STATISTICAL ANALYSIS PLAN

PROTOCOL TITLE	The impact of high versus standard enteral protein provision on functional recovery following intensive care admission: a randomized controlled, quadruple blinded, multicenter, parallel-group trial in mechanically ventilated patients
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Section 1. Introduction

Background and rationale

Critical illness is characterized by severe skeletal muscle wasting during Intensive Care Unit (ICU) stay due to a protein catabolic state, adversely affecting short- and long-term outcomes. Augmented protein delivery can potentially improve protein balance and attenuate muscle loss. Nevertheless, interventions to effectively attenuate this catabolic state and improve post-ICU functional recovery and quality of life, have not yet been identified. Despite the physiological rationale, clinical trials on nutritional interventions in ICU patients have infrequently assessed functional and muscle-related endpoints. Recently, a large, randomized trial comparing standard and higher protein provision found no difference in mortality or ICU length of stay, comparable to results of other large nutrition trials. (1) In addition to assessing functional outcomes instead of mortality, longitudinal assessment of outcomes is needed as post-ICU recovery trajectories may evolve and differ over time.

Objectives

Mechanically ventilated patients admitted to the ICU were randomly allocated to either enteral nutrition containing a high (2.0 g/kg/day) or standard (1.3 g/kg/day) amount of protein. Functional recovery was assessed at 30, 90, and 180 days after ICU admission and measured at 30, 90, and 180 days after ICU admission.

The primary objective is to investigate whether higher enteral protein provision improves health-related quality of life, assessed using the Euro-QoL-5D-5-level (EQ-5D-5L) health utility score over 180 days after ICU admission.

The null hypothesis is that there is no difference in EQ-5D-5L health utility score over 180 days, measured at the above mentioned three time points, between treatment groups. The alternative hypothesis is that there is a difference between the two groups.

Section 2. Study methods

Trial design

The PRECISe trial is a bi-national, quadruple-blinded, multicenter randomized controlled trial (RCT) assessing the superiority of high versus standard enteral protein provision in mechanically ventilated ICU patients. (2)

Randomization

A computer algorithm was used to generate the concealed, random allocation sequence. Patients were randomized in a 1:1 ratio, stratified per center, using block randomization with random permuted block sizes varying between 4 and 6.

Sample size

The sample size calculation was based on a published cross-sectional measurement of the EQ-5D-5L health utility score at 180 days following ICU admission, as longitudinal data were unavailable (3). A minimum difference of 0.06 points on the EQ-5D-5L health utility score was selected to represent the minimum clinically important between-group difference to be detected. (4)

Based on these data, the sample size for the PRECISe trial was calculated as follows: assuming a standard deviation (SD) of 0.3 at 180 days (3), considering a two-sided type I error rate α of 5% and a type II error rate β of 20% (yielding a statistical power of 80%), 392 participants per intervention group will be required to detect the minimum clinically important difference of 0.06 in the EQ-5D-5L health utility score. In line with other critical care trials, the sample size has been adjusted upwards for an estimated 5% loss to follow-up for the primary endpoint. (5) After this adjustment, the final sample size for the PRECISe trial was set at 824 participants.

During the preplanned interim safety analysis after inclusion of 50% of patients, it became apparent that mortality was higher than anticipated, resulting in a standard deviation of the EQ-5D-5L HUS that was larger than expected (0.38 vs 0.30). Since this potentially could reduce the power of the study, the DSMB advised to increase the sample size. By running a Monte Carlo simulation of the primary outcome analysis using raw longitudinal data of the actual study population at that time (n = 709), without unblinding, it was calculated that with the observed standard deviation, a sample size of 935 patients would be required to retain 80% power to detect the minimally important difference of 0.06, while correcting for the actual loss-to-follow-up rate of 9.4%.

Framework

A superiority hypothesis testing framework will be used for primary and secondary outcomes. The null hypothesis is that the mean EQ-5D-5L health utility score of the intervention group is equal to the mean EQ-5D-5L health utility score of the control groups.

Timing of final analysis

The final analysis for all endpoints is planned when 180 days of follow-up is completed for the last surviving patient included.

Timing of outcome assessments

Outcome assessments occurred 30, 90, and 180 days after ICU admission. A window ranging from 4 days before to 4 days after the calculated follow-up date was defined, within which outcomes were collected.

Section 3. Monitoring of the trial

eCRF and database

All study data, including questionnaires, were recorded and stored in an electronic case report form (eCRF) created with the CASTOR© software (Castor, Amsterdam, The Netherlands). To protect the participants' privacy, all collected data is encoded, consisting of a code specific to the recruitment site, the study's abbreviation (PRECISe) and an incremental 3-digit number per center (starting from 001 in order of inclusion). Data will be exported for analysis as a comma-separated file (.csv), Excel file (.xlsx), and SPSS file (.data). Data management was performed by the Clinical Trial Unit of Ziekenhuis Oost-Limburg A.V. A clinical research organization (Clinical Trial Center Maastricht) was responsible for source data verification.

Data Safety Monitoring Board

A data and safety monitoring committee has overseen the trial at regular, predefined intervals to protect and serve the safety of trial participants and protect the validity and credibility of the trial results.

Statistical interim analyses and stopping guidance

Following enrolment of 50% of the targeted sample size, a preplanned interim safety analysis was performed by the Data Safety Monitoring Board (DSMB). All analyzed data were blinded to treatment allocation. The safety data analyzed were ICU mortality and in-hospital mortality. No other differences in outcome measures of effectiveness were assessed. In addition, the DSMB received accumulating information relating to recruitment, data quality, missing data, and protocol compliance. The independent blinded DSMB statistician performed all analyses. The study would have been terminated if the rate of safety endpoints in any of the feeding labels was more than twofold the rate in the other feeding labels. The DSMB reserved the right to make additional recommendations regarding the execution of the trial, as per DSMB charter. No other interim analyses were planned. The preplanned interim safety analysis revealed no safety issues.

Section 4. Statistical Principles

General rules of statistical reporting

Categorical data will be presented as counts and percentages. Continuous variables will be described as mean and standard deviation if data are approximately normally distributed, and median and interquartile range (first and third quartile) otherwise. Normality will be assessed visually using histograms and pp- or qq-plots.

Confidence intervals and *P* values

Effect sizes with 95% confidence intervals will be reported, together with a 2-sided P-value. The alpha used for testing will be set at 0.05 in all cases except for testing for interactions. In that case, an alpha of 0.10 will be used. No adjustments for multiplicity will be carried out.

Adherence and protocol deviations

Adherence to the intervention

Per protocol, the intervention should have been initiated within 48 hours of ICU admission at 25% of the calculated target and increased by 25% per day until 100% of energy and protein targets were reached on day 4. Targets were set at 25 kcal/kg/day, using the patient's weight at admission. For those with a BMI >27 kg/m^2, the ideal body weight (defined as 27 x height^2) was used. The study nutrition was continued for the duration of ICU stay if enteral nutrition was required or until a maximum of 90 days.

Adherence to the intervention will be presented for the intervention and control group as daily mean (± SD) and median (interquartile range, IQR) protein and calorie delivery over the first 10 days after randomization. In addition, the daily percentage of target (i.e., nutritional adequacy) per treatment arm and a summary value for the entire study period (number of feeding days and percentage of total study target provided) will be reported. Total intake will be calculated as the sum of all calories and protein from enteral and parenteral nutrition, supplemental protein, and amino acids for all days where intake could completely be quantified, i.e. excluding days with oral intake.

The following parameters relating to protocol adherence, will be reported:

- Time from ICU admission to randomization
- Time from ICU admission to start of intervention

- Number of days receiving study nutrition
- Total protein adequacy (g of protein received versus prescribed), reported separately for day 1, day 2, day 3, and day 4 and onwards from randomization (up to ten days)
- Total energy adequacy (kcal received versus prescribed), reported separately for day 1, day 2, day 3, and day 4 and onwards from randomization (up to ten days)
- Number of patients receiving on average <80% of prescribed protein over the entire ICU stay
- Number of patients receiving on average 80-110% of prescribed protein over the entire ICU stay
- Number of patients receiving on average >110% of prescribed energy over the entire ICU stay

Protocol deviations

The following protocol deviations will be reported:

- Number of patients who did not fulfil all inclusion criteria or fulfilled one or more of the exclusion criteria
- Number of patients in whom invasive mechanical ventilation was initiated more than 48 hours after ICU admission
- Number of patients who were not randomized within 72 hours of ICU admission
- Number of patients of Belgian sites for whom no written informed consent was obtained
- Number of patients who received the incorrect intervention at any time during the treatment phase
- Number of patients who received parenteral nutrition in the first 7 days of ICU admission

Analysis populations

Intention-to-treat

Since it is a superiority trial, all analyses will be performed on an intention-to-treat (ITT) basis. The ITT population will include all randomized patients as per allocated treatment arm.

Per-protocol

A per-protocol analysis will additionally be performed in patients in whom the allocated protocol was strictly adhered to. This is defined as patients in whom enteral nutrition was initiated within 48 hours of ICU admission and continued for at least 72 hours. Furthermore, overall actual provision of allocated study nutrition must have been >80% of what was prescribed during mechanical ventilation.

These constraints ensure that possible crossover in terms of protein dose is excluded (e.g., higher protein dose as part of prolonged parenteral nutrition in the control arm). The results of this analysis will be reported separately.

Section 4. Trial Populations

Screening data

All adult patients with an unplanned admission to the ICU and initiation of invasive mechanical ventilation within 24 hours of admission, were screened for enrollment. The following summaries will be reported: number of days recruiting, number of patients screened, number of patients not eligible, and reasons for non-eligibility. Number of days recruiting, and number of patients recruited will be presented by study centre.

Eligibility

Patients were screened for enrolment using the in- and exclusion criteria specified below.

Inclusion criteria:

- Adult (18 years or above) patient admitted to ICU
- Unplanned ICU admission
- Invasive, mechanical ventilation initiated <24 hours following ICU admission
- Expected ICU stay on ventilator support of 3 days or more
- Signed written informed consent (Belgium)

Exclusion criteria:

- Contraindication to enteral nutrition
- Moribund or withholding of treatment
- Kidney failure AND a ”no dialysis”-code on ICU admission
- Hepatic encephalopathy (West Haven grade 3-4)
- Body-mass index <18 kg/m^2

Recruitment

The number of patients eligible but not included, reasons for non-inclusion, and number of randomized patients will be reported as part of the CONSORT flow diagram.

Withdrawal/follow-up

The progress of all patients through the trial will be displayed as part of the CONSORT flow diagram. The number of patients who did not receive the allocated intervention will be reported, including corresponding reasons. Number of patients for whom no endpoints could be collected due to early withdrawal, and reasons for withdrawal, will be reported per trial phase. Patients who died will receive a score of 0 for the primary outcome and will be included in the final analyses, as described in the EQ-5D-5L user guide provided by the EuroQol Research Foundation. (6)

Baseline patient characteristics

The baseline characteristics in Table 1 will be summarized per treatment arm.

Table 1. Baseline characteristics of the PRECISe trial.

Age	Sex	BMI
Type of admission	Admission diagnosis system	ICU admission due to COVID-19 infection
Sepsis	Acute kidney injury	Glasgow Coma Scale
History of diabetes mellitus	APACHE II score	APACHE IV score
SAPS II score	SOFA score	EQ-5D-5L health utility score
Charlson Comorbidity Index	Rockwood Frailty Score	NRS-2002 score

BMI, Body Mass Index; ICU, Intensive Care Unit; COVID-19, Coronavirus Disease 2019; APACHE, Acute physiology and chronic health evaluation; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; EQ-5D-5L, Euro-QoL-5D-5-level; NRS-2002, Nutritional Risk Screening 2002.

Section 5. Analysis

The purpose of this Statistical Analysis Plan (SAP) is to provide a comprehensive and detailed description of the methods of data analyses proposed for the PRECISe trial. This SAP is based on the study protocol version 5.0 (the Netherlands) and 4.0 (Belgium). The SAP is written in concordance with the guideline for statistical analysis plans, formulated by Gamble et al. (7)

The SAP will define the analyses that will minimally be executed. Statistical analysis will be performed under the responsibility of the authors of the SAP, under the supervision of the trial statistician, while following the statistical principles as formulated in the International Council for Harmonisation (ICH) guideline. (8) This SAP is reviewed and approved by the Trial Steering Committee.

Outcome definitions

Primary outcome

The primary outcome is health-related quality of life, assessed by the overall difference in EQ-5D-5L health utility score between the intervention and control groups over three time points (30, 90, and 180 days after ICU admission), adjusted for baseline EQ-5D-5L.

The health utility score is derived from the responses to the 5-item EQ-5D-5L questionnaire, which is converted into a 5-digit number and then weighted using country-specific value sets, resulting in the EQ-5D-5L health utility score. The health utility score ranges from -0.532 to 1.0, with a score of 0 indicating death, a score below 0 indicating a state worse than death, a higher score indicating better health, and a score of 1 indicating perfect health.

Secondary outcomes

Clinical outcomes

Overall survival up to 180 days after ICU admission, with the use of Kaplan–Meier plots and a Cox proportional-hazards model, after ensuring, with the Schoenfeld residuals method, that the proportional-hazards assumption was met.

Functional outcomes

The following outcomes are collected at 30, 90, and 180 days after ICU admission.

- Health-related quality of life assessed by the Short Form 36 (SF-36): overall score, physical component score (PCS), and mental component score (MCS). Overall score ranges from 0 to 100, with higher scores indicating better Health-related Quality of Life.
- Anxiety and depression, assessed by the Hospital Anxiety and Depression Scale (HADS): odd-numbered questions measure symptoms of anxiety, and even-numbered questions measure symptoms of depression. Overall score ranges from 0 to 42, with higher scores indicating worse symptoms of anxiety and depression.
- Pain intensity assessed by the EQ-5D-5L pain question: ranges from 1 to 5, with higher scores indicating a more severe perception of pain or discomfort.
- Self-reported health assessed by the EQ-5D-5L visual analogue scale (EQ-VAS): ranges from 0 to 100, with higher scores indicating better self-reported health.
- Post-traumatic stress assessed by the Impact of Event Scale-Revised (IES-R): ranges from 0 to 88, with higher scores indicating worse symptoms of post-traumatic stress.
- Physical function assessed by 6-minute walk distance: total distance (meters) covered over a time of 6 minutes, standardized for sex and age.
- Muscle and nerve function assessed by Medical Research Council (MRC)-sum score: ranges from 0 to 60, with higher scores indicating better muscle and nerve function.
- Muscle and nerve function assessed by handgrip strength: measured using a hand dynamometer and expressed in kilograms, standardized for sex and age.

Tertiary outcomes

Clinical outcomes

- Hospital mortality: number of patients who died during index hospital admission.
- 30-, 60-, and 90-day mortality: number of patients who died within 30, 60, and 90 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 ($DAAH_{90}$) after index ICU admission.
- Nutritional adequacy: the ratio between the total amount of calories and grams of protein actually received by patients and prescribed during the treatment period.
- Duration of mechanical ventilation: number of days on invasive mechanical ventilation.
- Duration of index ICU stay: number of days of index ICU admission.

- Incidence of ICU readmissions: number of patients readmitted to the ICU during index hospital stay and number of readmissions per patient.
- Administration of prokinetics: number of patients who received a prokinetic and number of days receiving a prokinetic drug.
- Incidence of gastrointestinal intolerance/symptoms: number of patients who experienced, at any time during index ICU stay, vomiting, ischemia, diarrhoea, abdominal distention, gastric paresis, or bleeding/ ulcer.
- Incidence of ICU-acquired infections: number of patients who contracted an ICU-acquired infection.
- Incidence of acute kidney injury: number of patients with Acute Kidney Injury (AKI), defined as a serum creatinine level higher than 2 times baseline level.
- Incidence and duration of renal replacement therapy: number of patients who received renal replacement therapy and number of days on renal replacement therapy.
- Incidence of hepatic dysfunction: number of patients with hepatic dysfunction, defined as a total bilirubin level > 3 mg/dL.
- Sequential Organ Failure Assessment (SOFA) score: mean and maximum SOFA score during first two weeks of index ICU admission.
- The difference in mobilization treatment: number of days and degree of daily mobilization (e.g., passive, active, in-bed cycling, out-of-bed, etc.).
- Duration of index hospital stay: number of days of index hospital admission.
- Destination of hospital discharge: i.e., home, rehabilitation center, care facility, etc.
- Length of stay at rehabilitation facility: number of days at a rehabilitation center.

Functional outcomes

- Frailty assessed by Rockwood Clinical Frailty Scale: ranges from 1 to 9, with higher scores indicating increasing frailty, collected at 30, 90, and 180 days after ICU admission.
- Domain data EQ-5D-5L: scores of subdomains of EQ-5D-5L at 30, 90, and 180 days after admission, with higher scores indicating increased impairment.
- Return to work: number of patients who return to work, and number of days between ICU admission and return to work.

Outcomes regarding protocol adherence are discussed separately under “Adherence and protocol deviations”.

Lastly, a health economic evaluation will be performed. Details of this analysis are discussed separately under “Additional analyses”.

Unblinding

To mitigate the consequences of an accidental unblinding during the trial, 4 randomization labels (A, B, C, D), were used. Each study group was coded by two different labels. The trial will be unblinded in a stepwise manner. After database lock, it will be revealed which two labels, , each belong together to form one of the groups (i.e., either the high protein or the standard protein group), but it will not yet be revealed which group they actually belong to. Therefore, subsequent analysis of the endpoints will be performed blinded. Only after the analyses are finalized, it will be revealed which group of labels is the high protein group and which group is the standard protein group. This way, the analyses will be done in a blinded fashion, preventing bias.

Analysis methods

Primary outcome

The primary outcome will be analyzed using a linear mixed effects model with a 3-level structure, i.e., repeated measurements are clustered within participants and participants are clustered within centers. The fixed factors are treatment group, time, treatment group*time, and baseline EQ-5D-5L.

With respect to the random-effects, two models will be considered: a random intercepts model and a random intercepts and slope model. The model with the lowest Akaike Information Criterion (AIC) will be selected. Correlations between follow-up measurements will be modelled either using an autoregressive model of the first order (AR1) or left unstructured. Again, the AIC will be used to select the model with the best fit to the data.

Homoscedasticity of the residuals will be assessed using Levene's test and inspected using residual plots. Normality of the residuals will be assessed using QQ-plots. In case of violation of homoscedasticity, the model will be extended with a variance function; in case of violation of normality, the outcome will be transformed. If the assumption is still violated after transformation, we will apply a robust mixed-effects fit.

As sensitivity analysis, the model will be further adjusted for sex, APACHE II score, APACHE IV admission diagnosis, and NRS-2002.

Secondary and tertiary outcomes

Survival outcome

For the secondary endpoint overall survival, survival curves for both treatment arms will be constructed using the Kaplan-Meier method. Then, a Cox proportional hazards frailty model, with a 2-level structure, i.e., participants clustered within centers, will be used to investigate a treatment effect. The crude, unadjusted Hazard ratios will be reported with a 95% confidence interval. The proportional hazard assumption will be assessed as the association between the scaled Schoenfeld residuals and follow-up time. Additionally, sensitivity analyses will be performed by adjusting for potential confounders (sex, APACHE II score, APACHE IV admission diagnosis, and NRS-2002) is similar as described for the primary endpoint analysis.

Longitudinally assessed outcomes

The treatment effects for longitudinally assessed secondary and tertiary endpoints (SF-36, HADS, IES-R, EQ-5D-5L (EQ-VAS and pain question), 6-minute walking distance, MRC-SUM, and handgrip strength, frailty assessed by Rockwood Clinical Frailty Scale and mean and maximum SOFA scores) are assessed using linear mixed-effects models. The statistical approach will be similar as described for the analysis of the primary endpoint, particularly concerning the calculation of between-group differences, the 3-level model structure (with fixed treatment effect and random effects for center and participants), reporting of effect size, adjustment for potential confounders, and model selection strategy.

Time-to-event outcome

For time-to-discharge-alive from hospital, data of non-survivors will be censored at a time point beyond that of the last surviving patient to account for death as a competing risk. Between-group differences will then be estimated similar to overall survival.

Categorical outcomes

The differences in all categorical tertiary outcomes (see **Appendices 3-5**) will be analyzed using Pearson's chi-square test or Fisher's exact test, as appropriate. The treatment effects on all other tertiary outcomes will be analyzed using the Student's t-test or Mann-Whitney U test, depending on the distribution of data.

Subgroup analyses

For the primary endpoint, the below mentioned subgroup analyses will be done to investigate heterogeneity in treatment effect. For the secondary endpoint overall survival up to 180 days, the prespecified subgroup analyses are to be regarded as exploratory subgroup analyses. All subgroups are defined based on index ICU admission characteristics. Analyses will be performed using model specification as determined by the primary analyses.

Subgroup	**Definition**
Males versus females	Male sex versus female sex
Older versus younger patients	Assessed using age at ICU admission, older patients defined as ≥ 65 years
Obese versus non-obese patients	Assessed using BMI, cut-off ≥ 30 (9)
Medical versus surgical admission	Assessed using APACHE IV admission diagnosis
Patients at nutritional risk versus low nutritional risk	Assessed using NRS-2002 score, cut-off ≥ 3 (10)
Frail versus non-frail patients	Assessed using Rockwood Clinical Frailty Scale, cut-off ≥ 5 (11)
Patients with limited comorbidity versus patients with multimorbidity	Assessed using Charlson comorbidity index, cut-off ≥ 2 (12)
Sepsis versus no sepsis	Assessed using SEPSIS-III criteria
Higher versus lower disease severity	Assessed using the APACHE II score, higher disease severity is defined as ≥ median of the entire population
Acute kidney injury (AKI) vs no AKI	Assessed using Kidney Disease: Improving Global Outcomes criteria, stage 1 or higher (13)
Patients with or without severe multi-organ failure	Assessed using the SOFA score, severe organ failure is defined as ≥ median of the entire population
Traumatic brain injury versus others	Assessed using APACHE IV admission diagnosis, including isolated traumatic brain injury as well as traumatic brain injury combined with other injuries
COVID-19 patients versus non-COVID-19 patients	ICU admission due to viral pneumonia with a positive PCR for SARS-CoV-2
Difference in muscle mass on admission	Assessed using BIA, muscle ultrasound, and/or computed tomography; cut-offs dependent on modality

As exploratory analyses of post-randomization groups, we will:

- Compare patients with prolonged ICU stay (>1 week) vs short-stay patients.
- Compare patients who underwent renal replacement therapy (RRT) vs patients who did not.
- Compare patients based on urea and urea-to-creatinine ratios over the first two weeks of admission.

Missing data

The assumed missing data mechanism for all endpoints is missing at random (MAR), given the amount of baseline covariates and other outcome variables collected. Longitudinal endpoints will be analyzed using mixed-effects models. This approach is robust with regard to MAR provided that variables contributing to the mechanism are used as covariates in the model.

In practice, baseline or outcome covariates will be introduced to the model if more than 5% of outcome data are missing. The baseline covariates in Table 1 and other outcome variables will be tested and added to the model if they are associated with the outcome or with a missingness indicator in univariate analysis with a P-value of < 0.05.

Missing data in other outcome data (not longitudinally assessed) and baseline covariates will be imputed using multiple imputation with fully conditional specification, in case the rate of missing data is more than 5%.

As a sensitivity analysis, we will perform the analysis of the primary outcome without modelling the MAR mechanism to test the robustness of our assumption.

Additional analyses

Health economic evaluation

The main question for the economic evaluation is to assess whether high enteral protein provision is cost-effective compared to standard enteral protein provision. The economic evaluation will be performed from a health care perspective over 180 days from ICU admission.

To quantify health care costs, data regarding ICU and hospital resource use will be collected, using the Dutch (Zorginstituut Nederland) and Belgian (RIZIV) guidelines for cost calculation. (14, 15) The following variables will be collected to quantify the most important medical costs within and outside

the hospital incurred by ICU patients: duration of mechanical ventilation, ICU and hospital length of stay, ICU and hospital readmissions, days on renal replacement therapy, days on intravenous antibiotics, complications, and admission to and duration of stay in a rehabilitation center.

To address the question regarding cost-effectiveness, we will perform a cost-utility analysis. A generic quality of life questionnaire, the EQ-5D-5L, will be taken 30, 90 and 180 days after ICU admission. The EQ-5D-5L scores will be translated to health state utilities with the Dutch and the Belgian value set. (16, 17) Subsequently, a quality-adjusted life year (QALY) will be calculated by multiplying the length of time with the utility scores between time points. The advantage of using a QALY is that it combines reduced morbidity (quality gain) and reduced mortality (quantity gain) in one measure. For 1 year in perfect health, the total maximum QALY will be 1.

Data will be analyzed on an intention-to-treat basis. As most volumes of resources follow a skewed distribution, differences in costs between the two groups will be analyzed with non-parametric bootstrap analysis. Bootstrap analysis will further be used to quantify the uncertainty surrounding the incremental cost-effectiveness ratio (ICER). The results of this analysis will be presented in cost-effectiveness planes and acceptability curves. Missing data will be imputed by a multiple imputation approach. Uncertainty related to the impact of different parameters on the incremental cost-effectiveness ratio will be assessed with uni- and multivariate sensitivity analysis. The trial-based cost-effectiveness analysis will follow the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines. (18)

Bayesian analysis of primary and secondary outcomes

The proposed secondary, preplanned Bayesian analysis of the PRECISe trial will provide additional information on the effects of high protein on functional and clinical outcomes in critically ill patients, such as probabilistic interpretation, probabilities of clinically important effect sizes, and the integration of prior evidence. As such, it will complement the interpretation of secondary endpoints and subgroup analyses. An extensive protocol for this Bayesian analysis has been published elsewhere. (19)

Outcomes and subgroups

The following outcomes will be assessed: EQ-5D-5L health utility score (longitudinal analysis), 6-minute walking test and handgrip strength over the entire follow-up period (longitudinal analyses), 60-day mortality, duration of mechanical ventilation as well as EQ-5D-5L health utility scores at 30, 90 and 180 days (cross-sectional analyses). Based on the available literature, patients with acute renal failure, sepsis and non-sepsis, and severe multi-organ failure at ICU admission were identified as

relevant subgroups. Non-surviving patients will be assigned an EQ-5D-5L health utility score of 0, in agreement with the primary analysis.

Statistical analysis

Dedicated software will be used, including R (R Core Team, R Foundation, Vienna, Austria, version 4.3.1 – *R2jags* package (20, 21)) and JASP (JASP team 2023, version 0.17.3, Amsterdam, the Netherlands (22)). If prior data from previous randomized trials is available to formulate an informative (literature-based) prior, such a prior will be incorporated. When no prior trial data are available, analyses will be performed under a weakly informative prior. In addition, skeptical and enthusiastic priors will be used to assess the robustness of the results.

Priors

For each endpoint, a minimal clinically important difference (MCID) is derived from the literature (see Table). For all analyses, we will use weakly informative priors centred around 'no effect' (mean difference [MD] of 0, or an odds ratio [OR] of 1 [0 on the log OR scale]). For the binary outcomes (ORs, denoted as the log of the OR), a mean of 0 will be applied for the weakly informative prior, while the standard deviation (SD) will be set to 3 on the log OR scale to capture all credible effect sizes. For the continuous outcomes (on the MD scale), we aim to be consistent and reproducible, but will also allow the distributions to capture all plausible effect sizes. As such, the standard deviation (SD) will be based on a multiplication of the MCID (x100). Table 1 presents the numerical values of these weakly informative priors. Skeptical and enthusiastic priors are defined following a modification of the approach suggested by de Grooth and Elbers. (23) Skeptical priors will be centred at a mean difference (MD) or log OR of 0. The distribution will incorporate a <10% probability that the estimated treatment effect will exceed +1 MCID. Conversely, the enthusiastic priors are centred around an effect of +2 MCID and will follow a similar distribution with a probability of <10% that the estimated effect size will be smaller than +1 MCID.

Outcome	**Effect size and approach**	**Weakly informative**	**Literature-based* (mean, SD)**	**MCID**	**Ref.**
Primary outcome					
EQ-5D-5L HUI (>0)	MD, longitudinal	(0, 6.0)	NA	0.06	(2)
EQ-5D-5L HUI (0)	OR, longitudinal	(0, 3.0)	NA	0.06	(2)
Secondary outcomes					
6MWT (m)	MD, longitudinal	(0, 1900)	NA	19 m	(24)
HGS (kg)	MD, longitudinal	(0, 500)	NA	5.0 kg	(25)

Duration of MV (days)	MD, cross-sectional	(0, 100)	(-0.42, 0.30) days	1.0 days	(26)
60-day mortality	OR, cross-sectional	(0, 3.0) Log-scale, OR	(-0.02, 0.09) Log-scale, OR	5% ARD	(27)
EQ-5D-5L HUI 30 days (>0)	MD, cross-sectional	(0, 6.0)	NA	0.06	(2)
EQ-5D-5L HUI 30 days (0)	OR, longitudinal	(0, 3.0)	NA	0.06	(2)
EQ-5D-5L HUI 90 days (>0)	MD, cross-sectional	(0, 6.0)	NA	0.06	(2)
EQ-5D-5L HUI 90 days (0)	OR, longitudinal	(0, 3.0)	NA	0.06	(2)
EQ-5D-5L HUI 180 days (>0)	MD, cross-sectional	(0, 6.0)	NA	0.06	(2)
EQ-5D-5L HUI 180 days (0)	OR, longitudinal	(0, 3.0)	NA	0.06	(2)
Subgroup analyses					
EQ-5D-5L HUI Sepsis (>0)	MD, longitudinal	(0, 6.0)	NA	0.06	(2)
EQ-5D-5L HUI Sepsis (0)	OR, longitudinal	(0, 3.0)	NA	0.06	(2)
EQ-5D-5L HUI Non-sepsis (>0)	MD, longitudinal	(0, 6.0)	NA	0.06	(2, 28)
EQ-5D-5L HUI Non-sepsis (0)	OR, longitudinal	(0, 3.0)	NA	0.06	(2, 28)
EQ-5D-5L HUI AKI (>0)	MD, longitudinal	(0, 6.0)	NA	0.06	(1, 2)
EQ-5D-5L HUI AKI (0)	OR, longitudinal	(0, 3.0)	NA	0.06	(1, 2)
EQ-5D-5L HUI Severe multi-organ failure (>0)	MD, longitudinal	(0, 6.0)	NA	0.06	(1, 2)
EQ-5D-5L HUI Severe multi-organ failure (0)	OR, longitudinal	(0, 3.0)	NA	0.06	(1, 2)

*Literature based priors are derived from an updated version of the meta-analysis of Lee et al (29), particularly containing data from the recently published EFFORT-protein trial. (30)

For the cross-sectional endpoints “60-day mortality” and “duration of mechanical ventilation”, informative priors could be derived from a meta-analysis of randomized trials addressing the clinical effectiveness of high protein nutrition in critical illness (29), which the same authors have recently updated after the publication of the EFFORT Protein trial (1). The authors kindly shared data from this updated meta-analysis that are relevant to the current Bayesian analysis protocol prior to publication. This meta-analysis also contains one study that reports on EQ-5D-5L (31), albeit on a survivors-only analysis. Since the PRECISe trial uses a complete-case analysis (including non-survivors), these data could not be used to formulate a reasonable literature-based prior for the estimation of the treatment effect on this outcome. Therefore, cross-sectional and longitudinal analyses of EQ-5D-5L will be performed under weakly informative priors, skeptical priors, and enthusiastic priors.

As all analyses will be performed with adjustment for the random center effect, a prior for this effect is uniformly formulated as well. These models incorporate random intercepts and the prior for these random effects follow a normal distribution with an effect centered around a mean of 0 and a large standard deviation, similar to the other priors.

If evidence from additional relevant randomized trials on high protein provision will be published before executing this Bayesian analysis, we will consider incorporating these data in the literature-based priors.

Presentation of results and summary statistics

Posterior distributions will be presented as MDs or mean ARDs and median OR, accompanied by 95% credible intervals (CrI) with reference to the used priors.

Analysis of the primary outcome (EQ-5D-5L over 180 days)

Given the mixture distribution of the EQ-5D-5L (the component of zero and the component other than 0), we will specify separate priors per longitudinally assessed outcome. Consequently, we will specify a prior for the mean difference with an EQ-5D-5L other than 0 and a prior for the proportion of patients who have an EQ-5D-5L score of 0 (i.e., deceased patients). This longitudinal analysis will be performed with adjustment for center as a random effect. The results of the analyses for the components will be presented separately and as weighted averages.

Analysis of longitudinally assessed secondary outcomes

Secondary outcomes for which no prior evidence was available will be estimated under a weakly informative prior, in a model similar to the longitudinally assessed primary outcome, with adjustment for the random effect of center.

Analysis of outcomes at one given time point

Secondary binary outcomes, such as 60-day mortality, will be expressed in ORs and absolute risk differences (ARD). These binary outcomes will be analyzed in a binary mixed regression model (Bernoulli distribution) with an adjustment for the random center effect. Priors for these binary outcomes are presented on the log OR scale in Table 1. Other secondary continuous outcomes, such as the duration of mechanical ventilation, will be reported in mean differences (MD) for the specific units of that endpoint. Finally, the abovementioned mixture distribution (the component of zero, and the component other than 0) will be used for the EQ-5D-5L assessment at the cross-sectional time points, and separate priors will be formulated, similar to the primary outcome assessment.

Handling of missing data

As the missingness of data is assumed to be missing at random (MAR), the linear mixed effects model will be appropriate to handle missing data.

Model settings and diagnostics

The models for our analysis will be implemented in *JAGS* using Markov Chain Monte Carlo (MCMC) algorithms, through the *R2jags* package (20, 21). Assessment of model convergence will be performed for key model parameters via potential scale reduction factors (Rhat) effective sample size (ESS), and other diagnostics such as density and trace plots. Model fit will be assessed in relative terms through the deviance information criterion (DIC and other criteria alike), and in absolute terms using posterior prediction checks (PPCs).

(Serious) Adverse events

Due to the nature of the patient population (i.e., critically ill patients), all participants entered the study in a state of life-threatening illness and were likely to experience many events that could be classified as an (S)AE. Therefore, only SAEs which result in death or life-threatening situations due to complications with study nutrition were reported.

In addition, several events of special interest will be compared between groups to compare the safety and harm of the two study feeds. These include:

- Incidence of ventilator-acquired pneumonia
- Incidence of acute kidney injury
- Refeeding hypophosphatemia
- Incidence of hepatic dysfunction
- Incidence of gastrointestinal intolerance/symptoms

These events are further specified in **Appendix 3**.

Statistical software

The statistical analysis and reporting will be done using R (version 4.3.1 or higher) and the code will be published on an online repository (included in the supplemental appendix).

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Appendix 1. Baseline and screening variables

All variables are defined as "at ICU admission".

Variable	Definition	Type of data
Hospital	Participating center	Nominal
Age	In years	Continuous
Sex	Sex, female	Binary
Weight	In kilograms (kg)	Continuous
Height	In centimetres (cm)	Continuous
BMI	In kg/cm^2	Continuous
Immunocompromised or severe organ failure	Immunosuppression or organ failure, i.e., liver insufficiency or cardiovascular, respiratory, or renal failure	Binary
Diabetes mellitus	With further specification: diet-controlled, uncomplicated, or with end-organ damage	Binary, ordinal
Chronic kidney disease	With further specification: dialysis dependent, post-transplant, creatinine >265 µmol/l or >3 mg/dl	Binary, nominal
Current malignancy	With further specification: solid localized, metastatic, lymphoma, leukaemia/myeloma	Binary, nominal
Liver disease	With further specification: limited (hepatitis without cirrhosis), mild (cirrhosis without portal hypertension), moderate (portal hypertension without variceal bleeding), severe (variceal bleeding history)	Binary, ordinal
Chronic lung disease	With further specification: COPD, asthma, cystic fibrosis	Binary, nominal
Myocardial infarction	Definite or probable myocardial infarction (ECG changes and/or enzyme changes)	Binary
Congestive heart failure	Exertional or paroxysmal nocturnal dyspnoea and responded to digitalis, diuretics, or afterload-reducing agents	Binary
Peripheral vascular disease	Intermittent claudication or past bypass for chronic arterial insufficiency, history of gangrene or acute arterial insufficiency, or untreated thoracic or abdominal aneurysm (≥6 cm)	Binary
Cerebrovascular accident	Transient Ischemic Attack or Cerebrovascular Accident	Binary
Dementia	Chronic cognitive deficit	Binary
Connective tissue disease	E.g. Marfan, Ehlers-Danlos, Loeys-Dietz syndrome	Binary

Peptic ulcer disease	History of treatment for ulcer disease or history of ulcer bleeding	Binary
Hemiplegia	One-sided paralysis	Binary
Immunosuppression	Recently received therapy that suppresses resistance to infection and still has an effect on subject or a disease sufficiently advanced to suppress resistance to infection	Binary
AIDS	Condition of AIDS, not just HIV positive	Binary
Nutritional Risk Screening 2002	Nutritional Risk Screening 2002, obtained via proxy & describing functioning before ICU admission	Ordinal/ continuous
EQ-5D-5L HUS	EuroQol-5D-5L questionnaire, obtained via proxy & converted to Health Utility Score (HUS) using land-specific tariffs, describing functioning before ICU admission	Continuous
Rockwood Clinical Frailty Scale	Frailty level using Rockwood Clinical Frailty Scale, obtained via proxy & describing functioning before ICU admission	Ordinal/ continuous

Appendix 2. Admission characteristics

All categorical variables are defined as "at ICU admission". All continuous variables, except the Glasgow Coma Scale, are defined as "within the first 24 hours of ICU admission".

Variable	Definition	Type of data
Date & time of ICU admission	Date and time of index ICU admission	Date and time
Date of hospital admission	Date of index hospital admission	Date
Origin of ICU admission	Last location of patient before index ICU admission, i.e., emergency department, hospital ward, other ICU, operating room	Nominal
Admission type	Nonoperative, emergency surgery, or elective post-surgery	Nominal
Primary system diagnosis	APACHE IV admission diagnosis system	Nominal
Admission diagnosis	APACHE IV admission diagnosis	Nominal
COVID-19	ICU admission due to COVID-19 infection	Binary
Acute renal failure	Renal replacement therapy, or serum creatinine level greater than 1.5 mg/100 ml (or 133µmol/l) during the previous 24 hours, associated with oliguria	Binary
Sepsis	According to SEPSIS-III criteria, i.e., suspected infection and SOFA score >=2	Binary
APACHE II score	Acute Physiology and Chronic Health Evaluation (APACHE) II disease severity score	Continuous
Laboratory values	Worst value of hemoglobin (g/dl), hematocrit (%), leukocytes (mm^3), platelets (mm^3), sodium (mmol/l), potassium (mmol/l), phosphate (mg/dl), urea (mg/dl), creatinine (mg/dl), lactate (mmol/l), total bilirubin (mg/dl), aspartate aminotransferase (U/l), alanine transaminase (U/l), gamma-glutamyl transferase (U/l), alkaline phosphatase (U/l), albumin (g/dl), C-reactive protein (mg/l), magnesium (mg/dl)	Continuous
Glucose	Lowest & highest value in mg/dl	Continuous
Heart rate	Lowest & highest value in beats per minute	Continuous
Respiratory rate	Lowest & highest value in breaths per minute	Continuous
Temperature	Lowest & highest value in degrees Celsius	Continuous
Systolic blood pressure	Lowest & highest value in mmHg	Continuous
Diastolic blood pressure	Lowest value in mmHg	Continuous
Mean arterial pressure	Lowest & highest value in mmHg	Continuous

Vasopressor	Use and highest dose (>1 hour) of noradrenaline, adrenaline, dobutamine, and/or dopamine in µg/kg/min	Binary, continuous
Bicarbonate	Lowest value in mmol/litre	Continuous
pH	Worst value	Continuous
PaO_2/FiO_2 ratio	Worst value	Continuous
PaO_2	Value corresponding to worst PaO_2/FiO_2 ratio in mmHg	Continuous
$PaCO_2$	Value corresponding to worst PaO_2/FiO_2 ratio in mmHg	Continuous
Urine output	Total urine output in millilitres per 24 hours	Continuous
Glasgow Coma Scale	Last known Glasgow Coma Scale before sedation	Continuous

Appendix 3. Treatment phase characteristics

Variable	Definition	Type of data
Duration of enteral nutrition	Total duration of enteral nutrition during index ICU admission in days	Continuous
Nutritional target	Nutritional target, expressed in kcal/day and ml/day	Continuous
Volume of study nutrition	Total administered volume of study nutrition in millilitres, collected daily until ICU discharge	Continuous
Propofol	Total administered volume of propofol in millilitres, collected daily during index ICU admission	Continuous
Insulin	Total administered volume of intravenous insulin in millilitres, collected daily during index ICU admission	Continuous
Mobilization	Maximum degree of mobilization, ranging from “none” to “out of bed”, collected daily during index ICU admission	Ordinal
Laboratory values	Worst value of hemoglobin (g/dl), hematocrit (%), leukocytes (mm^3), platelets (mm^3), potassium (mmol/l), phosphate (mg/dl), urea (mg/dl), creatinine (mg/dl), total bilirubin (mg/dl), aspartate aminotransferase (U/l), alanine transaminase (U/l), gamma-glutamyl transferase (U/l), alkaline phosphatase (U/l), albumin (g/dl), C-reactive protein (mg/l), magnesium (mg/dl), pH and PaO_2/FiO_2 ratio on treatment days 1, 3, 5, 7, 9, 11 & 13	Continuous
Glucose	Lowest & highest value in mg/dl on treatment days 1, 3, 5, 7, 9, 11 & 13	Continuous
Mean arterial pressure	Lowest value in mmHg collected on treatment days 1, 3, 5, 7, 9, 11 & 13	Continuous
Vasopressor	Use and highest dose (>1 hour) of noradrenaline, adrenaline, dobutamine, and/or dopamine in µg/kg/min collected on treatment days 1, 3, 5, 7, 9, 11 & 13	Binary/ continuous
Urine output	Total urine output in millilitres collected on treatment days 1, 3, 5, 7, 9, 11 & 13	Continuous
Fluid balance	Daily and cumulative fluid balance, in millilitres (per 24h), collected on treatment days 1, 3, 5, 7, 9, 11 & 13	Continuous
Glasgow Coma Scale	Glasgow Coma Scale, only scored when not sedated, collected on treatment days 1, 3, 5, 7, 9, 11 & 13	Continuous
Other enteral nutrition	Type & total volume of enteral nutrition administered other than the assigned intervention during index ICU admission	Nominal, continuous

Parenteral nutrition	Type & total volume of parenteral nutrition administered during index ICU admission	Nominal, continuous
Oral nutrition	Intake per os, collected daily during index ICU admission	Binary
Mechanical ventilation duration	Total duration of invasive mechanical ventilation during index ICU admission in days	Continuous
Reintubation	Reintubation during index ICU admission & duration of subsequent ventilation episode(s)	Binary, continuous
ICU acquired infection	ICU-acquired infection during index ICU admission	Binary
Ventilator acquired pneumonia	Ventilator-acquired pneumonia during index ICU admission	Binary
Acute Kidney Injury	Defined as creatinine level higher than 2 times baseline level (including start of Renal Replacement Therapy) during index ICU admission	Binary
Refeeding hypophosphatemia	Defined as phosphate levels below <0.65 mmol/l, a drop >0.16 mmol/l from the previous level in ICU and no other explanation for hypophosphatemia during index ICU admission	Binary
Hepatic dysfunction	Defined as cholestasis and liver dysfunction, i.e., bilirubin level higher than 3 mg/dl or 51,3 µmol/l during index ICU admission	Binary
Vomiting	Vomiting during index ICU admission	Binary
Ischaemia	Ischaemia during index ICU admission	Binary
Diarrhoea	Diarrhoea during index ICU admission	Binary
Abdominal distension	Abdominal distension during index ICU admission	Binary
Gastric paresis	Gastric paresis during index ICU admission	Binary
Bleeding/ulcer	Bleeding or ulcer during index ICU admission	Binary
Renal replacement therapy	Continuous veno-venous hemofiltration (CVVH) or intermittent hemodialysis during index ICU admission, including duration in days and type of anticoagulation	Binary, continuous, nominal
ECMO	Extracorporeal membrane oxygenation (ECMO) during index ICU admission, including duration in days and type of cannulation	Binary, continuous, nominal
SAE	Any Serious Adverse Event (SAE) during index ICU admission	Binary
Concomitant medication	Type and duration in days of administered IV antibiotics, prokinetics, glucocorticoids or muscle relaxants during index ICU stay	Nominal, continuous
ICU admission duration	Duration of index ICU admission in days	Continuous
ICU discharge location	Location where the patient is discharged to after index ICU admission	Nominal

ICU readmission	ICU readmission during index hospital admission, including reason and duration of subsequent ICU admissions in days	Binary, nominal, continuous
Hospital admission duration	Duration of index hospital admission in days	Continuous
Hospital discharge location	Location where the patient is discharged to after index hospital admission	Nominal

Appendix 4. Follow-up variables

All variables below are collected at 30, 90, and 180 days after ICU admission.

Variable	Definition	Type of data
EQ-5D-5L HUS	EuroQol-5D-5L questionnaire converted to Health Utility Score (HUS) using land-specific tariffs	Continuous
EQ-5D-5L VAS	EuroQol-5D-5L Visual Analogue Scale (VAS), i.e., self-rated health on a scale of 0-100	Continuous
EQ-5D-5L domain data	EuroQol-5D-5L sub-scores for domains mobility, self-care, usual activities, pain/discomfort, and anxiety/depression	Ordinal/ continuous
EQ-5D-5L pain intensity question	EuroQol-5D-5L sub scores pain/discomfort	Ordinal/ continuous
36-item Short Form Survey (SF-36)	Health-related quality of life using 36-item SF-36 Survey; overall score, physical component score (PCS), and mental component score (MCS)	Continuous
Hospital Anxiety and Depression Scale (HADS)	Anxiety and depressive symptoms using HADS; overall HADS score and sub-scores for anxiety and depressive symptoms	Continuous
Impact of Event Scale Revised (IES-R)	Post-traumatic stress symptoms using IES-R	Continuous
6-minute walking distance (6MWD)	Self-paced distance walked in 6 minutes in meters, including pre- and post-measurement pulse and saturation and use of any aids	Continuous, nominal, categorical
Medical Research Council (MRC)-sum score	Bilateral strength for six muscle groups: shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, and ankle dorsal flexion	Continuous
Handgrip strength	Maximum value out of three attempts per hand in kg	Continuous
Rockwood Clinical Frailty Scale	Frailty level using the Rockwood Clinical Frailty Scale	Ordinal/ continuous

Appendix 5. Trial termination characteristics

Variable	Definition	Type of data
Rehabilitation center admission	Admission to rehabilitation center during follow-up period and duration of stay in days	Binary, continuous
Return to work	Return to work (if applicable) and date of work resumption	Binary, date
Death	Survival status and date of death (if applicable)	Binary, date
Early trial termination	Reason for early trial termination, e.g., due to death or proxy or patient consent withdrawal, and date of early termination	Nominal, date
Unblinding	Occurrence of unblinding during trial participation	Binary