Electronic Supplementary Material to the EAT-ICU trial main publication

Inclusion and Exclusion Criteria for the EAT-ICU Trial

Inclusion
Patients will be randomised as soon as possible, and included and dosed at the latest 24 hours after admission to the ICU. Patients must meet all of the following criteria to be eligible for inclusion:

1. Age ≥ 18 years
2. Acutely admitted to the ICU
3. Expected length of stay in ICU > 3 days
4. Mechanically ventilated, which enables indirect calorimetry
5. Have a central venous catheter wherein PN can be administered
6. Written proxy consent obtained (proxy consent defined as consent from two doctors, who are independent of the trial)
7. Must be able to read and understand Danish.

Patients with one or more of the listed conditions will not be included, as they may have unique nutritional requirements:

- Contraindications to use enteral nutrition
- Contraindications to use parenteral nutrition, e.g. hypersensitivity towards fish-, egg or peanut protein, or any of the active substances in the PN products
- Receiving a special diet
- Burns > 10% total body surface area
- Severe hepatic failure (Child-Pugh class C) or severe hepatic dysfunction**:**
  Bilirubin ≥ 50 µmol/l (3 mg/dl) + alanine aminotransferase ≥ 3 times upper reference value
- Traumatic brain injury
- Diabetic ketoacidosis
- Hyperosmolar non-ketotic acidosis
- Known or suspected hyperlipidemia
- BMI ≤ 17 or severe malnutrition
- Pregnancy
- The clinician finds that the patient is too deranged (circulation, respiration, electrolytes etc.) or that death is imminent

Statistical Analysis Plan for the EAT-ICU Trial of March 23 2016

Amended May 20 2017 to clarify post-randomisation exclusions and populations.
Amended June 1 2017 to clarify the wording of the stratification variable to haematologic malignancy.
Details of the amendment are presented at the end of the SAP, p.5.

POPULATIONS

Intention-to-treat population

All randomised patients except those who withdrew their consent for the use of data.

Per-Protocol population

All randomised patients except patients having one or more protocol violations defined as:

Per-protocol Population #1:

1. Stopped / withdrawn patients
   OR
2. Monitoring revealed that one or more in- or exclusion criteria were violated

Per-protocol Population #2:

1. Stopped / withdrawn patients
   OR
2. Monitoring revealed that one or more in- or exclusion criteria were violated
   OR
3. One or more parental nutrition boluses (any combination of glucose and amino acids and/or lipids) given to patients randomised to the Control Group before trial day 8

Subgroup analysis

The two a priori identified subgroup analyses will be conducted on the following baseline characteristics:

1. P-urea > 20 mmol/l and/or any form of dialysis
2. SAPS II above the median of the included patients

OUTCOME MEASURES

Primary endpoint

1. Physical function 6 months after randomisation (PCS-score of SF-36)

Secondary endpoints

Points 9 - 11 have been specified in order to minimise survival bias.

2. Accumulated energy- and protein balance
3. New organ failure in the ICU (Y/N) (defined as SOFA score of 3 or above in any of the categories ex. Glasgow Coma Scale Score) in patients who did not have the particular organ failure at randomisation
4. Metabolic control:
5. Accumulated insulin administration to maintain B-glucose ≤10 mmol/l
6. Rates of severe hyper- and hypoglycaemia (number of patients with one or more episodes of B-glucose >15 mmol/l and ≤2.2 mmol/l, respectively).
7. Rate of nosocomial infections (Y/N, yes if positive in one of 6 specific type of infections)
8. New onset of renal replacement therapy (Y/N)
9. Percent of days alive without renal replacement therapy at day 90
10. Percent of days alive without mechanical ventilation at day 90
11. Percent of days alive without inotropic/vasopressor support at day 90
12. Length of stay in ICU and -hospital among survivors at 6 months
13. 28-days, 90-days and 6-months mortality, and survival status for all patients 6 months after randomisation of the last patient
14. Mental component summary (MCS) -score of SF-36
15. SARS in the ICU (allergic reactions and elevated plasma levels of liver enzymes)
16. Cost analyses

BASIC PRINCIPLES OF ANALYSIS

Data will be presented as mean (95% confidence interval), median (interquartile range [IQR]), or number (%) as appropriate. All statistical tests will be 2-tailed, and an alpha level of 5% will be used for all tests. All analysis will be computed in the software SAS version 9.4, GraphPad Prism 4 or R version 3.2.2.

PRIMARY ANALYSIS

Analysis of the Primary Outcome Measure

The primary analysis will be performed as regression analysis adjusted by the stratification variable (haematologic malignancy). Standard errors and P-values will be determined using robust standard errors to accommodate possible non-normality of the residuals induced by all diseased having the primary outcome value zero. As a sensitivity analysis the primary outcome will also be analysed using Wilcoxon's test.

Analysis of Secondary Outcome Measures

- Accumulated energy- and protein balance on day 3, 7 and for the entire ICU stay (the latter also adjusted for number of ICU days) will be analysed using repeated measures mixed effect model. The model will include days in ICU (as a factor variable), treatment group and an interaction term between the two.

- New organ failure in the ICU (defined as SOFA score of 3 or above in every category ex. Glasgow Coma Scale Score) in patients who did not have that particular organ failure at randomization. As the primary analysis the variable time-to-new-organ-failure will be analysed using Cox proportional hazards model. Death without preceding organ failure will be treated as a competing event. Secondary analysis will be presence of new organ failure (y/n) during ICU stay compared using Chi square test.

- Metabolic control:
    a. Accumulated insulin administration to maintain B-glucose ≤10 mmol/l will be analysed by regression adjusted for number of ICU days
    b. Rates of severe hyper- and hypoglycaemia (B-glucose >15 mmol/l and ≤2.2 mmol/l, respectively) will be analysed by Chi-squared test

- Nosocomial infections during ICU stay (Y/N). As the primary analysis the variable time-to-nosocomial-infection will be analysed using Cox proportional hazards model. Death without preceding nosocomial-infection will be treated as a competing event. Secondary analysis will be presence of nosocomial infection (y/n) during ICU stay compared using Chi square test.

- New onset of renal replacement therapy (Y/N) will be analysed by Chi-squared test.

- Percent of days alive without renal replacement therapy, mechanical ventilation, inotropic / vasopressor support in the 90-days will be analysed by Wilcoxon's test.

- Length of stay in ICU and -hospital among 6-month survivors will be analysed Wilcoxon's test.

- 28-days, 90-days and 6-months mortality will be analysed by Chi-square test, and survival status for all patients 6 months after randomisation of the last patient will be analysed by Cox proportional hazard models. If the assumption of proportional hazards is not met we will instead employ Kaplan-Meier plots and p-value derived from the log-rank test.

- Mental component summary (MCS) -score of SF-36 will be analysed using regression analysis.

- SARs in the ICU (allergic reactions and elevated plasma levels of liver enzymes). Primary analysis will be presence of SARs (y/n) during ICU stay compared using Chi-squared test. As a secondary analysis the variable time-to-first-SARs will be analysed using Cox proportional hazards model.

- Cost analyses will be performed as in Doig GS et al; Clinicoecon Outcomes Res. 2013;5:369-379. doi:10.2147/CEOR.S48821 and Doig GD et al; Clinicoecon Outcomes Res. 2013;5:429-436. doi:10.2147/CEOR.S50722.

SECONDARY ANALYSIS

Analysis of the Primary Outcome Measure

Regression analysis adjusted for the stratification variable, SOFA baseline and age.

MISSING DATA

Missing Primary Outcome Data

At <5% missing data for the primary endpoint (physical QoL), analysis will be performed on these data (complete case analysis). If data for the primary endpoint is missing for >5% of the included patients (e.g. lack of consent or no reply at follow-up) the primary analysis will be done on the imputed dataset (multiple imputation). The better imputation model will be chosen based on the data. The statistician will do this before being unblinded.

Missing Items

We do not expect missingness among items in the SF-36 interview as it is performed by phone.

Missing Scales

If it is not possible to obtain SF-36 from a patient, and the patient is not dead at 6 months after randomisation, multiple imputation will be used (based on MCMC simulations; all available baseline and follow-up date will be used in the imputation).

Death

Patients who are dead 6 months after randomisation will be given the value 0 in all items, and thereby PCS = 0.

Missing Secondary Outcome Data

Only complete case analysis will be made, except for the following:

- New organ failure in the ICU (SOFA-score)
- Days alive without renal replacement therapy, mechanical ventilation, inotropic/vasopressor support

SOFA score excluding the GCS score

If bilirubin or platelets are missing a given day, last observation will be carried forward. For the remaining SOFA domains we expect no missingness. If patients are transferred to another ICU, that ICU will be contacted regarded the remaining SOFA scores of the specific patient.

Days alive without renal replacement therapy, mechanical ventilation, inotropic/vasopressor

If data are not available, logical imputation will be used. If the patient was not in an ICU (according to the administrative database for Danish hospitals GSOpen) the patient will be considered free of ventilation and inotropic/vasopressor support. If the patient was in an ICU we will obtain data from that ICU. For RRT, the last observation will be carried forward. Because we use hospital registries to obtain RRT data, very few missing data are expected.

Missing Baseline Data

We register SOFA at baseline including values from the 24 hours prior to randomisation. Thus patients randomised immediately after ICU admission may also have missing values in this score.
For SOFA baseline, scores day 1 values may reflect patient's condition. However day 1 has variable lengths as it starts at time of randomisation and ends at 06:00 next day. Thus variables may be missing at both baseline and day 1. In these situations data from day 2 may be representative of the patient's condition.
If the frequency of missing data after the above implemented logical imputation is > 5% we will perform "best"/"worst" case scenarios where

1. Missing SOFA-components in group A will be given to the worst possible score AND missing SOFA-components in group B will be given the best score (zero)
   AND
2. Missing SOFA-components in group A will be given the best score (zero) AND missing SOFA-components in group B will be given the worst possible score. If there is no reasonable difference between the results of these two analyses, we will not do further imputation.

AMENDMENT
Statistical Analysis Plan for the EAT-ICU Trial May 20 2017

The statistical analysis plan (SAP) of March 23 2016 contained an insufficient and imprecise description of the intention-to-treat population used in the EAT-ICU Trial.

The following procedure for post-randomisation exclusions was used during the trial period to allow the exclusion of patients not contributing to the trial without increasing the risk of bias [1]. Following this, these patients are also excluded from the intention-to-treat population.

This procedure and definition of the intention-to-treat population was also used in other randomised trials initiated at Department of Intensive Care 4131, Copenhagen University Hospital, Rigshospitalet [2, 3].

PROCEDURE FOR POST-RANDOMISATION EXCLUSIONS
Patients were excluded post-randomisation, and new patients randomised to obtain the full sample size, if during trial they withdrew consent, died before receiving the intervention, or in- or exclusion criteria were violated and the patient had not received the intervention.

POPULATIONS
Intention-to-treat population (as of the SAP amended May 20 2017)
All randomised patients except those who:

- withdrew their consent for the use of data
- died before receiving the intervention
- were wrongly enrolled and never received the intervention

AMENDMENT
Statistical Analysis Plan for the EAT-ICU Trial June 1 2017

The statistical analysis plan of March 23 2016 contained an insufficient description of the stratification variable used in the EAT-ICU Trial. The variable was given as 'haematological disease'. The correct variable is 'haematologic malignancy'.

1. Fergusson D, Aaron SD, Guyatt G, Hébert P (2002) Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. BMJ 325:652–4.
2. Perner A, Haase N, Guttormsen AB, et al (2012) Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med 367:124–34.
3. Holst LB et al (2014) Lower versus Higher Hemoglobin Threshold for Transfusion in Septic Shock. N Engl J Med 371:1381–1391.

Table S1. Additional baseline characteristics

Variable	Early Goal-directed Nutrition (N=100)	Standard of care (N=99)
Ideal body weight, kg [a]	71 (60 – 75)	67 (62 – 75)
Height, meters	1.75 (1.67 – 1.80)	1.75 (1.65 – 1.80)
Severe co-existing illness [b] - no. (%)		
Myocardial infarct	6 (6%)	3(3%)
Congestive heart failure	12 (12%)	9 (9%)
Peripheral vascular disease	3 (3%)	2 (2%)
Cerebrovascular disease	4 (4%)	8 (8%)
Dementia	0 (0%)	1 (1%)
Chronic pulmonary disease	14 (14%)	10 (10%)
Connective tissue disease	3 (3%)	3 (3%)
Ulcer disease	15 (15%)	20 (20%)
Mild liver disease	2 (2%)	2 (2%)
Diabetes	15 (15%)	15 (15%)
Hemiplegia	2 (2%)	2 (2%)
Moderate/severe renal disease	16 (16%)	8 (8%)
Any tumor	13 (13%)	12 (12%)
AIDS	0 (0%)	0 (0%)
Organ failures [c] - no. (%)		
Respiratory failure	23 (23%)	21 (21%)
Circulatory failure	56 (56%)	46 (46%)
Hepatic failure	1 (1%)	0 (0%)
Kidney failure	9 (9%)	12 (12%)
Coagulation failure	0 (0%)	5 (5%)
Baseline p-triglyceride, mmol/l	1.71 (1.32 – 2.48)	1.63 (1.01 – 2.50)
No. of patients on nutrition pre-randomisation - no. (%) [d]	49 (49%)	49 (49%)
No. of patients receiving insulin in the ICU pre-randomisation - no. (%)	19 (19%)	7 (7%)
Insulin administration in patients receiving pre-randomisation insulin, IE/d [e]	20 (10 – 46)	40 (8 – 222)
Baseline blood glucose, mmol/l	8.1 (6.3 – 9.8)	7.5 (6.1 – 8.8)

Values are medians (interquartile ranges) or numbers (%).
AIDS, acquired immunodeficiency syndrome.
[a]Ideal body weight was calculated as estimated height (cm) minus 100 for men and minus 105 for women
[b]Defined according to a modified Charlson comorbidity index.
[c]Defined as Sequential Organ Failure Assessment score > 3 at time of randomisation. Data for cerebral failure not collected. Some patients had more than one organ failure at time of randomisation.
[d]Enteral nutrition commenced before randomisation.
[e]Timespan from admission to randomisation, not necessarily 24 hour period.

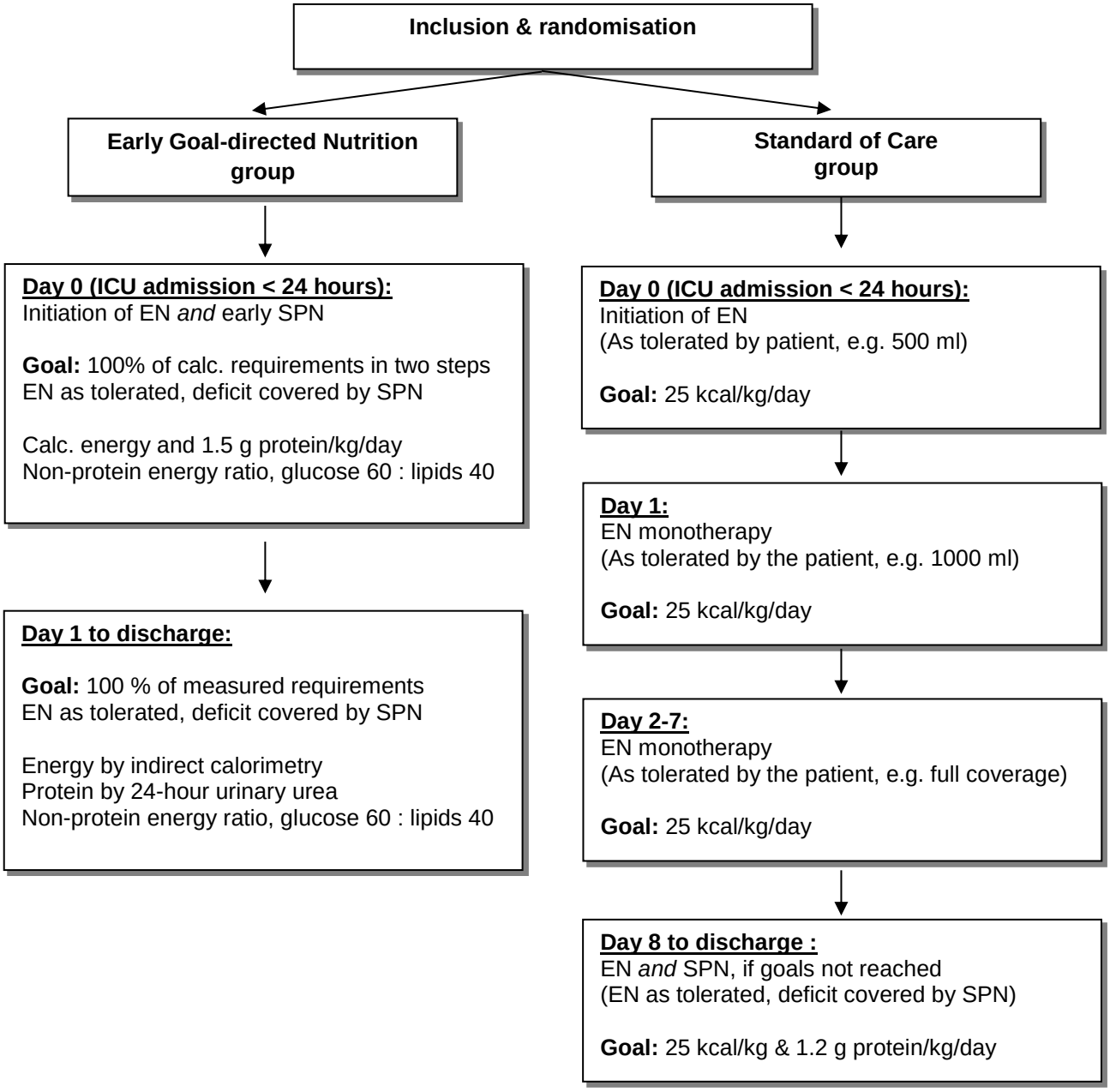

Figure S1. Flowchart summarising the nutrition protocols in the two intervention groups.
EN, Enteral Nutrition; SPN, Supplementary Parenteral Nutrition

Table S2. Additional information on feeding and protocol procedures after randomisation

Variable	**Early Goal-directed Nutrition (N=100)**	**Standard of Care (N=99)**
No. of indirect calorimetry measurements, no./patient	2 (2 – 4)	2 (1 – 3)
Time from ICU admission to commencement of nutrition, hours		
Enteral nutrition	16 (10 – 21)	15 (8 – 21)
Parenteral nutrition [a]	18 (13 – 23)	NA
Blood glucose 8 hours after commencement of nutrition, mmol/l	9.4 (7.2 – 11.3)	7.9 (6.4 – 9.3)
Lowest daily blood glucose in ICU, mmol/l	7.0 (6.1 – 7.8)	6.6 (6.0 – 7.3)
Highest daily blood glucose in ICU, mmol/l	11.0 (9.3 – 12.4)	9.4 (8.5 – 10.9)
Lipid intake in ICU, g/day [b]	53 (39 – 67)	32 (17 – 46)
Median p-triglyceride in ICU, mmol/l	1.82 (1.35 – 2.36)	1.76 (1.18 – 2.43)

Values are medians (interquartile ranges).
ICU, Intensive Care Unit.
[a]Seven patients in the standard of care group had received 50% glucose after randomisation (mean 148 ml, min 20 ml, max 280 ml). No patients in the standard of care group had parenteral nutrition prescribed (defined as any combination of glucose and amino acids and/or lipids) before day 8, but 5 patients received this in error (protocol violation). In contrast, all patients in the EGDN group received parenteral nutrition from the first trial day.
[b]Including fat from non-nutrition sources, e.g. propofol. There was no difference in propofol administration between the two groups.

Table S3. Characteristics on the collection of data for the primary outcome measure (PCS-score) 6 months after randomisation by the SF-36 questionnaire

Variable	Early Goal-directed Nutrition (N=100)	Standard of Care (N=99)
Completed questionnaires – no (%)	51/100 (51%)	53/99 (54%)
Not completed questionnaires – no (%)		
Death [a]	37/100 (37%)	35/99 (35%)
Alive, but not responding	12/100 (12%)	11/99 (11%) [b]
Mode of survey – no (%)		
Telephone interview	37/51 (73%)	44/53 (83%)
Face-to-face	1/51 (2%)	1/53 (2%)
Self-administration	13/51 (25%) [c]	8/53 (15%)

Values are number (%).
SF-36, Short Form 36
[a]Patients who had died at 6 month follow-up were given the value zero.
[b]One patient in the standard of care group returned an incomplete questionnaire by mail, on which PCS and MCS-scores could not be generated, and was therefore counted as missing.
[c]For one patient in the EGDN group the questionnaire was completed by two surrogates as the patient was still in the ICU on trial day 180 and unable to complete the questionnaire independently.

Table S4. Results of the pre-defined supplementary analyses of the primary outcome measure (PCS-score) 6 months after randomisation

	Early Goal-directed Nutrition (N=100 in the ITT population)	Standard of Care (N=99 in the ITT population)	Mean Difference (95% CI)	P-value
Complete case analysis, n=176	22.4 (21.9)	22.4 (21.3)	-0.0 (-6.4 to 6.4)	0.99
Complete case analysis using Wilcoxon's test, n=176	25.1 (0 – 42.3)	27.2 (0 – 39.7)	NA	0.98
Complete case analysis adjusted for stratification variable (haematological malignancy), n=176	22.4 (21.9)	22.4 (21.3)	-0.2 [a] (-6.4 to 6.0)	0.95
Complete case analysis adjusted for stratification variable, baseline SOFA score and age, n=176	22.4 (21.9)	22.4 (21.3)	-0.7 [a] (-6.9 to 5.4)	0.81
Per-protocol population #1, n=168 [b]	23.7 (22.0)	22.9 (21.3)	0.8 (-5.5 to 7.2)	0.79
Per-protocol population #2, n=163 [c]	23.7 (22.0)	22.7 (21.2)	1.1 (-5.3 to 7.6)	0.72
PCS-score in 6-month survivors only, n=104 [d]	38.6 (14.0)	37.2 (14.2)	2.0 (-3.5 to 7.5)	0.48

Values are means (SD) or medians (IQR).

ITT, intention-to-treat; SOFA, Sequential Organ Failure Assessment.

[a]Discrepancies between the mean differences and groups means are due to the adjustments performed in the analyses.

[b]Per-protocol population #1 defined as stopped/withdrawn patients (n=8) or monitoring revealed that one or more in- or exclusion criteria were violated (n=0).

[c]Per-protocol population #2 defined as stopped/withdrawn patients (n=8) or monitoring revealed that one or more in- or exclusion criteria were violated (n=0) or one or more parental nutrition boluses (any combination of glucose and amino acids and/or lipids) given to patients randomised to the standard of care group before trial day 8 (n=5).

[d]Post-hoc analysis not defined in the Statistical Analysis Plan.

Table S5. Results of analyses of the primary outcome measure (PCS-score) 6 months after randomisation in the pre-defined subgroups in the complete case population

Baseline subgroup	Early Goal-directed Nutrition (N=88)		Standard of Care (N=88)		Mean Difference (95% CI)	P-value of the test of interaction
	N	Mean (SD)	N	Mean (SD)		
Plasma urea >20 mmol/l or use of RRT						
Yes	17	13.3 (17.5)	14	14.6 (21.4)	-1.6 (-16.5 - 13.1)	0.58
No	71	24.5 (22.4)	74	23.9 (21.1)	0.9 (-5.9 - 7.8)	
SAPS II > median of all included patients						
Yes	43	16.0 (19.8)	43	16.6 (21.0)	-0.2 (-9.0 - 8.5)	0.92
No	45	28.5 (22.3)	45	27.9 (20.3)	-1.2 (-9.6 - 7.1)	

Values are numbers in subgroup and means (SD).

PCS, Physical Component Summary; RRT, Renal Replacement Therapy; SAPS, Simplified Acute Physiology Score.

Table S6. Results of post-hoc analyses [a]

	Early Goal-directed Nutrition (N=100)	Standard of Care (N=99)	Mean Difference (95% CI)	P-value [b]
Length of ICU stay, median days (IQR)	8 (5-25)	7 (4-12)	NA	0.03
Length of mechanical ventilation, median days (IQR)	6 (4-15)	5 (3-10)	NA	0.10
Length of RRT in patients requiring RRT, median days (IQR)	4 (2-17)	6 (3-8)	NA	0.56

Values are medians (IQR).

ICU, Intensive Care Unit; IQR, Interquartile Range; RRT, Renal Replacement Therapy.

[a]Analyses performed post-hoc after the request of a reviewer.

[b]Analysed by Wilcoxon's test.