



PRECISe
The impact of high versus standard enteral protein provision on functional recovery following Intensive Care admission: a randomized controlled, multicenter, parallel group trial in mechanically ventilated, critically ill patients

Clinical Study Report

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First patient in 19 NOV 2020

Last patient last visit 12 OCT 2023

Early Study Termination ☐Yes ☒No

CONTACT DETAILS

National Coordinator Belgium:

Prof. dr. Dieter Mesotten

Department of Anaesthesiology & Intensive Care Medicine, Ziekenhuis Oost-Limburg, Genk, Belgium

Faculty of Medicine and Life Sciences, Limburg Clinical Research Center (LCRC), Hasselt University, Diepenbeek, Belgium

Chief Investigator Sponsor MUMC+:

Prof. dr. Marcel van de Poll

Department of Intensive Care Medicine & Department of Surgery, Maastricht University Medical Center, Maastricht, Netherlands

Maastricht School for Nutrition and Translational Research in Metabolism (NUTRIM), Maastricht University, Maastricht, Netherlands

The study was performed in compliance with Good Clinical Practices, including archiving of essential documents.



1. DOCUMENT HISTORY

Version No	Version date	Author	Reason for change
1.0	6 DEC 2024	Dieter Mesotten	

2. SYNOPSIS

Trial title	The impact of high versus standard enteral protein provision on functional recovery following Intensive Care admission: a randomized controlled, multicenter, parallel group trial in mechanically ventilated, critically ill patients
Short title	PRotEin provision in Critical IllneSs (PRECISE)
Study type	Interventional
Final sample size	935 patients
Trial duration (FPI -LPLV)	19 NOV 2020 – 12 OCT 2023
Purpose and rationale	To investigate whether increased protein provision in critically ill patients during Intensive Care Unit (ICU) admission can improve functional outcome and recovery following ICU discharge
Primary endpoint	Overall between group-differences in health Related Quality of Life (HRQL) at 30 days, 90 days, and 180 days after index ICU admission, assessed by EuroQoL (EQ-5D-5L)
Secondary endpoints	Established Core Outcome Measures Set developed by an international expert panel using Delphi consensus methods: • Overall survival at 30, 60, 90 and 180 days after ICU admission • Changes in health-related quality of life, as assessed by Short Form 36 (SF-36) questionnaire, completed at 30 days, 90 days, and 180 days after ICU admission • Changes in the mental health status, assessed by the Hospital Anxiety and Depression Scale (HADS) and IES-R Impact of Event Scale, all completed at 30 days, 90 days, and 180 days after ICU admission • Changes in self-reported health, assessed by the EQ-VAS of the EQ-5D-5L, completed at 30 days, 90 days, and 180 days after ICU admission • Changes in the pain level, assessed by the pain question of the EQ-5D-5L questionnaire, completed at 30 days, 90 days, and 180 days after ICU admission • Changes in physical function, as assessed by the 6-minute walk test performed at 30 days, 90 days, and 180 days after ICU admission • Changes in muscle and nerve function, as assessed by the MRC-SUM score and Handgrip strength (Dynamometer), performed at 30 days, 90 days, and 180 days after ICU admission

Tertiary endpoints	• Hospital mortality • Sixty-day mortality • Time-to-discharge-alive from hospital • Days alive and at home at 90 days (DAAH₉₀) • Domain data EQ-5D-5L: scores of subdomains of EQ-5D-5L at 30, 90, and 180 days after admission • Duration of mechanical ventilation during index ICU stay • The incidence of ICU-acquired infections during index ICU stay • The incidence of acute kidney injury (AKI) (serum creatinine level > 2 times baseline level) during index ICU stay • The incidence and duration of renal replacement therapy (number of patients who received renal replacement therapy and days on it)The incidence of hepatic dysfunction (bilirubin level > 3 mg/dl) during index ICU stay • Maximum and mean SOFA score during the first 14 days of index ICU stay • The difference in frailty at 30 days, 90 days, and 180 days, assessed by the Rockwood Clinical Frailty Scale • Administration of prokinetics during index ICU stay (number of patients who received a prokinetic and number of days on it) • The difference in mobilization treatment during index ICU stay • Length of index ICU stay • Length of index hospitalisation • The incidence of ICU-readmissions during index hospitalisation • Destination after hospital discharge • Length of stay at a rehabilitation facility after index hospitalisation • Time to return to work • The incidence of gastrointestinal intolerance/symptoms (i.e. vomiting, ischemia, diarrhea, abdominal distension, gastric paresis, bleeding/ulcer) during index ICU stay
Trial design	The PRECISE trial was a pragmatic, international multi-center, randomized controlled, quadruple-blinded study comparing two isocaloric, isovolumetric enteral feeds with either a standard (5g protein/100 kcal) or high (8g protein/100 kcal) protein content in adult, mechanically ventilated patients, admitted to an Intensive Care Unit. The study consisted of 3 phases: • <u>Screening phase</u>: starting from identifying a study subject until the first nutrition will be given. • <u>Treatment phase</u>: starting from the first nutrition until ICU discharge or a maximum of 90 days of ICU admission. • <u>Follow-up phase</u>: starting when the treatment phase ends or at 30 days after ICU admission (whichever comes first) until 180 (± 4) days after ICU admission.

Trial participants	The study population consisted of adult patients with an unplanned admission to the ICU, who are mechanically ventilated within 24 hours following ICU admission and who have an expected duration of mechanical ventilation of at least 3 days (i.e. indication for enteral nutrition support).
Main inclusion criteria	• Adult (≥ 18 years) patient admitted to the ICU • Unplanned ICU admission • Invasive mechanical ventilation initiated <24 hours following ICU admission • Expected ICU stay on mechanical ventilation of ≥ 3 days
Main exclusion criteria	• Contraindication for enteral nutrition at the discretion of the treating physician • Moribund or expected withholding of treatment • Kidney failure and “no dialysis”-code on admission • Hepatic encephalopathy (West Haven criteria 3-4) • Body mass index <18 kg/m²
Safety assessments	Interim safety analysis on mortality by independent Data Safety Monitoring Board (DSMB). The interim safety analysis was performed after finalization of the follow-up phase of the 412 th enrolled patient.
Statistical analysis	• Treatment effect for the primary endpoint, the EQ-5D-5L index score, was evaluated by means of a linear mixed model for longitudinal data analysis with a 3-level structure. The statistical model included a fixed effect for treatment, a random effect for center and a random effect for participants (intercept, slope). • For the secondary endpoint ‘survival’, Kaplan-Meier curves were constructed for both treatment arms. A mixed effect Cox proportional hazard model with a 2-level structure (patients clustered within centers) was subsequently used to investigate treatment effect. • Other secondary endpoints were calculated similar to the primary endpoint. Missing values for the secondary endpoints were, expectedly much higher than for the primary endpoint due to ‘truncation by death’. • All hypotheses are 2-sided and tested with a significance level of $\alpha=0.05$
Summary - Conclusion	• Results: Between Nov 19, 2020, and April 14, 2023, 935 patients were randomly assigned. 335 (35.8%) of 935 patients were female and 600 (64.2%) were male. 465 (49.7%) of 935 were assigned to the standard protein group and 470 (50.3%) were assigned to the high protein group. 430 (92.5%) of 465 patients in the standard protein group and 419 (89.1%) of 470 patients in the high protein group were assessed for the primary outcome. The primary outcome, EQ-5D-5L health utility score during 180



	days after randomization (assessed at 30 days, 90 days, and 180 days), was lower in patients allocated to the high protein group than in those allocated to the standard protein group, with a mean difference of -0.05 (95% CI -0.10 to -0.01; $p=0.031$). Regarding safety outcomes, the probability of mortality during the entire follow-up was 0.38 (SE 0.02) in the standard protein group and 0.42 (0.02) in the high protein group (hazard ratio 1.14, 95% CI 0.92 to 1.40; $p=0.22$). There was a higher incidence of symptoms of gastrointestinal intolerance in patients in the high protein group (odds ratio 1.76, 95% CI 1.06 to 2.92; $p=0.030$). Incidence of other adverse events did not differ between groups. • Conclusion: High enteral protein provision compared with standard enteral protein provision resulted in worse health-related quality of life in critically ill patients and did not improve functional outcomes during 180 days after ICU admission.
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4. LIST OF ABBREVIATIONS

5. ETHICS

5.1. Independent Ethics Committee (IEC)

The protocol, protocol amendments, informed consent form (ICF), and other relevant documents were submitted to the central and local Independent Ethics Committees (IECs) of the participating hospitals by the Principal Investigator or sponsor and reviewed and approved by the Independent Ethics Committee of UZ Brussel (BE) and MUMC+ (NL) before the study was initiated. Any amendments to the protocol obtained IEC approval before implementation of changes made to the study design. The list of independent Ethical Committees consulted can be found in the appendix.

5.2. Ethical Conduct of the Study

This study was conducted in accordance with the protocol and consensus ethical principles derived from international guidelines including the Declaration of Helsinki, International Ethical Guidelines, applicable ICH GCP Guidelines, and other applicable laws and regulations.

5.3. Patient information and Consent

The investigator or his/her representative explained the nature of the study to the participant or his/her legally authorized representative and answered all questions regarding the study. Participants and/or their legally authorized representative were informed that their participation was voluntary. Participants or their legally authorized representative were required to sign a statement of informed consent that met the requirements of local regulations, and the IEC or study centre. Investigative sites were instructed to obtain written informed consent before the participant was enrolled in the study and document the date the written consent was obtained. The authorized person obtaining the informed consent was also instructed to sign the ICF. A copy of the ICF was provided to the participant or the participant's legally authorized representative.

5.4. Regulatory approval

As applicable according to local regulations, the protocol and all protocol amendments were reviewed and approved by all relevant regulators.

6. CHIEF INVESTIGATORS AND ADMINISTRATIVE STRUCTURE

Chief Investigator (NL)	Prof. dr. Marcel van de Poll Department of Intensive Care Medicine & Department of Surgery, Maastricht University Medical Center, Maastricht, Netherlands
National Coordinator (BE)	Prof. dr. Dieter Mesotten Department of Anaesthesiology & Intensive Care Medicine, Ziekenhuis Oost-Limburg, Genk, Belgium
Trial Steering Committee	<i>Chief Investigator</i> (NL): Marcel van de Poll <i>National Coordinator</i> (BE): Dieter Mesotten

	<i>Representatives of funders:</i> Nelle Stocquart (KCE) and Marlous Dillingh (ZonMW) <i>Patient representatives:</i> Frieda Demuydt (BE) and Lilian Vloet (NL) <i>Independent experts:</i> Adam M Deane Zudin Puthucheary Peter J M Weijs <i>Trial statistician:</i> Sander M J van Kuijk <i>Study site principal investigators:</i> Albertus Beishuizen (NL) Arthur R H van Zanten (NL) Ashley De Bie Dekker (NL) Clarissa Scheeren (NL) Vincent Fraipont (BE) Stoffel Lamote (BE) Didier Ledoux (BE) Elisabeth De Waele (BE) <i>Trial management:</i> Julia L M Bels
Data Safety Monitoring Board	Liesbeth Bruckers (statistician) Riet Smets Dylan.W. de Lange Sophie van Cromphaut (chair)
Trial Statistician	Sander M J van Kuijk
Authors of this report	Dieter Mesotten Marcel van de Poll

7. INTRODUCTION

Patients who survive critical illness often have low quality of life. This reduced quality of life has been attributed to persistent muscle wasting and weakness, among other factors, which develop during the first week of intensive care unit (ICU) admission. Quality of life can remain impaired for years after ICU discharge, but increased protein provision could improve functional outcomes after critical illness by alleviating muscle catabolism and weakness. However, evidence is controversial as observational data show both benefit and harm.

Due to scarce prospective data, uncertainty remains about whether high dose protein is beneficial, with contemporary guidelines recommending wide targets of between 1.2 g/kg per day and 2.0 g/kg per day. The EFFORT Protein trial reported no effect of high protein nutrition on time-to-discharge-alive from hospital or on 60-day mortality in critically ill patients.

In addition to mortality, long-term physical function and patient reported quality of life are important outcomes after critical illness. Although health-related quality of life has been included as a secondary outcome in some previous trials of nutritional therapy, no large clinical trial of a nutritional intervention in critical care has used quality of life as the primary outcome.

On the basis of strong evidence and consensus, guidelines from the European Society for Clinical Nutrition and Metabolism recommend enteral feeding over parenteral feeding to administer nutrition. These guidelines recommend a daily protein intake of 1.3 g/kg, whereas guidelines from the American Society for Parenteral and Enteral Nutrition recommend a daily protein intake ranging from 1.2 g/kg to 2.0 g/kg.

The aim of the PRECISE trial was to assess whether higher enteral protein provision (ie, 2.0 g/kg per day) would improve health-related quality of life and functional outcomes in critically ill patients who were mechanically ventilated compared with standard enteral protein provision (ie, 1.3 g/kg per day).

8. STUDY OBJECTIVES AND ENDPOINTS

The PRECISE study will investigate whether enteral nutrition with increased protein content during critical illness is able to improve functional recovery following ICU admission, compared to a standard enteral formula. Improving nutritional support to attenuate the catabolic state during ICU stay could lead to a reduction in hospital length of stay, increased physical functioning, and preservation of strength, faster return to work, and most importantly improved health-related quality of life in the longer term.

The choice for functional endpoints is motivated by the fact that it is nowadays increasingly recognized that primary endpoints in ICU trials should be shifted away from classical outcomes such as survival or length of stay, and instead should focus more on patient-defined, functional outcomes. For ICU trials in particular, HRQL has been suggested as potential primary trial endpoint, since it reflects functional outcome at best. To this end, the Core Outcome set (COS) from the Outcomes After Critical Illness and Surgery (OACIS) Group, registered in the COMET initiative database, will be used for primary and secondary outcomes measures. This COS consists of seven measurable items including HRQL, mental health, physical and muscle function (Table 1). After the Delphi process, the conclusion was that at least Survival, Health Related Quality of Life, Mental Health and Pain should be assessed as part of a minimum acceptable COS configuration, whereas the assessment of Cognition, Physical function and

Muscle/Nerve function is optional. The primary and secondary objectives in the PRECISE trial are based on the COS of the OACIS Group.

Table 1 Core Outcome Set for Clinical Research in Acute Respiratory Failure Survivors.

Minimum acceptable configuration (consensus achieved during Delphi process)				
Outcomes	Survival	Health Related Quality Of Life	Mental Health	Pain
Measures	Date and location of death	EQ-5D SF-36 (optional)	HADS IESR	EQ-5D pain question
Optional extensions (no consensus achieved during Delphi process)				
Outcomes	Cognition	Physical Function	Muscle and/or Nerve Function	Pulmonary Function
Measures	MoCA BLIND	6-Minute Walk Test	Manual Muscle Test Handgrip Strength	None
Needham et al. AJRCCM 2017; 196 (9): 1122-1130				

8.1. Primary Objective and Endpoint

The primary objective of the PRECISE study was to assess whether increased enteral protein provision during critical illness improves HRQL after ICU admission.

To address this research question, the **EuroQoL EQ-5D-5L** was used as primary endpoint measure. Since mortality can be taken into account within the EQ-5D-5L, no data imputation due to mortality was required, which makes the EQ-5D-5L particularly applicable in this vulnerable population where mortality had been expected to be high.

The EQ-5D-5L consists of a descriptive system in 5 dimensions; i.e. mobility, self-care, usual activities, pain/discomfort and anxiety/depression; and a visual analogue scale for overall self-rated health (EQ-VAS). The EQ-5D can be converted into a single summary index, using a country specific value set. The PRECISE trial will use country specific value sets for Belgium and the Netherlands. The single summary index ranges from -0.532 0 to 1.0 (with a score of 0 indicating death, a score below 0 a state worse than death, a higher score indicating better health and a score of 1 indicating perfect health). The fact that the EQ-5D incorporates death and the unconscious state into the single summary index in a robust and valid way has major methodological advantages in an ICU trial with an expected high mortality, in contrast to other functional outcome questionnaires (including the SF-36) or physical function measures. An additional advantage for an intensive care international multicenter trial is that the EQ-5D is valid for both patient and proxies and has been translated in different languages (<https://euroqol.org/eq-5d-instruments>).

8.2. Secondary Objectives and Endpoints

In other landmark studies on functional outcome in prolonged critically ill patients, the SF-36 questionnaire has been used as indication for health-related quality of life. Therefore, in addition to the EQ-5D-5L, the SF-36 questionnaire was incorporated in the PRECISE Trial.

Measures to assess physical and muscle function were incorporated in the PRECISE trial to investigate whether a high-protein enteral provision will result in more physical and muscle strength (i.e. the 6-minute walk test, the Medical Research Council (MRC)- SUM score and handgrip strength). Because muscle weakness is a key determinant of long-term functional outcomes and quality of life, this should also translate into improved quality of life (SF-36), pain level (assessed by the pain question in the EQ5D questionnaire) and mental health status (assessed by Hospital Anxiety and Depression Scale (HADS) and Impact of Event Scale Revised (IES-R) the EuroQol Visual analogue scale (EQ-VAS) of the EQ-5D-5L).

Although prospective data have never shown any effect of nutrition on mortality, there is retrospective data suggesting that our protein strategy in the intervention arm might improve survival.

Summarized, the secondary objectives of the PRECISE Trial were to investigate whether increased enteral protein provision ICU admission resulted in:

- Lower mortality
- Improvement of the Mental Health Status
- Improvement of physical functioning and health-related quality
- Less pain
- Improvement of muscle and nerve function

Secondary endpoints

- Overall Survival at 30, 60, 90 and 180 days after ICU admission
- Changes in health-related quality of life, as assessed by the Short Form 36 (SF-36) questionnaire, completed at 30 days, 90 days, and 180 days after ICU admission;
- Changes in the mental health status, assessed by the Hospital Anxiety and Depression Scale (HADS) and IES-R Impact of Event Scale, all completed at 30 days, 90 days and 180 days after ICU admission;
- Changes in self-reported health assessed by the EQ-VAS of the EQ-5D-5L, completed at 30 days, 90 days and 180 days after ICU admission;
- Domain data of the EQ-5D-5L questionnaire, completed at 30 days, 90 days, and 180 days after ICU admission;
- Changes in physical function, as assessed by the 6-minute walk test, performed at 30 days, 90 days, and 180 days after admission to ICU;

- Changes in muscle and nerve function, as assessed by the MRC-SUM score and Handgrip strength (Dynamometer), performed at 30 days, 90 days, and 180 days after admission to ICU.

8.3. Tertiary (exploratory) Objectives and Endpoints

The tertiary endpoints had been described and detailed in the full Statistical Analysis Plan that was published before the end of the recruiting period of the PRECISE trial. The tertiary endpoints included:

- Hospital mortality: number of patients that died during index hospital admission.
- Sixty-day mortality: number of patients that died within 60 days after ICU admission.
- Time-to-discharge-alive from hospital: number of days until live hospital discharge.
- Days alive and at home at day 90 (DAAH₉₀) after index ICU admission
- Duration of mechanical ventilation during index ICU stay
- The incidence of ICU-acquired infections during index ICU stay (including ventilator-associated pneumonia's (VAPs))
- The incidence of acute kidney injury (AKI; serum creatinine level higher than 2 times baseline level) during index ICU stay
- Incidence and duration of renal replacement therapy (number of patients who received renal replacement therapy and days on it)
- The incidence of hepatic dysfunction (bilirubin level higher than 3 mg/dl) during index ICU stay
- Maximum and mean SOFA score during the first 14 days of index ICU stay
- Domain data EQ-5D-5L: scores of subdomains of EQ-5D-5L at 30, 90, and 180 days after ICU admission
- The difference in frailty at 30 days, 90 days, and 180 days, as assessed by the Rockwood Clinical Frailty Scale
- Administration of prokinetics (number of patients who received a prokinetic and number of days on it)
- The difference in mobilization treatment during index ICU stay (number of days and degree of daily mobilization (passive/active, in-bed cycling, etc.))
- Length of index ICU stay
- Length of index hospitalisation
- The incidence of ICU-readmissions during index hospitalisation
- Destination after hospital discharge
- Length of stay at a rehabilitation facility after index hospitalisation
- Time to return to work

- The incidence of gastrointestinal intolerance/symptoms (i.e. vomiting, ischemia, diarrhea, abdominal distention, gastric paresis, bleeding/ulcer) during index ICU stay

9. INVESTIGATIONAL PLAN

9.1. Overall Study Design and Plan Description

The scientific rationale for features of the study design were described in the study protocol. Changes in the conduct of the study were implemented via approved protocol amendment(s). The approved protocol and amendments can be found in the appendix.

The final version of the Case Report Forms can be found in the appendix.

9.2. Selection of Study Population

This study enrolled patients who are adult patients with an unplanned admission to the ICU and an expected stay on ventilator support of at least 3 days. Detailed inclusion and exclusion criteria were provided in the protocol (Appendix). The eligibility criteria had been chosen to recruit patients who are truly 'critically ill' and in a catabolic state. This patient group would represent a group of patients who have a clear indication for enteral nutrition according to the current standards of care and had been hypothesized to benefit from a potential effect of high enteral protein provision.

9.3. Study Intervention

9.3.1. Study intervention administered

The enteral nutrition under study was supplied in blinded identical packages by Nutricia (Utrecht, the Netherlands). Both feeds were isocaloric and isovolemic and identical in terms of colour, odor and consistency, enabling a quadruple blind design.

- The intervention is a **high protein** enteral feeding formula (**8g** protein/100 kcal), commercially available from Nutricia, Danone (Nutrison Protein Intense). When the *final energy target of 25 kcal/kg/day* would be met, patients in the interventional arm received **2.0g** protein/kg/day.
- The comparator is a **standard protein** enteral feeding formula (**5g** protein/100 kcal), commercially available from Nutricia, Danone (Nutrison Protein Plus). When the *final energy target of 25 kcal/kg/day* would be met, patients in the comparator arm received **1.25g** protein/kg/day.

9.3.2. Measures to minimize bias

- Method of assigning patients to treatment groups
All participants were centrally randomized to the investigational intervention using an electronic randomization system (ALEA). The method used to allocate participants is further described in the protocol (Appendix)

b) Blinding

The study design included assessor, investigator, caregiver, participant quadruple blinding. The methods used for blinding were described in detail in the protocol (Appendix).

9.3.3. Study intervention compliance

The method(s) used to assess study intervention compliance are described in the protocol (Appendix).

9.3.4. Prior, concomitant and/or post intervention therapy

The nutritional interventions allowed or disallowed before, during, and/or after study intervention, including any exceptions to these requirements, were described in the protocol (Appendix).

9.4. Study Assessments and Procedures

9.4.1. Planned measurements and timing of assessments

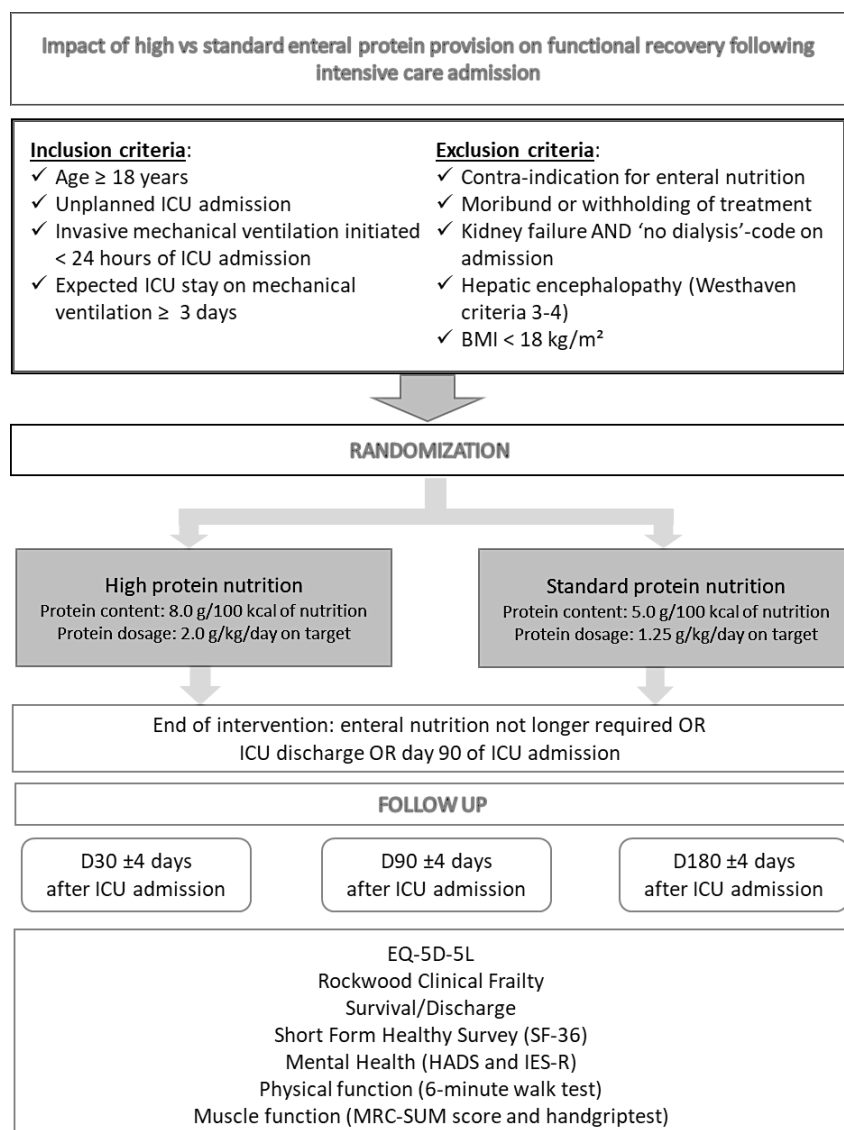


Figure 1 Trial flow chart.

The specific study assessments, their schedule and measurement/collection methods are provided in Table 2 below. The collection and assessment of safety information during the study (evaluation, definitions, recording, and reporting of AEs, SAEs, SUSARs and other reportable safety events) is evaluated at each study timepoint.

Table 2 Overview of study assessments

PRECISe Study	Screening phase	Treatment phase		Follow-up phase (during ICU stay or after ICU discharge)		
		Daily at ICU stay (max 90 days after ICU admission)	Only on treatment day 1, 3, 5, 7, 9, 11 and 13	FU visit 1 (30 days ± 4 days after ICU admission)	FU visit 2 (90 days ± 4 days after ICU admission)	FU visit 3 (180 days ± 4 days after ICU admission)
Informed consent	X					
Inclusion/exclusion criteria	X					
Randomization	X					
Demographics ^a	X					
Medical history ^b	X					
Admission information ^c	X					
Glasgow Coma Scale	X		X			
Height and weight ^d	X					
Vital signs	X ^e		X ^f			
Fluid balance	X		X			
Local Lab	X ^g		X ^h			
NRS score ⁱ	X					
Rockwood Clinical Frailty Scale	X			X	X	X

EQ-5D-5L questionnaire	X			X	X	X
Initiate study feeding/re-adjust study feeding rate		X ⁱ				
Collect the daily volume nutrition received		X ^j				
Mobilization treatment		X ^k				
HADS score ^l				X	X	X
IES-R score ^m				X	X	X
SF-36 questionnaire ⁿ				X	X	X
Handgrip strength				X	X	X
6-minute walk test				X	X	X
MRC – sum score ^o				X	X	X
Destination after discharge ^p (if applicable)				X	X	X
Length of stay at a rehabilitation facility (if applicable)				X	X	X
Work activity re-started (if applicable)				X	X	X
Ventilation status		X				
Concomitant medication	X ^q	X ^r	X ^s			
Events of special interest		X ^t		X ^u	X ^u	X ^u

^a Age and sex^b comorbidities including the Charlson Comorbidity index^c Admission information, admission diagnosis^d Pre-admission weight. If patient has a BMI > 27 kg/m², ideal body weight will be used to calculate caloric targets.^e Vital signs required for calculation of ICU scores

^f Vital signs required for the SOFA score

^g Haemoglobin, haematocrit, white blood cell count (WBC), platelets, CRP, urea, creatinine, Na⁺, K⁺, PO₄, magnesium, albumin, bilirubin, ALT, AST, GGT, ALP, pH, bicarbonate, lactate, glucose, PaO₂/FiO₂ ratio

^h Haemoglobin, haematocrit, WBC, platelets, CRP, urea, creatinine, K⁺, PO₄, magnesium, albumin, bilirubin, ALT, AST, GGT, ALP, glucose, PaO₂/FiO₂ ratio and pH

ⁱ Nutritional Risk Score

^j See section [12.3 Feeding protocol](#)

^k Passive/active in bed, passive/active on bed bicycle, out of bed

^l The Hospital Anxiety and Depression Scale to determine the levels of anxiety and depression in hospitalized patients.

^m Impact of Event Scale- Revised: to detect Post-Traumatic Stress Disorder.

ⁿ Short form 36 health survey questionnaire. A 36-item, patient-reported survey of patient health.

^o Medical Research Council – sum score

^p Home, rehabilitation home, other hospital ward or nursing home.

^q Chronic use of glucocorticoids, antibiotics, noradrenaline, adrenaline, dopamine and dobutamine

^r Glucocorticoids, antibiotics, prokinetics, muscle relaxants, and medication/infusions with substantial non-nutritional calories (e.g. insulin, propofol)

^s Noradrenaline, adrenaline, dopamine and dobutamine

^t All-cause mortality, life threatening event caused by the nutrition, hepatic dysfunction (bilirubin > 3 mg/dl), index ICU acquired infections, ventilator acquired pneumonia (VAP), ECMO, Acute Kidney Injury (including the use of renal replacement therapy), refeeding hypophosphatemia and gastrointestinal events (i.e. vomiting, ischaemia, diarrhoea, abdominal distention, gastric paresis, bleeding/ulcer)

^u All-cause mortality

9.4.2. Appropriateness of measurements

The measurements used in this study were standard, considered to be reliable, and relevant to the objectives set forth in the protocol (Appendix).

9.5. Data Quality Assurance

9.5.1. Study monitoring

Study centres were monitored by the sponsor. Centres were visited at regular intervals and a Visit Log was maintained. Monitors were responsible for reviewing adherence to the protocol; compliance with GCP; and the completeness, accuracy, and consistency of the data. Direct access to participant medical and laboratory records was permitted to verify entries on the study-specific CRFs.

9.5.2. Investigator training

The monitor trained the investigators to comply with Good Clinical Practice (GCP) and to conduct the study in accordance with the study protocol. The monitor obtained written commitments by investigators and these are available upon request.

9.5.3. Laboratory procedures

According to the standard of care, local laboratories were used to analyse the blood samples. Their participation in internal and external quality control, quality assurance, and accreditation schemes was evaluated by the study monitors.

9.5.4. Principal investigator responsibilities

The Principal Investigators (PI) were responsible for all data entered in the CRFs and documented their review and approval of the data, verifying the validity and completeness of the data at their centre. The PIs were responsible for appropriate retention of essential study documents during the study at their centre. The PIs are responsible to archive the essential study documents according to the national legislation.

9.5.5. Clinical data management

Case report form data were captured via data entry by the qualified study centre personnel in the database created by the sponsor with the software of CASTOR EDC. Data quality checks were applied using manual and electronic verification methods.

9.5.6. Clinical quality assurance audit

A clinical quality audit was done by assessing predicted mortality through the APACHE IV and SAPS 3 severity scores, adjusted for case-mix, in each study site. The higher than anticipated mortality rate in the study was also discussed in the DSMB meetings.

9.6. Statistical Methods Planned in the Protocol and Determination of Sample Size

9.6.1. Statistical analysis plan

The planned analysis and determination of sample size are described in the final version of the Statistical Analysis Plan (SAP) (Appendix)

9.6.2. Changes in the conduct of the study or planned analyses

No changes in the planned analysis for the study took place. However, additional analyses and a different presentation of the results were requested by the (statistical) reviewers.

10. STUDY PATIENTS

10.1. Disposition of patients

Of the 4306 patients who were assessed for eligibility, 3371 (78.3%) were not eligible and 935 (21.7%) were randomly assigned between Nov 19, 2020, and April 14, 2023. Of these 935 patients, 465 (49.7%) were assigned to the standard protein group and 470 (50.3%) were assigned to the high protein group. Two (0.4%) of 465 patients in the standard protein group and nine (1.9%) of 470 patients in the high protein group did not receive study nutrition. 35 (7.5%) of 465 patients in the standard protein group and 51 (10.9%) of 470 patients in the high protein group were lost to follow-up before assessment of the primary outcome. 430 (92.5%) of 465 patients in the standard protein group and 419 (89.1%) of 470 patients in the high protein group were assessed for the primary outcome. Baseline EQ-5D-5L was collected for 394 (84.7%) of 465 patients in the standard protein group and 391 (83.2%) of 470 patients in the high protein group.

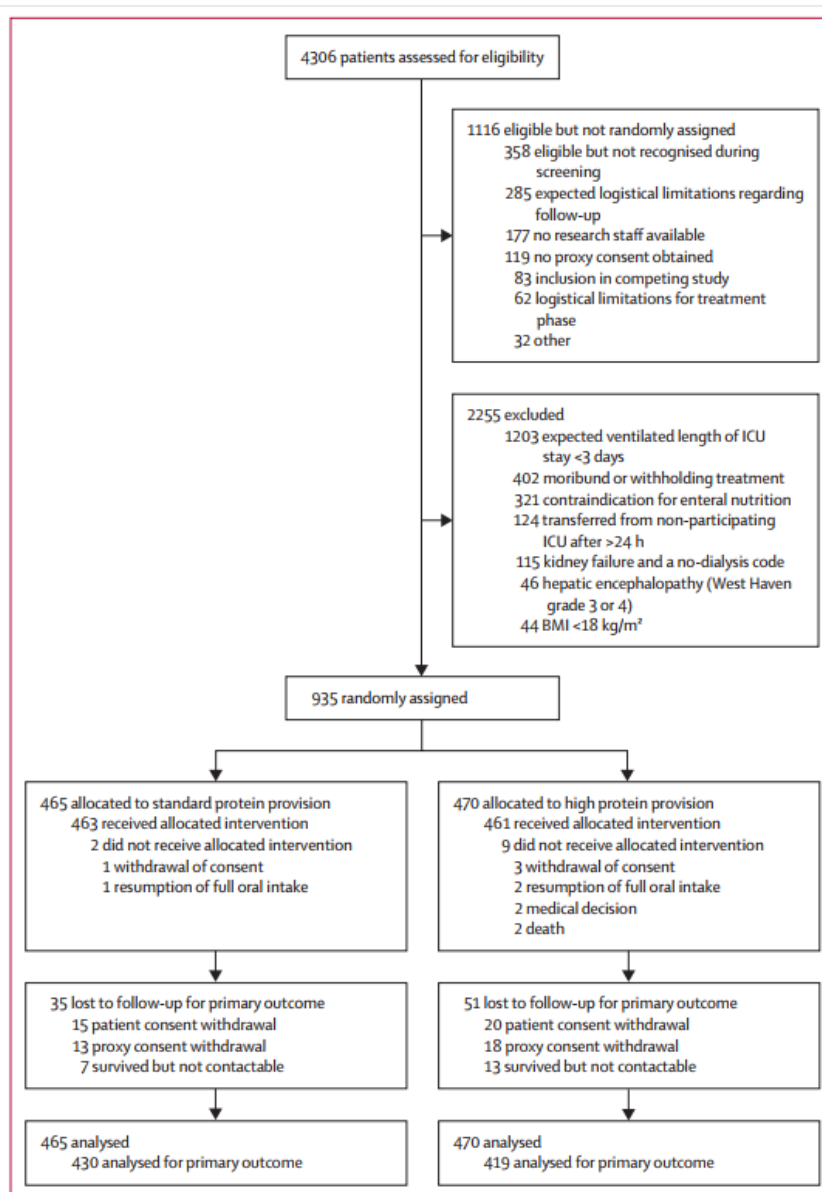


Figure 2 Trial profile

10.2. Protocol Deviations

During the study protocol deviations were reported by the centres, monitors and data reviewers. These deviations were documented and analysed by the study monitor. When needed actions were taken to reduce the occurrence of similar protocol deviations. The reported protocol deviations did neither affect the integrity of the collected study data nor the safety of the patients. An overview of the major protocol deviations was annually provided to the Independent Ethics Committee of UZ Brussel and MUMC+.

Below an overview of the substantial deviations reported during the study.

Table 3 Protocol deviations

	Standard Protein (n = 465)	High Protein (n = 470)
Patients who did not fulfil all inclusion criteria or fulfilled one or more of the exclusion criteria – no./no. (%)	12/465 (3)	17/470 (4)
Initiation of invasive mechanical ventilation between 24-48 hours after ICU admission – no./no. (%)	10/465 (2)	13/470 (3)
Initiation of invasive mechanical ventilation more than 48 hours after ICU admission – no./no. (%)	2/465 (0)	2/470 (0)
No written informed consent obtained (Belgian sites)* – no./no. (%)	0/198 (0)	2/202 (1)
Not randomised within 72 hours of ICU admission – no./no. (%)	0/465 (0)	3/470 (1)
Incorrect intervention at any time during the treatment phase [†] – no./no. (%)	0/465 (0)	2/470 (0)
Parenteral nutrition in the first 7 days of ICU admission – no./no. (%)	12/465 (3)	9/470 (2)

ICU, Intensive Care Unit.

* Oral consent from proxy was obtained and documented prior to randomisation.

† Total administered volumes of incorrect label per patient were 400 and 500ml.

11. EFFICACY EVALUATIONS

11.1. Data Sets Analysed

The primary endpoint statistical analysis was based on an intention-to-treat analysis set, including all randomized patients. Patients were analysed according to the treatment group they were allocated to according to the electronic randomization system (irrespective of the actual treatment received).

The primary endpoint could not be assessed in 86 randomized patients because of loss to follow-up.

The secondary endpoints statistical analyses were based on the same data set as used for the primary endpoint analysis.

The safety endpoints analyses were based on all patients that were randomized and received study nutrition, either standard or high protein. For the safety analysis, patients will be grouped based on the actual study treatment received. All patients received the treatment they were allocated to by the electronic randomization system.

The data set analysed contained a total of 849 patients with 430 patients in the standard group and 419 patients in the high protein group.

11.2. Demographics and Other Baseline Characteristics

Table 4 Baseline characteristics of the intention-to-treat population

	Standard protein (n=465)	High protein (n=470)
Age, years	63 (14)	62 (14)
Sex		
Female	156 (34%)	179 (38%)
Male	309 (67%)	291 (62%)
BMI	27 (5)	28 (6)
Type of admission		
Medical	341 (73%)	308 (66%)
Surgical	124 (27%)	162 (35%)
Emergency surgery	107/124 (86%)	138/162 (85%)
Complications of elective surgery	17/124 (14%)	24/162 (15%)
Admission diagnosis system		
Respiratory	173 (37%)	149 (32%)
Cardiovascular	128 (28%)	129 (27%)
Neurological	67 (14%)	82 (17%)
Trauma	42 (9%)	48 (10%)
Sepsis*	21 (5%)	26 (6%)
Gastrointestinal	19 (4%)	22 (5%)
Miscellaneous	8 (2%)	4 (1%)
Metabolic or endocrine	4 (1%)	5 (1%)
Genitourinary	2 (<1%)	4 (1%)
Haematological	1 (<1%)	1 (<1%)
Diabetes	84 (18%)	90 (19%)
COVID-19 infection	73 (16%)	71 (15%)
Acute kidney injury†	97 (21%)	105 (22%)
Sepsis	229 (49%)	230 (49%)
Glasgow Coma Scale	15 (6–15)	15 (8–15)
APACHE II score‡	22 (7)	21 (7)
APACHE IV score‡	83 (26)	81 (26)
SOFA score§	10 (3)	9 (3)
SAPS II¶	48 (14)	47 (14)
EQ-5D-5L health utility score	0.78 (0.25)	0.77 (0.26)
Charlson Comorbidity Index**	3 (2–4)	3 (1–4)
NRS-2002 score††	4 (1)	4 (1)
Rockwood Clinical Frailty Scale‡‡	3 (2)	3 (2)

Data are mean (SD), n (%), n/N (%), or median (IQR). APACHE=Acute Physiology and Chronic Health Evaluation. EQ-5D-5L=EuroQoL 5-Dimension 5-level. KDIGO=Kidney Disease Improving Global Outcomes. NRS-2002=Nutritional Risk Screening 2002. SAPS=Simplified Acute Physiology Score. SOFA=Sequential Organ Failure Assessment. *Only patients with a not-otherwise-specified cause of sepsis as admission diagnosis. Patients with a specified cause of sepsis were categorised under the corresponding system. †Acute kidney injury was defined on the basis of KDIGO classification, which ranges from 1 to 3. KDIGO scores were calculated at randomisation and a score of 1 or more was considered to indicate acute kidney injury. ‡APACHE II scores range from 0 to 71. APACHE IV scores range from 0 to 286. Higher scores indicate greater severity of disease. §SOFA scores range from 0 to 20. Higher scores indicate greater severity of organ failure. ¶SAPS II ranges from 0 to 163. Higher scores indicate greater severity of disease. ||EQ-5D-5L health utility score ranges from -0.5 to 1.0. Deceased patients are assigned a score of 0. A score less than 0 is valued as a health-related quality of life worse than death, a higher score indicates better health-related quality of life, and a score of 1.0 indicates perfect health-related quality of life. **The Charlson Comorbidity Index provides a weighted score by considering comorbid conditions. Higher scores indicate more severe comorbid conditions. ††NRS-2002 ranges from 0 to 7. Higher scores indicate greater risk of malnutrition. ‡‡The Rockwood Clinical Frailty Scale is a global clinical measure of fitness and frailty in older people and ranges from 1 to 9. Higher scores indicate greater severity of frailty.

Table 1: Baseline characteristics of the intention-to-treat population

11.3. Performance of nutritional intervention in study arms

Median duration of study nutrition was 9 days (IQR 4–19) in patients allocated to standard enteral protein and 10 days (5–21) in patients allocated to high enteral protein. Daily energy intake did not differ between groups.

Nutritional energy intakes more than 25 kcal/kg per day occurred incidentally in individual patients, mostly due to catch-up feeding that was given to compensate for missed targets the day before.

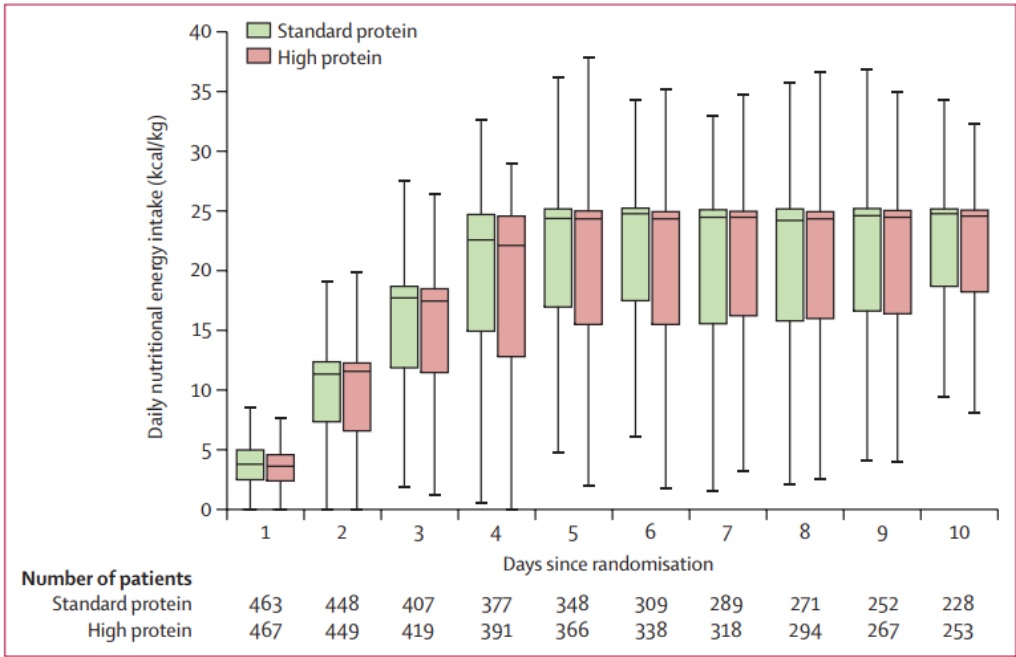


Figure 3: Nutritional energy intake on days 1–10 after randomisation
Daily amount of delivered nutritional energy (kcal/kg) during the first 10 days after randomisation. Intake of nutritional energy was calculated for all days during ICU admission where nutritional intake could be fully quantified. Days with oral intake and partly observed days due to ICU discharge or consent withdrawal were not included. Horizontal lines in boxes represent medians; bottoms of boxes show 25th percentile and tops of boxes show 75th percentile. Ends of whiskers represent the upper adjacent value (ie, 75th percentile plus 1.5 times the IQR) and the lower adjacent value (ie, 25th percentile minus 1.5 times the IQR). Nutritional energy intakes more than 25 kcal/kg per day occurred incidentally, mostly due to catch-up feeding that was given to compensate for missed targets on the previous day (appendix p 23). ICU=intensive care unit.

Figure 3 Nutritional energy intake on days 1-10 after randomisation

Protein intake was delivered in line with the protocol, leading to nicely separated study groups. Median cumulative protein intake, both enteral and parenteral, during the entire intervention period was 1.19 g/kg per day (0.63–1.26) in the standard protein group and 1.87 g/kg per day (0.96–2.00) in the high protein group.

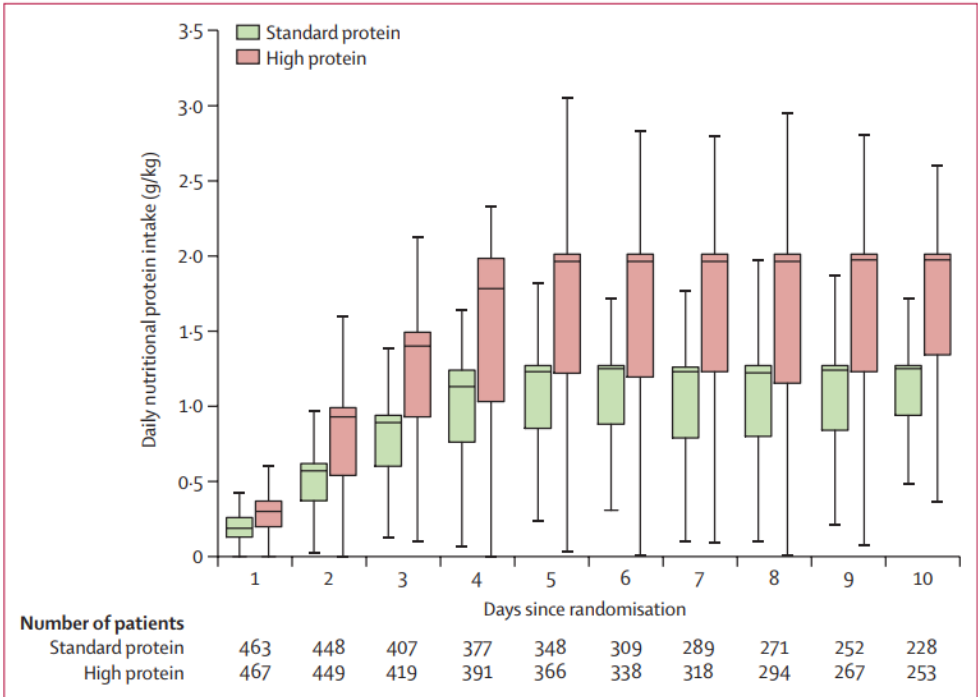


Figure 2: Protein intake on days 1-10 after randomisation
Daily amount of delivered protein (g/kg) during the first 10 days after randomisation. Intake of protein was calculated for all days during ICU admission where nutritional intake could be fully quantified. Days with oral intake and partly observed days due to ICU discharge or consent withdrawal were not included. Horizontal lines in boxes represent medians; bottoms of boxes show 25th percentile and tops of boxes show 75th percentile. Ends of whiskers represent the upper adjacent value (ie, 75th percentile plus 1.5 times the IQR) and the lower adjacent value (ie, 25th percentile minus 1.5 times the IQR). ICU=intensive care unit.

Figure 4 Protein intake on days 1-10 after randomisation

11.4. Endpoint analyses

11.4.1. Primary endpoint analysis

The primary outcome, EQ-5D-5L health utility score during 180 days after randomisation (assessed at 30 days, 90 days, and 180 days), was lower in patients allocated to the high protein group than in those allocated to the standard protein group, with a mean difference of -0.05 (95% CI -0.10 to -0.01 ; $p=0.031$).

Table 5 Evaluation of the primary endpoint (Table format)

	Standard protein (n=465)	High protein (n=470)	Treatment effect	p value
Primary outcome				
EQ-5D-5L health utility score	430	419	-0.05 (-0.10 to -0.01)	0.031
After 30 days	0.33 (0.33)	0.29 (0.32)	..	..
After 90 days	0.38 (0.38)	0.34 (0.38)	..	..
After 180 days	0.39 (0.39)	0.36 (0.40)	..	..

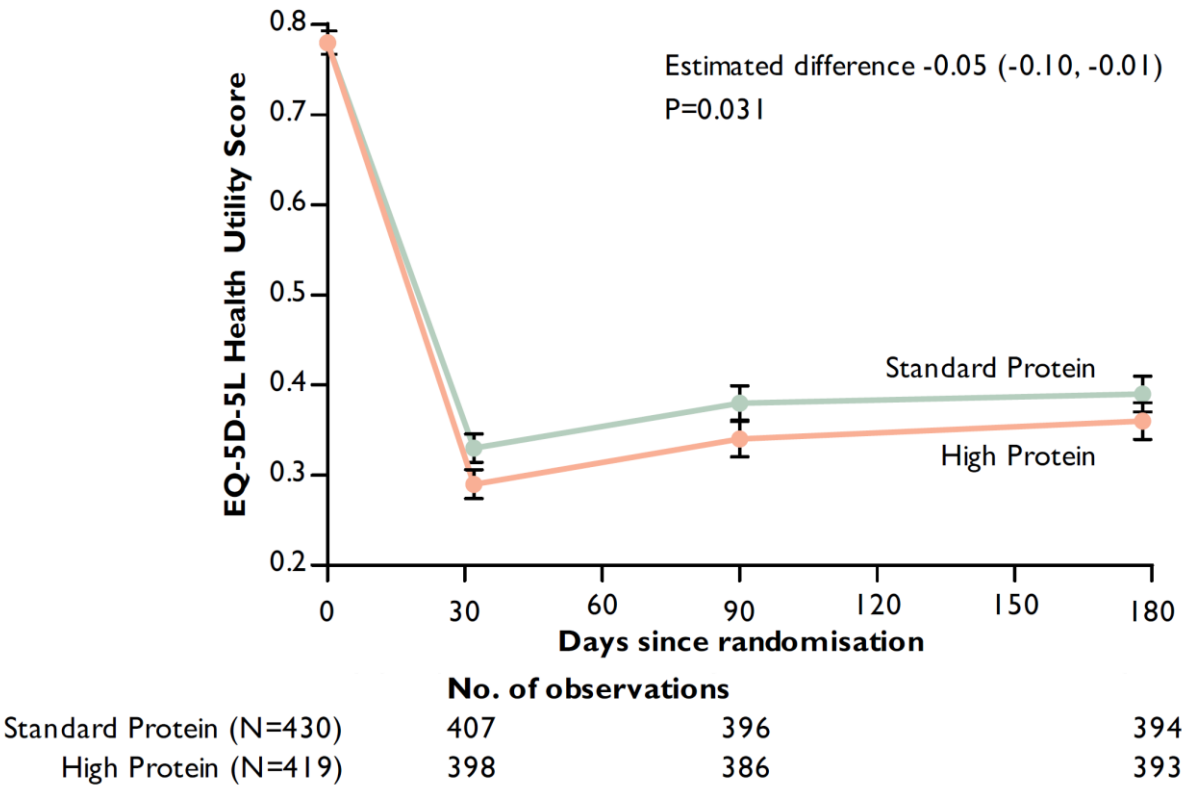


Figure 5 Evaluation of the primary endpoint (Visual format)

11.4.2. Secondary endpoint analyses

Table 6 Secondary endpoints

	Standard protein (n=465)	High protein (n=470)	Treatment effect	p value
Primary outcome				
EQ-5D-5L health utility score	430	419	-0.05 (-0.10 to -0.01)	0.031
After 30 days	0.33 (0.33)	0.29 (0.32)	..	..
After 90 days	0.38 (0.38)	0.34 (0.38)	..	..
After 180 days	0.39 (0.39)	0.36 (0.40)	..	..
Secondary outcomes				
SF-36	219	192	0.70 (-0.98 to 2.38)	0.41
After 30 days	41.7 (17.3)	45.0 (19.2)	..	..
After 90 days	50.7 (21.8)	53.3 (21.7)	..	..
After 180 days	58.4 (22.6)	60.3 (22.7)	..	..
Physical component summary of SF-36	219	192	0.46 (-1.22 to 2.14)	0.59
After 30 days	31.9 (8.1)	32.7 (9.2)	..	..
After 90 days	36.4 (10.1)	37.3 (10.3)	..	..
After 180 days	40.2 (10.8)	41.0 (10.9)	..	..
Mental component summary of SF-36	219	192	1.02 (-0.80 to 2.84)	0.27
After 30 days	37.0 (9.9)	38.5 (10.3)	..	..
After 90 days	41.0 (11.5)	42.5 (10.4)	..	..
After 180 days	43.7 (11.2)	44.6 (10.7)	..	..
Hospital Anxiety and Depression Scale	225	198	-0.43 (-1.02 to 0.15)	0.15
After 30 days	17.3 (3.9)	16.9 (3.7)	..	..
After 90 days	17.5 (3.8)	17.0 (3.4)	..	..
After 180 days	17.4 (3.5)	17.3 (3.5)	..	..
Impact of Event Scale-Revised	219	195	-1.54 (-4.26 to 1.18)	0.27
After 30 days	20.2 (16.1)	17.6 (14.3)	..	..
After 90 days	17.6 (16.0)	16.2 (15.7)	..	..
After 180 days	16.5 (15.5)	16.7 (16.8)	..	..
Percentage of predicted 6-min walking distance	154	133	5.55 (0.04 to 11.07)	0.048
After 30 days	60.6 (23.9)	61.6 (24.2)	..	..
After 90 days	68.0 (28.3)	73.9 (25.8)	..	..
After 180 days	72.6 (24.9)	81.8 (23.4)	..	..
MRC-SUM score	221	201	-0.23 (-1.60 to 1.12)	0.73
After 30 days	48.8 (11.5)	49.6 (11.7)	..	..
After 90 days	54.3 (6.7)	54.0 (8.5)	..	..
After 180 days	56.6 (5.6)	56.9 (5.9)	..	..
Percentage of predicted handgrip strength	212	188	-3.87 (-9.53 to 1.80)	0.18
After 30 days	66.8 (32.2)	68.5 (31.1)	..	..
After 90 days	83.0 (30.1)	75.0 (31.4)	..	..
After 180 days	92.8 (31.4)	89.5 (30.7)	..	..
EQ-5D-5L visual analogue score	289	254	-1.53 (-4.47 to 1.42)	0.31
After 30 days	52.0 (23.0)	47.7 (22.9)	..	..
After 90 days	61.4 (21.0)	63.0 (19.6)	..	..
After 180 days	66.7 (17.9)	66.0 (20.4)	..	..

(Table 2 continues on next page)

Table 7 Secondary endpoints (continued)

	Standard protein (n=465)	High protein (n=470)	Treatment effect	p value
(Continued from previous page)				
Rockwood Clinical Frailty Scale	300	269	0.03 (-0.25 to 0.31)	0.83
After 30 days	5.5 (1.9)	5.7 (1.9)	"	"
After 90 days	4.3 (1.8)	4.3 (2.0)	"	"
After 180 days	3.7 (1.8)	3.7 (1.9)	"	"

Data are mean (SD); coefficients from linear mixed-regression analysis, with study site as a random effect; or p values. For EQ-5D-5L and SF-36, higher scores indicate better health-related quality of life. For the Hospital Anxiety and Depression Scale and Impact of Event Scale-Revised, higher scores indicate worse symptoms and more disability. The number of patients for each outcome is the number of patients contributing to the mixed linear model (ie, each patient with at least one observed value). Number of observations per timepoint differed from the total number of patients contributing to the mixed linear model. The exact number of observations per timepoint are reported in the appendix (p 13). EQ-5D-5L=EuroQoL 5-Dimension 5-level. MRC-SUM=Medical Research Council Scale for Muscle Strength. SF-36=36-Item Short Form Health Survey.

Table 2: Primary and secondary efficacy outcomes in the intention-to-treat population

The secondary endpoint overall survival over 180 days.

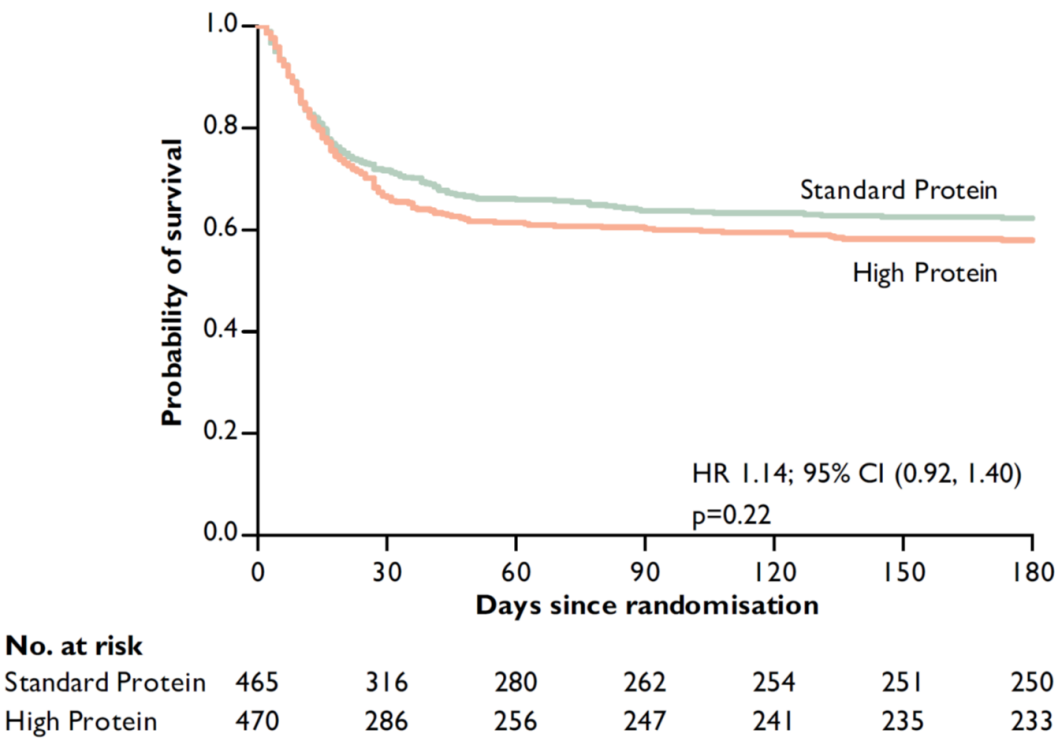


Figure 6 Kaplan – Meier curve of survival over 180 days

11.4.3. Sensitivity analyses

The preplanned sensitivity analysis for the primary outcome EQ-5D-5L HUS, correcting for APACHE II score, sex, APACHE IV admission diagnosis, and NRS-2002 score, yielded similar results as the primary analysis (mean difference -0.05; 95% CI -0.10 to -0.00; p=0.038).

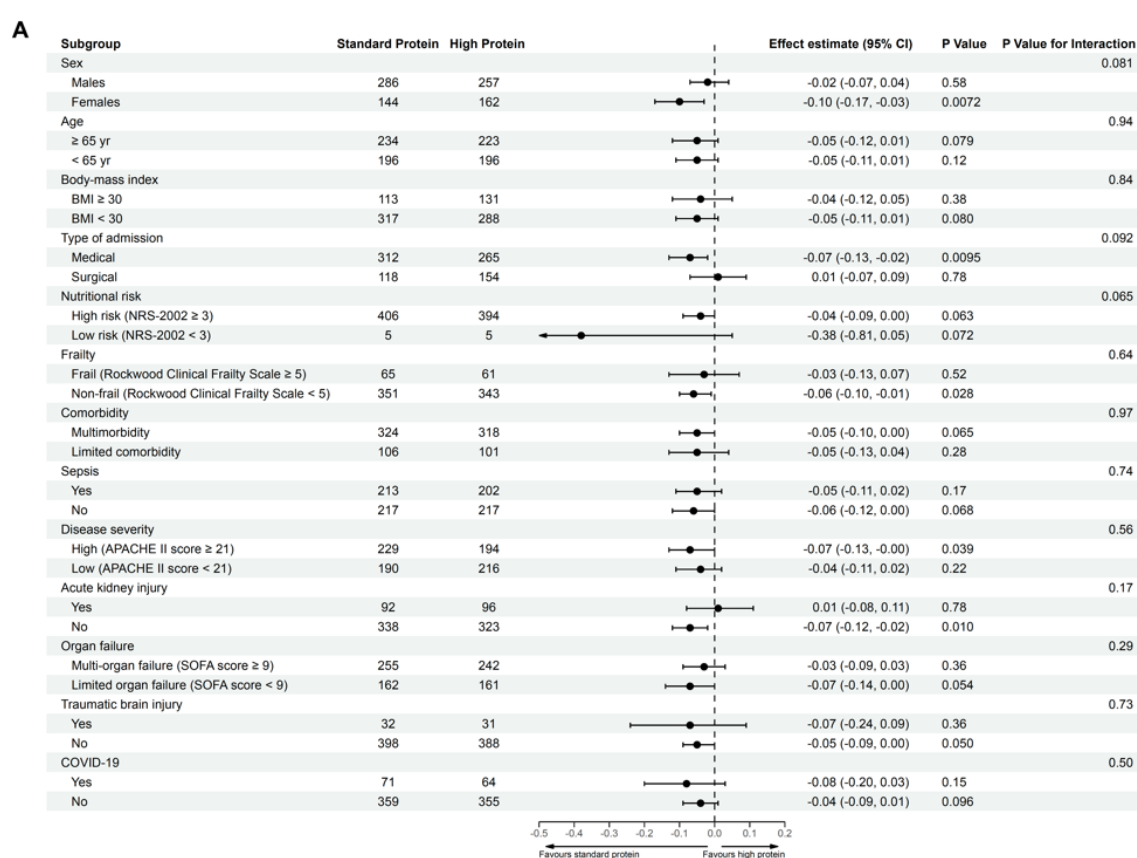
In the preplanned sensitivity analysis for *overall mortality*, correcting for APACHE II score, sex, APACHE IV admission diagnosis, and NRS-2002 score, the hazard ratio for overall mortality in patients allocated to high enteral protein increased to 1.24 (95% CI 0.99 to 1.55; $p=0.063$).

11.4.4. Subgroup analyses

Preplanned subgroup analyses favoured standard enteral protein across most subgroups regarding EQ-5D-5L health utility score and overall mortality, indicating a lack of treatment heterogeneity.

1. EQ-5D-5L health utility score

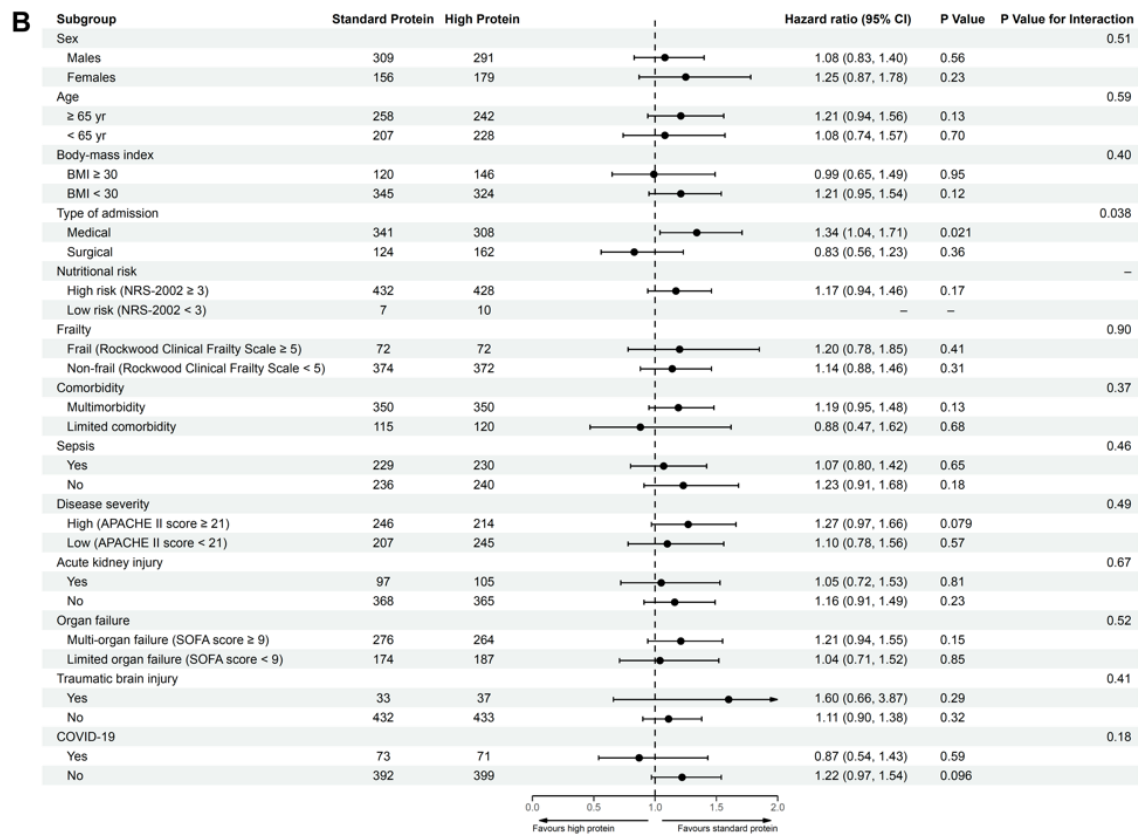
Table 8 Subgroup analyses of primary endpoint (EQ-5D-5L HUS)



These analyses suggest that the unfavourable effects of high enteral protein were most prominent in female patients and patients with a medical admission. We observed no unfavourable effects of high enteral protein in patients with acute kidney injury or multiorgan failure on ICU admission, as was seen in the EFFORT Protein trial.

2. Overall survival over 180 days

Table 9 Subgroup analyses of secondary endpoint survival over 180 days



11.4.5. Tertiary, exploratory analyses

Table 10 Tertiary, exploratory outcomes

	Standard protein	High Protein	Treatment effect	P-value
	(N=465)	(N=470)		
Hospital mortality – no./no. (%)	158/448 (35)	176/444 (40)	1.21 (0.92, 1.59)	0.18
Duration of ICU stay - days				
No. of patients	456	452		
Median (IQR)	13 (7, 24)	14 (8, 26)	0.06 (-0.05, 0.17) [§]	0.28
Patients with ICU readmission – no./no. (%)	31/451 (7)	28/447 (6)	0.90 (0.53, 1.53)	0.70
Median number of ICU readmissions per patient				
No. of Patients	31	28		
Median (IQR)	1 (1, 1)	1 (1, 1)	N.A.	0.20
Administration of prokinetic – no./no. (%)	107/465 (23)	140/469 (30)	1.45 (1.07, 1.96)	0.02
Duration of prokinetic				

administration - days				
No. of patients	107	139		
Median (IQR)	5 (3, 13)	6 (3, 11)	-0.78 (-3.56, 2.01)	0.58
Renal replacement therapy – no./no. (%)	67/465 (14)	81/469 (17)	1.24 (0.87, 1.77)	0.23
Duration of renal replacement therapy				
No. of patients	66	79		
Median (IQR)	8 (5, 14)	8 (4, 15)	-0.05 (-0.37, 0.26) [§]	0.75
Sequential Organ Failure Assessment score				
No. of patients	445	455		
Mean	8 ± 3	8 ± 3	-0.14 (-0.52, 0.24)	0.47
Maximum	10 ± 3	10 ± 3	-0.15 (-0.55, 0.24)	0.45
Days with any mobilization treatment				
No. of patients	464	469		
Median (IQR)	6 (2, 16)	7 (2, 18)	0.51 (-1.20, 2.22)	0.56
Days with passive mobilization treatment				
No. of patients	464	469		
Median (IQR)	3 (1, 9)	4 (1, 12)	0.90 (-0.29, 2.09)	0.14
Days with active mobilization treatment				
No. of patients	464	469		
Median (IQR)	2 (0, 6)	2 (0, 5)	-0.40 (-1.36, 0.56)	0.41
Duration of hospital stay - days				
No. of patients	448	442		
Median (IQR)	23 (13, 44)	24 (14, 42)	0.04 (-0.07, 0.15) [§]	0.50
Destination of hospital discharge – no./no. (%)				
Home	146/290 (50)	131/266 (49)	Reference	Reference
Rehabilitation facility	126/290 (43)	113/266 (42)	1.11 (0.35, 3.54)	0.85
Other hospital	9/290 (3)	10/266 (4)	1.01 (0.71, 1.43)	0.96
Nursing home	6/290 (2)	6/266 (2)	1.24 (0.49, 3.14)	0.65
Other	3/290 (1)	6/266 (2)	2.09 (0.50, 8.69)	0.31
Admission to rehabilitation facility – no./no. (%)	131/287 (46)	118/261 (45)	0.99 (0.70, 1.40)	0.96
Duration of stay at rehabilitation facility - days				
No. of patients	125	108		
Median (IQR)	45 (25, 64)	52 (28, 88)	10.84 (1.06, 20.61)	0.03

Return to work – no./no. (%)				
No (did not work before ICU admission)	125/272 (46)	127/244 (52)	Reference	Reference
No (did work before ICU admission)	102/272 (38)	81/244 (33)	0·83 (0·57, 1·20)	0·33
Yes	45/272 (17)	36/244 (15)	0·89 (0·55, 1·45)	0·65
Number of days between ICU admission and work resumption				
No. of patients	37	27		
Median	90 (61, 118)	102 (82, 146)	10 (-13, 33)	0·38

*Plus–minus values are means $\pm$ SD. Percentages may not total 100 because of rounding. Effect estimates for continuous outcomes are coefficients from linear mixed regression analysis, with study site as a random effect. Effect estimates for categorical outcomes are analysed using generalized linear models (GLM) with study site as random effect, presented as odds ratios. No. of patients represent the number of patients with data.

† No. of patients is the number of patients contributing to the mixed linear model, i.e. each patient with at least one observed value.

‡ The number of observations per timepoint differs from the total number of patients contributing to the mixed linear model. The exact number of observations per time point is reported in Figure S3.

§ Presented effect estimate represents the log-transformed outcome.

|| Limited to first two weeks of ICU admission.

¶ Different from the number of patients discharged from the hospital to a rehabilitation facility as not all patients admitted to a rehabilitation facility were immediately transferred from the hospital

Days alive and at home at day 90 (DAAH90)

The tertiary outcome measure Days alive and at home at day 90 (DAAH90) after index ICU admission, was not reported in the published manuscript and has not been included in this Clinical Study Report, as the data are not yet complete. The DAAH90 is the primary outcome measure of the TARGET Protein trial from the ANIZICS Trial group.

Time-to-discharge-alive from hospital

Time-to-discharge-alive from hospital was the primary outcome measure of the EFFORT Protein trial (Heyland D et al Lancet 2023;401:568–76). In the PRECISE study, the hazard ratio for being discharged alive during 180 days after randomization was 0·91 (95% CI 0·80–1·04) for patients allocated to the high protein group. The post-hoc generalised Wilcoxon test showed $p=0·043$, indicating a statistically significant longer time-to-discharge-alive for the high protein group than for the standard protein group.

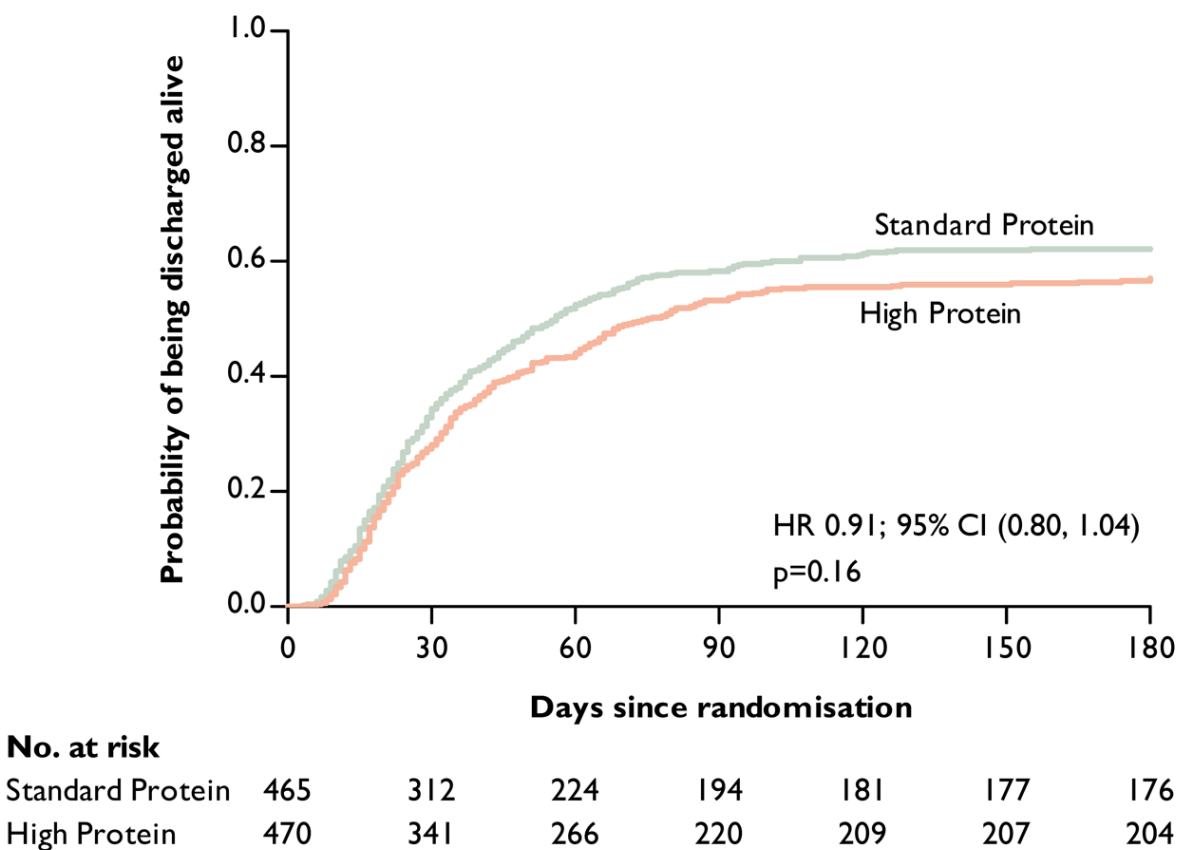


Figure 7 Time-to-live discharge

12. SAFETY EVALUATION

Adverse events of special interest were recorded in the daily electronic case-report form and reported to the ethical review boards. Study-emergent special adverse events were immediately reported to the study team, discussed by the principal investigators, and reported to the medical ethical committees.

Safety was assessed in the 924 patients (98.8%) who received standard or high protein enteral protein. Regarding safety outcomes, the probability of mortality during the entire follow-up was 0.38 (SE 0.02) in the standard protein group and 0.42 (0.02) in the high protein group (hazard ratio 1.14, 95% CI 0.92 to 1.40; p=0.22). There was a higher incidence of symptoms of gastrointestinal intolerance in patients in the high protein group. Incidence of other adverse events did not differ between groups.

Table 11 Adverse events in the safety population

	Standard protein	High protein
Deaths		
Overall mortality*	0.38 (0.02)	0.42 (0.02)
Study-emergent serious adverse events†		
Pneumotosis intestinalis	0/465 (<1%)	1/470 (<1%)
Adverse events of special interest		
ICU-acquired infections	112/465 (24%)	112/469 (24%)
Ventilator-acquired pneumonia	115/465 (25%)	111/469 (24%)
Extracorporeal membrane oxygenation	27/465 (6%)	28/469 (6%)
Acute kidney injury‡	98/465 (21%)	95/469 (20%)
Refeeding hypophosphataemia§	40/465 (9%)	53/469 (11%)
Hepatic dysfunction¶	39/465 (8%)	35/469 (8%)
Gastrointestinal intolerance or symptoms	26/465 (6%)	43/469 (9%)
All-cause mortality after ICU discharge**	36/286 (13%)	35/268 (13%)

Data are mortality probability (SE) or n/N (%), unless otherwise stated.
ICU=intensive care unit. *Mortality probabilities 180 days after randomisation, calculated with the Kaplan–Meier method. †No study emergent adverse events were collected. Due to the nature of the patient population (ie, critically ill), patients could have many events that might be classified as adverse events. As this is part of the expected disease course, only serious adverse events that resulted in death or life-threatening situations, likely related to possible complications of nutritional support, are reported. ‡Defined as creatinine concentration more than two times baseline concentration (including the use of renal replacement therapy). §Defined as phosphate <0.65 mmol/L, a decrease of >0.16 mmol/L from previous phosphate in ICU and no other explanation for hypophosphataemia. ¶Defined as a bilirubin >3 mg/dL. ||Vomiting, ischaemia, diarrhoea, abdominal distension, gastric paresis, bleeding, or ulcer. **Occurring between ICU discharge and end of trial.

Table 3: Adverse events in the safety population

13. DISCUSSION AND OVERAL CONCLUSIONS

In this investigator-initiated, double-blinded, multicentre, parallel-group, randomised controlled trial, high enteral protein provision in critically ill patients who were mechanically ventilated resulted in a lower health-related quality of life than provision of standard enteral protein, measured by the EQ-5D-5L health utility score during 180 days after ICU admission. Moreover, our post-hoc analysis showed a statistically significant increase in time-to-discharge-alive from the hospital in patients allocated to high protein provision compared with patients allocated to standard protein provision.

Furthermore, incidence of gastrointestinal intolerance and use of prokinetics were greater in patients assigned to the high protein group. These findings contrast with the original notion that high protein provision during critical illness might improve functional outcome.

Subgroup analyses indicated that high enteral protein provision might be particularly harmful in female patients and patients with a medical admission, although these results should be interpreted with care as subgroup analyses were not corrected for multiplicity.

The PRECISE trial, as is being increasingly advocated for, focused on patient-reported and functional outcomes as long-lasting functional disabilities can result in low health-related quality of life in patients in an ICU. The EQ-5D-5L health utility score is an appropriate outcome measure for studies with a high mortality rate because it addresses death as a potential competing risk by retaining deceased patients and assigning them a score of 0. When patient-reported and functional outcomes are exclusively assessed in surviving patients, death as a potential competing risk is ignored.²⁷ This exclusion of deceased patients could explain why the results of our secondary and tertiary outcomes, which were measured in surviving patients only, were inconsistent with the EQ-5D-5L health utility score.

The effect of high versus low protein provision on a wide array of outcome measures in critically ill patients has been addressed in several randomised controlled trials,²⁸ of which the EFFORT Protein trial is the largest. Some smaller randomised trials have dealt with the effect of protein intake on health-related quality of life and functional outcomes after critical illness; however, the PRECISE trial is the first with adequate power to detect a statistically and clinically significant difference in a functional outcome. In addition to providing new evidence concerning the harmful effects of high protein provision on health-related quality of life in critically ill patients, the PRECISE trial strengthens the results of the EFFORT Protein trial, which could not support the hypothesis that high protein nutrition improves clinical outcome in critically ill patients. This open-label, registry-based trial found a hazard ratio for the primary outcome, time-to-discharge-alive from the hospital, of 0.91 (95% CI 0.77–1.07). To enable comparison of our results with those of the EFFORT Protein trial, we added this outcome to our statistical analysis plan and found an almost identical hazard ratio and CI.

However, dissimilar to the EFFORT Protein trial, we found no signal of harm for high enteral protein provision in patients with acute kidney injury and multiorgan failure. However, in the EFFORT Protein trial, the onset of acute kidney failure was monitored for 7 days after randomisation, whereas we assigned only patients with acute kidney failure at the time of randomisation to this particular subgroup.

The mechanism underlying the deleterious effects of higher enteral protein doses is unknown. The increased amino acid supply might have surpassed the capacity for protein synthesis, leading to increased amino-acid oxidation and production of potentially toxic deamination products. Additionally, exogenous protein in the acute phase of critical illness might delay recovery by

suppressing autophagy, the process of intracellular breakdown and recycling of old, damaged, or atypical proteins and other harmful substances from the cytoplasm.

The observed sex difference in the subgroup analyses is intriguing but hypothesis-generating, and requires substantiation in future research. An explanation for the possible interaction between high enteral protein provision and sex could be the relatively lower lean body mass in women, leading to a higher protein delivery relative to muscle mass when protein is dosed per total body mass. Exploratory analyses further showed that the negative effects of high protein were more prominent in medical than in surgical patients. These findings need substantiation in future research, but protein demands might be higher in post-operative patients (eg, to facilitate wound healing).

A limitation of this trial is that the difference in EQ-5D-5L health utility scores between study groups was less than the chosen minimum clinically important difference of 0.06. However, there is no consensus on this value, and differences ranging from 0.04 to 0.07 are considered clinically relevant. Second, the dose of the study feed was not adjusted for non-nutritional calories, as it would have affected protein dose. Although the contribution of non-nutritional calories was low, it might have caused overfeeding in specific patients. However, energy delivery was similar between both groups, suggesting that it was not a systemic issue within the trial. A similar strategy has been used in other trials, such as the TARGET trial, that reported no detrimental effects of energy provision exceeding 30 kcal (including non-nutritional calories) per kg of ideal bodyweight regarding clinical outcomes and EQ-5D-5L health utility score at 6-month follow-up. Finally, although the longitudinal assessment during 6 months of patient-reported and functional outcomes is considered a strength of our trial, there was a relatively high amount of missing data. The percentage of incomplete records was higher for physical tests, requiring in-person follow-up, than for questionnaires. The highest amount of missing data was observed for the 6-min walking test, which is the most demanding physical test, making it likely prone to bias.

Physical performance or in-person follow-up was no hindrance to assessing the primary outcome, for which missingness was considered to be missing at random (ie, conditional on observed covariates). Inclusion of only complete data would likely have resulted in bias in effect measures, as the sample available for analysis would not be a random sample of the population anymore. Moreover, it would have greatly decreased power to detect differences between groups. The generalised linear mixed effects model assumes data are missing at random and, therefore, will produce unbiased estimates. For that reason, we conducted sensitivity analyses in which covariates likely contributing to the missing-at-random mechanism were added as fixed effects.

Considering death as a competing risk appeared to be particularly important in the PRECISE trial, considering the numerical difference in mortality between the two groups. Strengths of this trial included the double blinding; high achievement of enteral protein targets, which enhanced internal validity; and the use of a patient reported primary outcome that incorporated mortality as a competing risk.

Further research is needed to clarify protein needs during different stages of critical illness and to investigate the influence of physical therapy and exercise on muscle anabolism and protein use. Our results warrant further research on sex differences in the response to protein provision in critically ill people.

To conclude, caution is warranted when dosing nutritional protein in critically ill patients. Further research should aim to clarify protein requirements in different subgroups and in different phases of critical illness.

14. IMPORTANT ADDITIONAL TABLES AND FIGURES

14.1. Details of participating sites

Table 12 Details of participating study sites

Study site	City	Country	Language	Hospital type	Number of days actively recruiting	Number of participants recruited
Maastricht Universitair Medisch Centrum+	Maastricht	the Netherlands	Dutch	Academic hospital	876	239
Ziekenhuis Oost-Limburg	Genk	Belgium	Dutch	Teaching hospital	875	239
Universitair Ziekenhuis Brussel	Brussels	Belgium	Dutch, French	Academic hospital	820	35
Ziekenhuis Gelderse Vallei	Ede	the Netherlands	Dutch	Teaching hospital	788	72
Catharina Ziekenhuis	Eindhoven	the Netherlands	Dutch	Teaching hospital	103	14
Medisch Spectrum Twente	Enschede	the Netherlands	Dutch	Teaching hospital	822	134
Zuyderland Medisch Centrum	Heerlen	the Netherlands	Dutch	Teaching hospital	794	76
AZ Groeninge	Kortrijk	Belgium	Dutch	Teaching hospital	821	61
Centre Hospitalier Régional de la Citadelle	Liège	Belgium	French	Teaching hospital	766	41
Centre Hospitalier Universitaire de Liège	Liège	Belgium	French	Academic hospital	857	24

14.2. Timing of start and duration of study nutrition

Table 13 Timing of start and duration of study nutrition

	Standard Protein (n = 465)	High Protein (n = 470)
Days from ICU admission to randomisation – median (IQR)	1 (0, 1)	1 (0, 1)
Days from ICU admission to start of intervention – median (IQR)	1 (0, 1)	1 (1, 1)
Days receiving study nutrition during the entire ICU stay – median (IQR)	9 (4, 19)	10 (5, 21)

14.3. Summary of nutritional intake during the intervention period

Table 14 Summary of nutritional intake during the intervention period

	Standard Protein (n = 465)	High Protein (n = 470)
Protein intake in g/kg/day, mean (SD)	0.95 (0.44)	1.48 (0.70)
Protein intake in g/kg/day, median (IQR)	1.19 (0.63, 1.26)	1.87 (0.96, 2.00)
Protein adequacy in % of prescribed, mean (SD)	83 (33)	80 (32)
Protein adequacy in % of prescribed, median (IQR)	98 (69, 101)	97 (62, 100)
Energy intake in kcal/kg/day, mean (SD)	19 (9)	19 (9)
Energy intake in kcal/kg/day, median (IQR)	24 (13, 25)	24 (12, 25)
Energy adequacy in % of prescribed, mean (SD)	83 (32)	82 (32)
Energy adequacy in % of prescribed, median (IQR)	98 (70, 101)	98 (67, 100)

14.4. Domain data of EQ-5D-5L

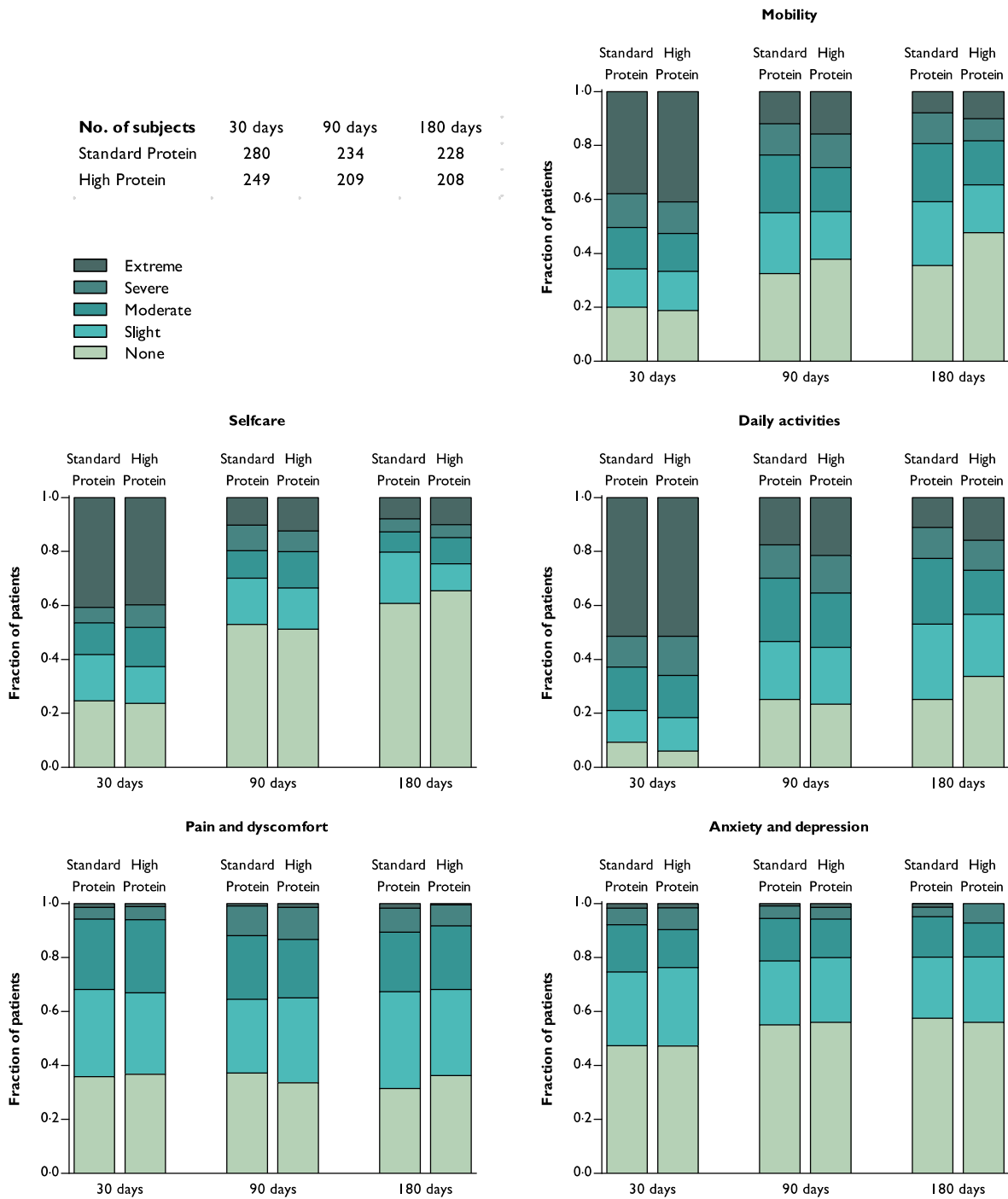


Figure 8 Domain data of EQ-5D-5L

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16. APPENDICES

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Table 4 Baseline characteristics of the intention-to-treat population
Baseline characteristics of the intention-to-treat population

Pagina **Table 4**

	Standard protein (n=465)	High protein (n=470)
Age, years	63 (14)	62 (14)
Sex		
Female	156 (34%)	179 (38%)
Male	309 (67%)	291 (62%)
BMI	27 (5)	28 (6)
Type of admission		
Medical	341 (73%)	308 (66%)
Surgical	124 (27%)	162 (35%)
Emergency surgery	107/124 (86%)	138/162 (85%)
Complications of elective surgery	17/124 (14%)	24/162 (15%)
Admission diagnosis system		
Respiratory	173 (37%)	149 (32%)
Cardiovascular	128 (28%)	129 (27%)
Neurological	67 (14%)	82 (17%)
Trauma	42 (9%)	48 (10%)
Sepsis*	21 (5%)	26 (6%)
Gastrointestinal	19 (4%)	22 (5%)
Miscellaneous	8 (2%)	4 (1%)
Metabolic or endocrine	4 (1%)	5 (1%)
Genitourinary	2 (<1%)	4 (1%)
Haematological	1 (<1%)	1 (<1%)
Diabetes	84 (18%)	90 (19%)
COVID-19 infection	73 (16%)	71 (15%)
Acute kidney injury†	97 (21%)	105 (22%)
Sepsis	229 (49%)	230 (49%)
Glasgow Coma Scale	15 (6–15)	15 (8–15)
APACHE II score‡	22 (7)	21 (7)
APACHE IV score‡	83 (26)	81 (26)
SOFA score§	10 (3)	9 (3)
SAPS II¶	48 (14)	47 (14)
EQ-5D-5L health utility score	0.78 (0.25)	0.77 (0.26)
Charlson Comorbidity Index**	3 (2–4)	3 (1–4)
NRS-2002 score††	4 (1)	4 (1)
Rockwood Clinical Frailty Scale‡‡	3 (2)	3 (2)

Data are mean (SD), n (%), n/N (%), or median (IQR). APACHE=Acute Physiology and Chronic Health Evaluation. EQ-5D-5L=EuroQoL 5-Dimension 5-level. KDIGO=Kidney Disease Improving Global Outcomes. NRS-2002=Nutritional Risk Screening 2002. SAPS=Simplified Acute Physiology Score. SOFA=Sequential Organ Failure Assessment. *Only patients with a not-otherwise-specified cause of sepsis as admission diagnosis. Patients with a specified cause of sepsis were categorised under the corresponding system. †Acute kidney injury was defined on the basis of KDIGO classification, which ranges from 1 to 3. KDIGO scores were calculated at randomisation and a score of 1 or more was considered to indicate acute kidney injury. ‡APACHE II scores range from 0 to 71. APACHE IV scores range from 0 to 286. Higher scores indicate greater severity of disease. §SOFA scores range from 0 to 20. Higher scores indicate greater severity of organ failure. ¶SAPS II ranges from 0 to 163. Higher scores indicate greater severity of disease. ||EQ-5D-5L health utility score ranges from -0.5 to 1.0. Deceased patients are assigned a score of 0. A score less than 0 is valued as a health-related quality of life worse than death, a higher score indicates better health-related quality of life, and a score of 1.0 indicates perfect health-related quality of life. **The Charlson Comorbidity Index provides a weighted score by considering comorbid conditions. Higher scores indicate more severe comorbid conditions. ††NRS-2002 ranges from 0 to 7. Higher scores indicate greater risk of malnutrition. ‡‡The Rockwood Clinical Frailty Scale is a global clinical measure of fitness and frailty in older people and ranges from 1 to 9. Higher scores indicate greater severity of frailty.

Table 1: Baseline characteristics of the intention-to-treat population

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19. SIGNATURES

Role	Name	Date	Signature
Chief Investigator (NL)	Marcel van de Poll	06 december 2024	2:40 PM CET DocuSigned by: 437742095398428...
National Coordinator (BE)	Dieter Mesotten	06 december 2024	4:52 AM PST DocuSigned by: 2EA2BB4CCC814BC...
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julia.bels@mumc.nl
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Katrien Tartaglia
Katrien.tartaglia@zol.be
Ziekenhuis Oost-Limburg
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Dieter Mesotten
Dieter.Mesotten@zol.be
Prof. Dr.
ZOL - UHasselt
Beveiligingsniveau: E-mailadres, Accountverificatie
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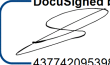
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