and fall from height. Includes Penetrating trauma.

**Infection, severe** <value="1.65">

- Any infection, or suspected infection, that expresses itself systemically as sepsis.

**Burns, less than or equal to 20% TBSA** <value="1.7">

- Chemical or thermal burns to less than 20% of total body surface area.

**Malnourished (high risk of refeeding syndrome)** <value="0.85">

- Body mass index of less than 17 or history and physical exam consistent with malnourishment or high risk of malnourishment. Based on clinical grounds decided by attending clinician.

**Note:** Harris-Benedict calculated targets were capped at 35 kcal/kg/day and obese patients (BMI  $\geq$  30 kg/m<sup>2</sup>) used ideal body weight (BMI = 21 kg/m<sup>2</sup>) in all Harris-Benedict calculations.

**eTable 4: Nutritional therapy received during ICU stay, Standard Care and Early PN patients**

	<b>Standard Care</b> 682 patients	<b>Early PN</b> 681 patients
Patients receiving PN at any time, n (%)	254 (37.2%)	679 (99.7%)
Patients receiving EN at any time, n (%)	298 (43.7%)	274 (40.23%)
Patients starting PN first, n (%)	186 (27.3%)	679 (99.7%)
Time from enrolment to starting PN first, mean (95% CI)	1.99 days (1.45 to 2.70)	44 minutes (36 to 55)
Patients commencing EN after starting PN, n (%)	80/186 (43.0%)	405/679 (59.6%)
Time to commencing EN after starting PN, mean (95% CI)	5.08 days (4.66 to 5.52)	3.83 days (3.52 to 4.17)
Patients starting EN first, n (%)	199 (29.2%)	0 (0%)
Time from enrolment to starting EN first, mean (95% CI)	1.98 days (1.43 to 2.78)	
Patients receiving PN after starting EN, n (%)	48/199 (24.1%)	0 (0%)
Time to receiving PN after starting EN, mean (95% CI)	4.59 days (4.09 to 5.17)	
Patients starting EN+PN together, n (%)	19 (2.8%)	0 (0%)
Time from enrolment to starting EN+PN together, mean (95% CI)	5.58 days (3.90 to 7.96)	
Patients who never received EN or PN, n (%)	278 (40.8%)	2 (0.3%)
Time from enrolment to ICU discharge or death in patients never receiving EN or PN, mean (95% CI)	3.72 days (2.65 to 5.20)	4.50 days (3.21 to 6.30)

**PN:** parenteral nutrition, **EN:** enteral nutrition, **CI:** confidence interval

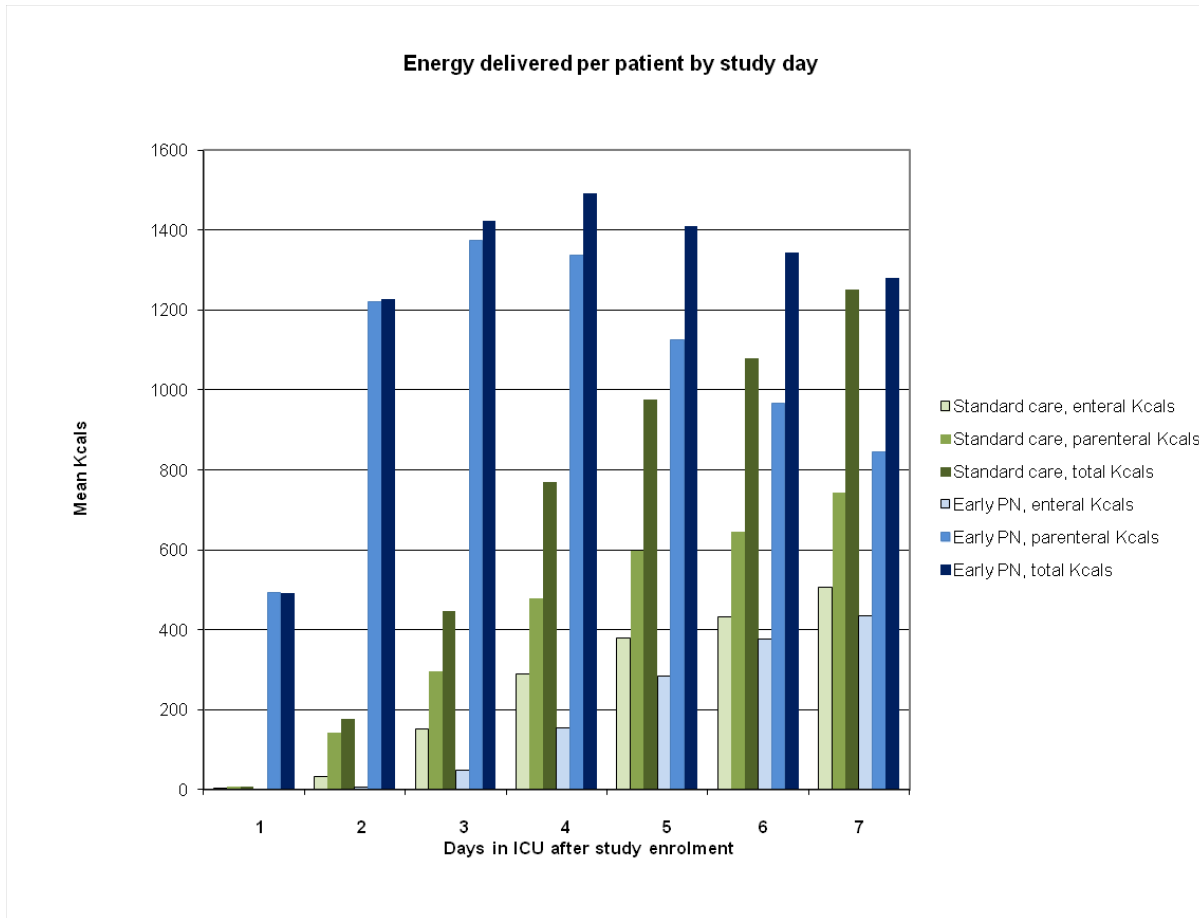


**eTable 5: Clinically Significant Organ Failure and Concomitant Interventions, crude event rates, not adjusted for time at risk (ICU stay)**

Organ system failures, Not adjusted for time at risk of failure (ICU stay) <i>failure days</i>	<b>Standard Care</b> 682 patients mean (95% CI)	<b>Early PN</b> 681 patients mean (95% CI)	<b>mean difference</b> (95% CI) days	<b>p-value*</b>
<b>Renal failure,</b> <i>creatinine &gt; 2.0 mg/dL (170 μmol/L)</i>	1.63 (1.41 to 1.88)	1.74 (1.51 to 2.01)	<b>0.11</b> (-0.32 to 0.69)	0.65
<b>Pulmonary failure,</b> <i>PaO<sub>2</sub>:FiO<sub>2</sub> ratio &lt; 301</i>	7.94 (7.55 to 8.33)	7.31 (6.97 to 7.69)	<b>-0.62</b> (-1.30 to 0.14)	0.11
<b>Hepatic failure,</b> <i>total bilirubin &gt; 2.0 mg/dL (32.5 μmol/L)</i>	1.29 (1.09 to 1.52)	1.20 (1.01 to 1.42)	<b>-0.09</b> (-0.43 to 0.40)	0.69
<b>Coagulation failure,</b> <i>platelets &lt; 81 x10<sup>9</sup>/L</i>	1.91 (1.77 to 2.04)	1.48 (1.38 to 1.58)	<b>-0.43</b> (-0.62 to -0.21)	<0.001
<b>Cardiovascular</b> <i>systolic blood pressure &lt; 90mmHg, not fluid responsive</i>	1.08 (0.97 to 1.21)	0.85 (0.76 to 0.95)	<b>-0.23</b> (-0.40 to 0.02)	0.04
<b>MODs</b> <i>Number of days with two or more organ system failures on the same day</i>	3.78 (3.53 to 4.06)	3.57 (3.34 to 4.83)	<b>-0.21</b> (-0.67 to 0.32)	0.42
<b>Number of patients developing MODS during ICU stay, n (%)</b>	542 (79.5%)	526 (77.2%)	<b>-2.2%</b> (-7.5% to 3.1%)	0.32**
<b>Concomitant therapies and tertiary outcomes,</b> <i>adjusted for time at risk (ICU stay)</i> days per 10 patient•ICU days				
<b>Renal replacement therapy</b>	1.58 (0.94 to 1.43)	0.90 (0.72 to 1.11)	<b>-0.26</b> (-0.57 to 0.22)	0.25
<b>Invasive mechanical ventilation</b>	7.41 (6.99 to 7.85)	6.34 (5.98 to 6.72)	<b>-1.07</b> (-1.77 to -0.29)	0.009
<b>Pressure ulcer treatment</b> <i>Treatment for Stage 1 or greater</i>	1.28 (1.04 to 1.58)	1.02 (0.82 to 1.25)	<b>-0.26</b> (-0.61 to 0.27)	0.28
<b>Low serum albumin</b> <i>&lt; 2.5 g/dL (25 g/L)</i>	5.44 (5.11 to 5.78)	5.25 (4.93 to 5.59)	<b>-0.20</b> (-0.81 to 0.50)	0.56
<b>Systemic antibiotic use</b>	7.35 (7.00 to 7.71)	6.89 (6.56 to 7.24)	<b>-0.46</b> (-1.09 to 0.25)	0.20
<b>Witnessed aspiration</b> events per patient	0.015 (0.012 to 0.017)	0.018 (0.014 to 0.020)	<b>0.003</b> (-0.002 to 0.010)	0.28
<b>Witnessed aspiration</b> <i>with new pulmonary infiltrates</i> events per patient	0.004 (0.002 to 0.010)	0.006 (0.003 to 0.014)	<b>0.001</b> (-0.003 to 0.028)	0.74

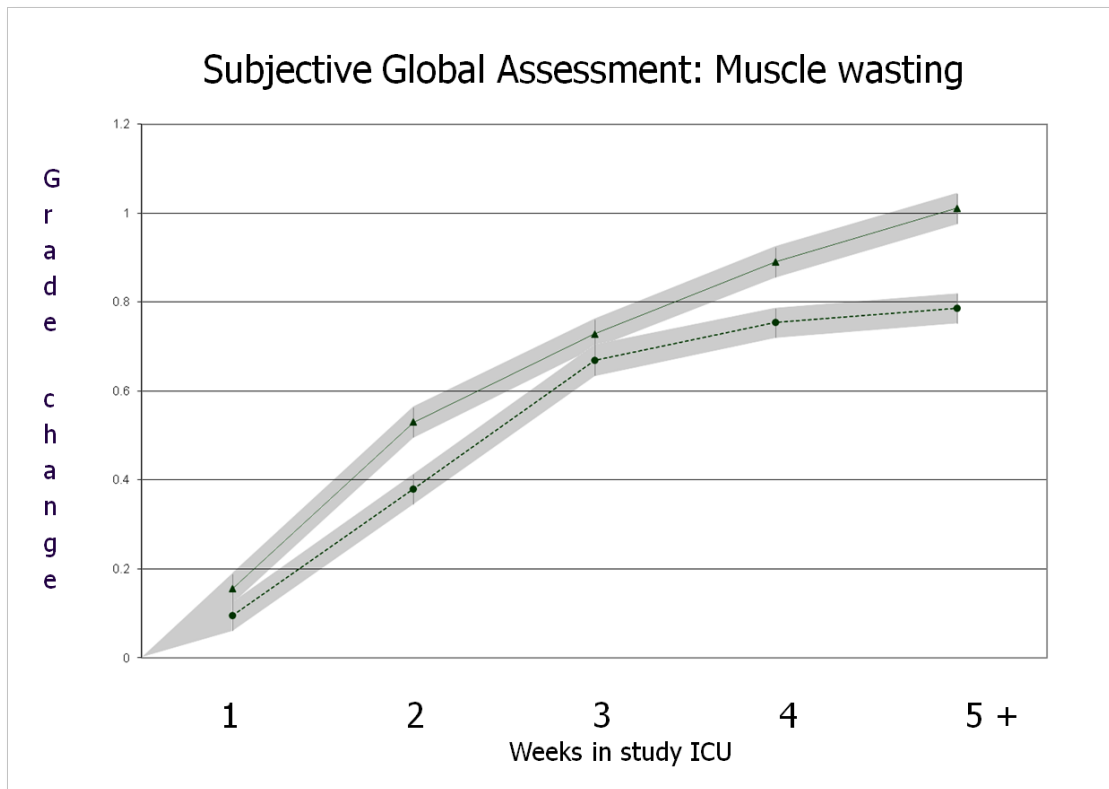
\*p-values from Negative Binomial model. \*\* p-value from exact Pearson chi-square. **PN:** Parenteral Nutrition, **CI:** Confidence Interval, **MODs:** Multiple organ dysfunction syndrome, **ICU:** Intensive Care Unit.

**eFigure 1. Energy intake from enteral nutrition and/or parenteral nutrition during ICU stay**

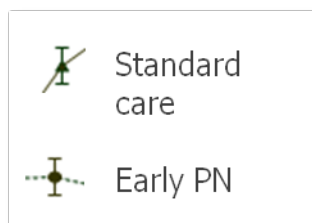


**PN:** parenteral nutrition, **EN:** enteral nutrition, **ICU:** intensive care unit, **Kcals:** kilocalories. Day 1 equals day of study enrolment.

eFigure 2: Subjective Global Assessment of muscle wasting during ICU stay.

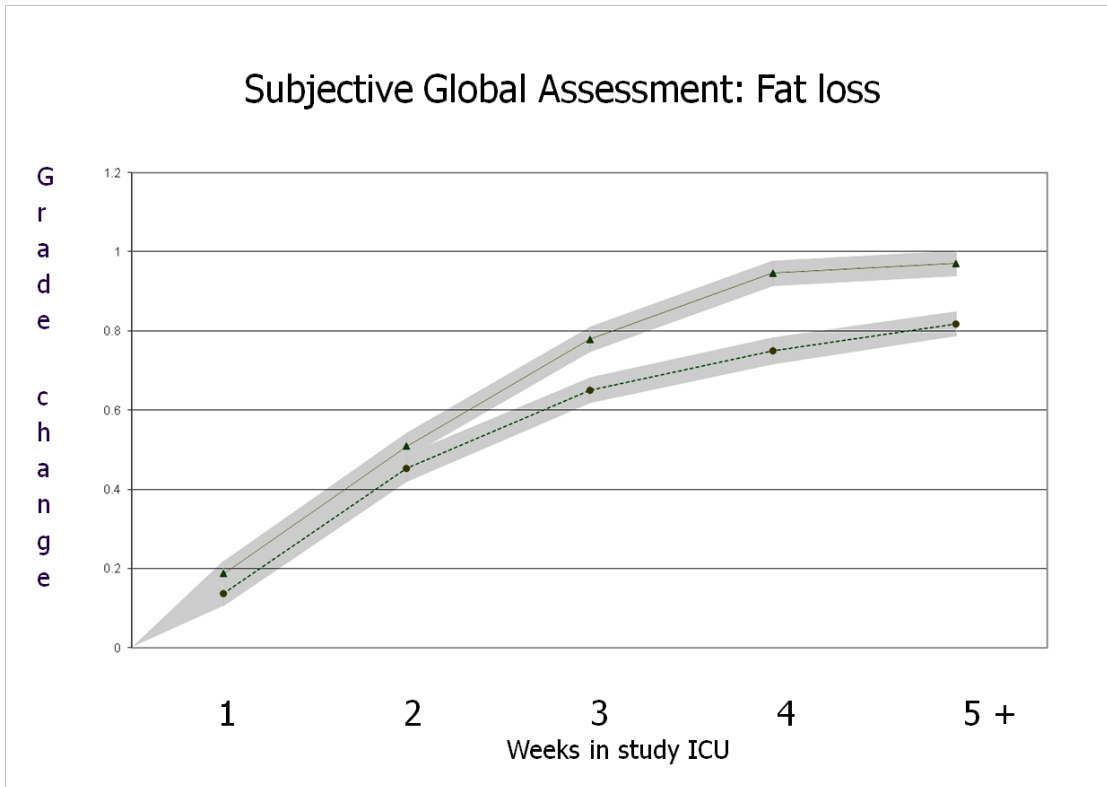


Patients:	681	264	101	44	26	Early PN
	682	254	104	64	38	Standard Care

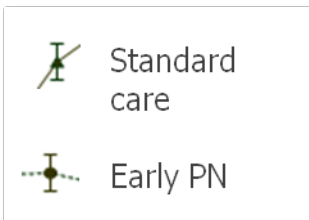


**Legend:** P-values from fully factorial repeated measures ANOVA:  $p < 0.0001$  change over time,  $p = 0.014$  difference between groups (0.16 grade per week). Grey shaded area represents test based 95% confidence interval from fully factorial repeated measures ANOVA analysis between groups. **ICU:** Intensive Care Unit. **PN:** parenteral nutrition.

eFigure 3: Subjective Global Assessment of fat loss during ICU stay.



Patients:	681	264	101	44	26	Early PN
	682	254	104	64	38	Standard Care



**Legend:** P-values from fully factorial repeated measures ANOVA:  $p < 0.0001$  change over time,  $p = 0.045$  difference between groups (0.13 grade per week). Grey shaded area represents test based 95% confidence interval from fully factorial repeated measures ANOVA analysis between groups. **ICU:** Intensive Care Unit. **PN:** parenteral nutrition.