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 STUDY TITLE/ACRONYM

PRotEin provision in Critical IllneSs (PRECISe)

PROTOCOL VERSION NUMBER AND DATE

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TABLE OF CONTENTS

1. TRIAL SUMMARY

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
Planned sample size	824 patients
Trial duration	Approximately 30 months (including 6 months follow-up per patient)
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 • 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) EQ-VAS of the EQ-5D-5L and IES-R Impact of Event Scale, all 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	• 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 • Days on renal replacement therapy during index ICU stay

	• 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 • The number of days on prokinetics during index ICU stay • 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 is a pragmatic, international multi-center, randomized controlled, triple-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 consists of 3 phases: • Screening phase: starting from identifying a study subject until the first nutrition will be given. • Treatment phase: starting from the first nutrition until ICU discharge or a maximum of 90 days of ICU admission. • Follow-up phase: 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 will consist 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 will be performed after finalization of the follow-up phase of the 412th enrolled patient.
Statistical analysis	• Treatment effect for the primary endpoint, the EQ-5D-5L index score, is evaluated by means of a linear mixed model for longitudinal data analysis with a 3-level structure. The statistical model will include 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 will be constructed for both treatment arms. A mixed effect Cox proportional hazard model with a 2-level structure (patients clustered within centers) will subsequently be used to investigate treatment effect. • Other secondary endpoints will be calculated similar to the primary endpoint. Missing values for the secondary endpoints are expected to be much higher than the primary endpoint due to 'truncation by death'. Because these data cannot be assumed missing at random, a modified multiple imputation method will be applied as described in the statistical analysis plan. • All hypotheses are 2-sided and tested with a significance level of α=0.05

2. KEY TRIAL CONTACTS

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3. SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted, and that the undersigned agree to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the requirements for the conduct of clinical trials in the EU as provided for in "Directive 2001/20/EC", and any subsequent amendment, GCP guidelines, the Belgian law of May 7th 2004 regarding experiments on the human person, the Dutch 'Wet medisch-wetenschappelijk onderzoek met mensen' (WMO) and the General Data Protection Regulation (GDPR) of May 25th 2018, the Sponsor's SOPs, and other regulatory requirements as amended. The undersigned agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor. The undersigned also confirm that they will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:	**For and on behalf of the Belgian Coordinating Center:**
academisch Ziekenhuis Maastricht Signature: Marcel CG van de Poll, MD, PhD Chief Investigator	Ziekenhuis Oost-Limburg A.V. Signature: D. MESOTTEN Dieter Mesotten, MD, PhD Coordinating Investigator

4. LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)**
AKI	**Acute Kidney Injury**
AE	**Adverse Event**
APACHE	**Acute Physiology And Chronic Health Evaluation**
AUC	**Area Under the Curve**
AR	**Adverse Reaction**
ALP	**Alkaline phosphatase**
ALT	**Alanine transaminase**
AST	**Aspartate amiotransferase**
BMI	**Body mass index**
CI	**Chief Investigator**
COS	**Core Outcome Set**
CRF	**Case Report Form**
CRP	**C-reactive protein**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EC	**Ethical Commission**
ECMO	**Extracorporeal membrane oxygenation**
EQ-VAS	**EuroQol visual analogue scale**
ERAS	**Enhanced Recovery After Surgery**
ESICM	**European Society of Intensive Care Medicine**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
GGT	**Gamma-glutamyl transferase**
HADS	**Hospital Anxiety and Depression Scale**
HR	**Heart Rate**
HRQL	**Health Related Quality of Life**
ICF	**Informed Consent Form**
ICU	**Intensive Care Unit**
ICU-AW	**Intensive Care Unit Acquired Weakness**
IEC	**Independent Ethics Committee**
IES-R	**Impact of Event Scale-Revised**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
ISF	**Investigator Site File**
IWRS	**Interactive Web Response System**
LoS	**Length of Stay**

MAP	**Mean Arterial Pressure**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
MRC-SUM	**Medical Research Council-SUM scale**
NRS	**Nutrition Risk Score**
OACIS	**Outcomes After Critical Illness and Surgery**
PI	**Principal Investigator**
UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
QALY	**Quality-Adjusted Life Year**
RCT	**Randomized-controlled trial**
RR	**Respiratory rate**
(S)AE	**(Serious) Adverse Event**
SAPS III	**Simplified Acute Physiology III Score**
SD	**Standard deviation**
SI	**Sub-investigator**
SF-36	**Short Form 36 Health survey questionnaire**
SmPC	**Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst**
SOFA	**Sequential Organ Failure Assessment**
Sponsor	**The sponsor is the party that commissions the organization or performance of the research, for example a pharmaceutical company, academic hospital, scientific organization or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidizing party.**
TMF	**Trial Master File**
TSC	**Trial Steering Committee**
VAP	**Ventilator-acquired pneumonia**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

5. INTRODUCTION

Every year, more than 92.000 patients are acutely admitted to an intensive care unit (ICU) across Belgium and the Netherlands (*Data NICE foundation*). 25-30% of these patients require more than 3 days of invasive ventilation, with an average ICU stay of 10 days (*Data NICE foundation*). Although life threateningly ill, the likelihood of surviving an ICU admission has slowly increased over the past decades due to (technical) advances in treatment and a focused effort on improving mortality rates in the ICU.

Recently however, it has also become evident that surviving an ICU admission is not enough. Many patients are faced with long recovery periods and persistent debilitating health problems that remain after critical illness. Collectively termed the 'Post-Intensive Care Syndrome', the enormous impact of an ICU admission on patient's health and quality of life has now been clearly established. With an increasing number of patients surviving their ICU admission, ICU survivorship is considered the number one public health challenge in modern day intensive care medicine [1].

The key determinant of poor post-ICU health status is the development of ICU acquired weakness (ICU-AW). ICU-AW is the consequence of the body's reserves being depleted during critical illness and results in severe skeletal muscle wasting during the first week of ICU admission [2]. Loss of muscle mass and function is an important determinant and predictor of disability and quality of life in post-ICU recovery [3]. Developing ICU-AW adversely affects ICU and hospital length of stay, 1-year mortality rates, discharge destination, and health care costs [4]. The impact of an ICU admission is not only limited to these short-term outcomes, but similarly lowers patients' long-term health-status. Even 5 years after ICU admission, impaired physical function persists in ICU survivors and reduces quality of life [5]. To illustrate, only half of patients surviving severe critical illness are able to return to work within one year after ICU discharge [5]. Combining this with increased medical costs in the first years after ICU discharge, the burden ICU-AW places on the public health care system is serious. Therefore, measures aimed at preserving muscle mass during critical illness and improving recovery after ICU discharge are placed high on both scientific as well as patient representative's agenda [6, 7].

Retrospective observational cohort studies suggest that the administration of high protein nutrition is associated with improved survival and outcome [8]. The provision of dietary protein is a well-known anabolic stimulus able to promote and maintain muscle mass in both healthy and various clinical settings [9]. In this light, optimizing nutritional support and protein provision during ICU stay is a promising, easily applicable tool to preserve muscle mass and improve functional outcomes after ICU

discharge. The ability of optimized nutritional support to improve functional recovery has already been proven in other clinical settings. Early initiation of oral nutrition following major surgery is able to speed up the recovery of patients, and is firmly established within the ERAS protocol (Enhanced Recovery After Surgery) [10]. Providing optimal nutritional support may enhance recovery after critical illness analogous to post-surgical patients. However, prospective high level evidence for optimal protein provision is lacking in critically ill patients supported by mechanical ventilation and urgently warranted by the field. Investigating the effectiveness of increased protein provision on functional recovery after ICU admission is considered as the number 1 prioritized trial to be performed according to the recent research agenda from the European Society of Intensive Care Medicine (ESICM) [11].

6. RATIONALE

From a pathophysiological point of view, the development of ICU-AW is the result of a prolonged catabolic state, where protein breakdown exceeds the patient's capacity for protein synthesis. Skeletal muscle represents the body's largest reservoir of proteins. As such, during critical illness this muscle-bound protein reservoir is broken down and used to fuel gluconeogenesis and the synthesis of acute phase proteins, resulting in a net protein loss. Nutritional support and particularly protein provision is believed to be essential to restore loss of protein and avoid muscle weakness.

In the past decade, several large randomized controlled trials, which investigated the provision of more calories during ICU stay, failed to show a consistent effect on mortality or other hard clinical endpoints [12-14]. As a result, the 'optimal' nutritional support for ICU patients has become a matter of active debate. Based on the roles of proteins in the pathophysiology of muscle wasting and the apparent minimal effects of caloric optimization, interest has shifted from optimization of caloric intake towards optimization of protein intake, as a more promising tool to improve functional recovery [11].

Retrospective cohort analyses have shown that high dietary protein administration, initiated at an early stage of the ICU admission, is associated with decreased muscle loss and improved functional recovery [8]. In addition, small translational studies, using stable isotope tracers and nitrogen balances to study protein metabolism in ICU patients, demonstrate that protein feeding improves whole-body protein balance and stimulates (muscle) protein synthesis [15]. However, true robust evidence on the clinical and functional effectiveness of a high protein feeding strategy is lacking.

Despite the plausibility of the presumed positive physiological effects of protein-rich nutrition on clinical outcome and the data from observational studies supporting these effects, there is also data arguing against high protein provision in critical illness. It has been postulated that too early administration of high dose dietary protein, superimposed on the increased endogenous protein

supply from muscle breakdown, during the acute phase of critical illness may be deleterious [16]. It may lead to overfeeding, impaired renal function and inhibition of the beneficial process of autophagy, which clears the cells from damaged organelles.

Strong, clinical evidence of the effectiveness and safety of high enteral protein delivery is lacking and is urgently warranted by the field of intensive care nutrition [11]. Therefore, the aim of the present study is to investigate the effect of high versus standard protein provision on the functional recovery of critically ill patients. In accordance with the priorities set within the intensive care community, the PRECISe trial investigates whether enteral protein provision can improve functional outcome following ICU admission.

The focus on functional, patient-centered outcomes rather than traditional clinical endpoints like mortality is an important aspect and strength of the study. Previous nutritional intervention studies focusing primarily on improving mortality have repeatedly shown no effect. Therefore, it is nowadays increasingly recognized to move primary ICU trial endpoints away from classical outcomes, such as survival or length of stay, towards more functional outcomes, which are also patient-defined and relevant outcomes [17]. This also makes sense from a pathophysiological point of view. Optimizing nutrition aims to attenuate the rapid loss of muscle mass and the development of ICU-AW. Besides ICU-AW mainly affects patients' quality of life and functional outcomes, and thus, interventions aimed at reducing ICU-AW are unlikely to find an effect on mortality and more likely to affect functional outcomes and health-related quality of life (HRQL). For ICU trials in particular, HRQL, assessed by the EQ-5D questionnaire, has been suggested to be a relevant functional outcome and potential primary trial endpoint [18]. The PRECISe study will for the first time systematically investigate whether protein provision has an effect on a complete set of patient relevant functional outcomes. To understand the progression of these functional outcomes over a longer period of time, the items forming a core outcome set will be assessed longitudinally over a period of 6 months following ICU admission.

The PRECISe trial will be conducted in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

7. OBJECTIVES

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 [17]. For ICU trials in particular, HRQL, has been suggested as potential primary trial endpoint, since it reflects functional outcome at best [18]. To this end, the Core Outcome set (COS) from the Outcomes After Critical Illness and Surgery (OACIS) Group, registered in the COMET initiative database [17], will be used for primary and secondary outcomes measures. This COS consists of seven measurable items including HRQL, mental health, physical and muscle function (Figure 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.

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				

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

7.1 Primary Objective

The primary objective of the PRECISe study is to assess whether increased enteral protein provision during critical illness improves HRQL after ICU admission. This question has gained top priority in the recently published ICU research agenda [11]. To address this research question, the EuroQoL EQ-5D-5L will be used as primary endpoint measure. Since mortality can be taken into account within the EQ-

5D-5L, no data imputation due to mortality will be required, which makes the EQ-5D-5L particularly applicable in this vulnerable population where mortality is expected to be high.

The EQ-5D is a standardized measure of health status, developed by the EuroQoL Group, in order to provide a simple, generic measure of health for clinical and economic appraisal [19]. Used already in several multicenter clinical trials, the EuroQol has become widely recognized as a valid and well-noted instrument for measuring health status by patient- and health-care decision makers [18, 20, 21].

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 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 [22, 23]. 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).

7.2 Secondary Objectives

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 will be incorporated in the PRECISe Trial. [5]. Aside from the hypothesized general improvement of health-related quality of life due to provision of higher enteral protein (and the attenuation of catabolic processes), it can be hypothesized that the driving factor behind this improvement is preservation of muscle strength during critical illness [24]. Measures to assess physical and muscle function will be 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) [3, 5].

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 [8].

Summarized, the secondary objectives of the PRECISe Trial are to investigate whether increased enteral protein provision ICU admission results 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

7.3 Primary endpoint

Overall between group-differences in health related quality of life (EQ-5D-5L summary index) at 30 days, 90 days, and 180 days after index ICU admission.

7.4 Secondary endpoints

- Overall Survival
- 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), EQ-VAS of the EQ-5D-5L and IES-R Impact of Event Scale, all 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 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.

7.5 Tertiary endpoints

The tertiary endpoints will be further described and detailed in the full Statistical Analysis Plan that will be published before the end of the recruiting period of the PRECISe trial. The tertiary endpoints include:

- 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 higher than 2 times baseline level) during index ICU stay
- Days on renal replacement therapy during index ICU stay
- 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
- The difference in frailty at 30 days, 90 days, and 180 days, as assessed by the Rockwood Clinical Frailty Scale
- The number of days on prokinetics during index ICU stay
- 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 distention, gastric paresis, bleeding/ulcer) during index ICU stay

To be able to correct for baseline risk factors, body weight, height, lean body mass, sex, age, lactate concentration, pre-admission comorbidity (Charlson comorbidity index), chronic use of glucocorticoids, severity of illness (APACHE II scores), Nutrition Risk Score (NRS), and pre-admission frailty (Rockwood Clinical Frailty Scale) will be recorded.

In addition, other post-randomization variables affecting the intervention, such as the amount of proteins and calories delivered, including non-nutritional calories (i.e. medication/infusion-related), and time-to-delivery of the nutrition goal, will be recorded in order to perform ancillary, post-hoc analyses.

7.6 Health economic endpoints

If health-economic analyses are performed, the data could be retrieved from the PRECISe database or administrative databases.

The following list of health economic endpoints could be analysed by using the data collected during the PRECISe study:

- Duration of mechanical ventilation during index ICU stay
- Days on renal replacement therapy during index ICU stay
- Length of index ICU stay
- Length of index hospitalisation
- Destination after index ICU and index hospital discharge
- Length of stay at a rehabilitation facility after index hospitalisation
- Time to return to work
- Days on antibiotics during index ICU stay

Post-hoc analyses and health economic analyses will be performed after the analysis of the defined primary, secondary, and tertiary endpoints. Accordingly, these analyses will not be part of the Clinical Study Report which will be finalized within approximately 6 months after the end of the study.

8. STUDY DESIGN

The PRECISe study will be a pragmatic international, multi-center randomized controlled trial (RCT) to investigate the effect of enteral protein provision on functional recovery following ICU admission. The design of the study, in particular the selection of patients, the intervention, and outcome measures has taken into consideration 1) the recommendations by our patient panel (see also section 'patient and public involvement') and 2) the recommendations of the intensive care medicine research agenda on nutrition and metabolism. Based on recent literature and the ICU research agenda by the international experts in the field, the subject of the PRECISe study is rated as the study with the highest priority for the coming years [11].

The PRECISe study has a parallel-group design with a 1:1 allocation ratio. The study will compare the effectiveness of two treatment modalities currently used in clinical care, without robust evidence supporting one over the other (true equipoise). Furthermore, the RCT is triple blinded (i.e. patient, physician, and monitoring committee-blinded) and in accordance with CONSORT statement criteria [25].

Prior to the intervention, patients will be randomized in a 1:1 ratio, using permuted block randomization with varying blocks of 4 or 6 patients per center, into one of the two intervention parallel groups. One group will receive enteral nutrition with a high protein content of 8g/100 kcal (expected intake 1,6 - 2,0 g/kg/day), and the other group will receive enteral nutrition with a standard protein content of 5g/100 kcal (expected intake 0,8 - 1,25 g/kg/day). Only the protein content will differ between the two groups. Total energy content and volume of the enteral nutrition across both groups will be the same (i.e. enteral nutrition is both isocaloric and isovolumetric). The study nutrition will be continued throughout the entire ICU stay as long as enteral nutrition is required with a maximum of 90 days. For the primary, secondary, and tertiary outcomes a follow-up period of 6 months following ICU admission will take place, with landmark time points at 30, 90, and 180 days. The objective is to show superiority of increased enteral protein delivery during ICU stay with regards to improving health-related quality of life and other items of the extended core outcome set.

9. STUDY SETTING

The study population will consist of adult, mechanically ventilated patients who are unplanned admitted to the ICU and have a clear indication for enteral nutrition (i.e. expected stay of at least 3 days). The PRECISe trial aims to randomize 824 patients in approximately 9 hospitals across Belgium (hospitals in Flanders and Wallonia) and the Netherlands.

10. ELIGIBILITY CRITERIA

Adult patients with an unplanned admission to the ICU and an expected stay on ventilator support of at least 3 days will be screened for enrolment using the in- and exclusion criteria as specified below. The eligibility criteria have been chosen to recruit patients who are truly 'critically ill' and in a catabolic state. This patient group represents a group of patients who have a clear indication for enteral nutrition according to the current standards of care and is hypothesized to benefit from a potential effect of high enteral protein provision.

10.1 Inclusion criteria

- Adult (≥ 18 years-old) patient admitted to ICU
- Unplanned admission to the ICU
- Invasive, mechanical ventilation initiated <24 hours following ICU admission
- Expected ICU stay on mechanical ventilation of ≥ 3 days

10.2 Exclusion criteria

- Contra-indication for enteral nutrition at the discretion of the treating physician
- Moribund or withholding of treatment
- Kidney failure AND a ”no dialysis”-code on admission
- Hepatic encephalopathy (West Haven criteria 3-4)
- Body-mass index <18 kg/m^2

Based on data from the participating sites and from studies with similar selection criteria, the defined patient group has a median ICU stay of 10 days, which is sufficiently long to expect a beneficial effect of the study intervention on health-related quality of life [26].

These selection criteria also reflect the pragmatic trial design, as they include the majority of patients who receives enteral nutrition in our intensive care units. Moreover, it is avoided to include patients in whom ICU stay is expected to be short. Hence, less critically ill patients, who are unlikely to benefit from any nutritional intervention, will not be included. By avoiding strict eligibility criteria, the study results will be generalizable to a general ICU population.

11. TRIAL PROCEDURES

11.1 Trial flow chart

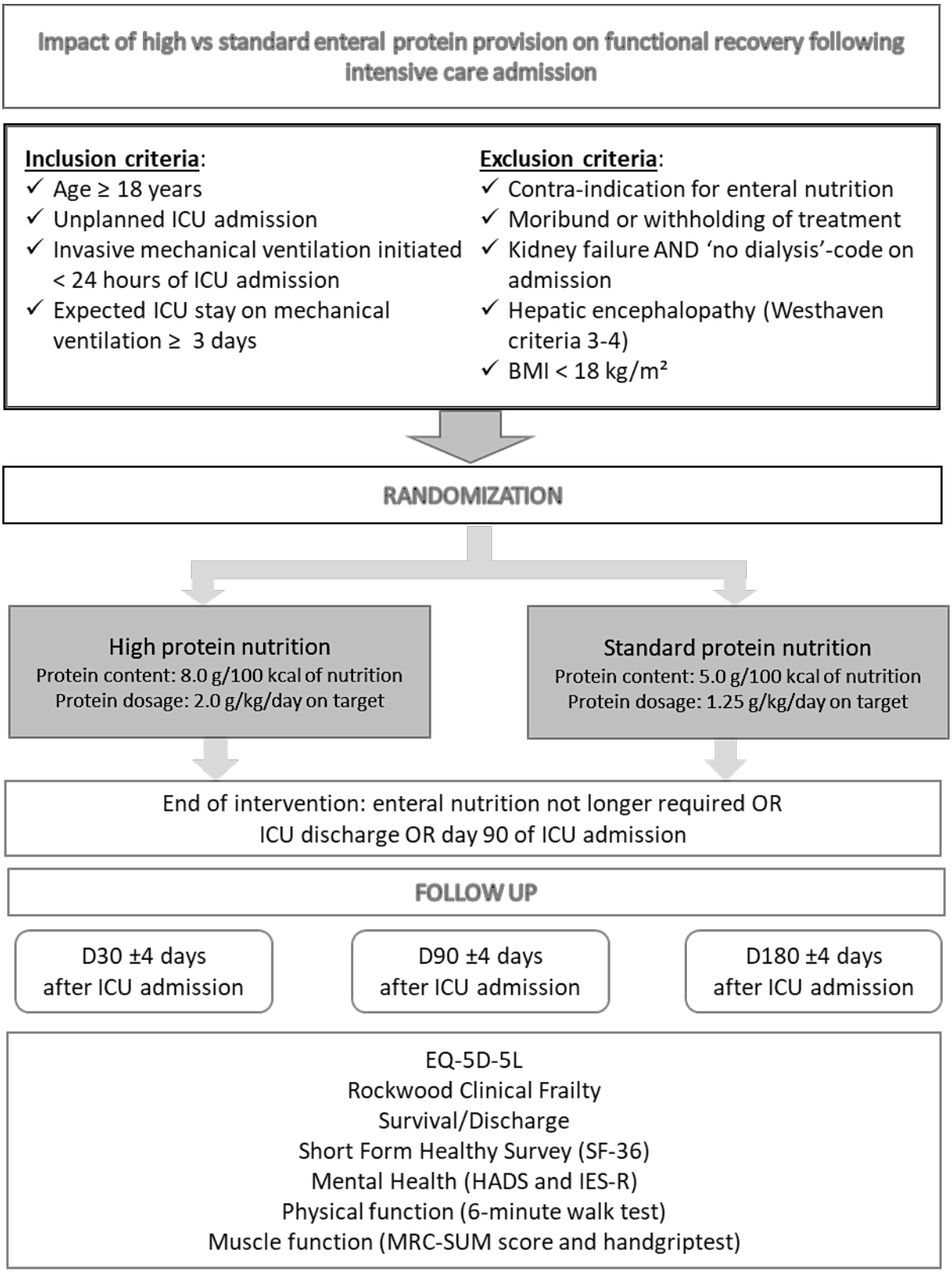

Figure 2. Trial flow chart.

11.2 Consent

For this study, inclusion using 'deferred consent' is applicable according to the CCMO guideline regarding deferred consent, as the study involves the comparison of two treatment strategies during a time of a sudden, severe, and life-threatening condition. We will elaborate briefly on why the conditions of deferred consent are met.

11.2.1 *Deferred consent*

Patients are eligible for participation if intubated within 24 hours of ICU admission and if enteral nutrition is initiated within 24 hours after endotracheal intubation. As a result, enteral nutrition will be started within 48 hours of ICU admission, which is in agreement with ESPEN guidelines [27]. Therefore, patient enrolment and randomization into one of the two nutritional study feeds has to be performed within the first 48 hours of ICU admission. Because the study will be conducted in mechanically ventilated, critically ill patients, who suddenly find themselves in an emergency situation due to a life-threatening condition, subjects will be unable to give informed consent themselves at time of screening. Due to the acute, serious, and life-threatening situation, the legal presentative will not be immediately approachable, even if they were to be present at the moment. Furthermore, because the study population involves unplanned admissions and because the study relates directly to the subject's medical condition, it is not possible to inform patients or their legal representatives about the study and obtain informed consent prior to arrival in the ICU or prior to developing the critical illness. Finally, the study involves a therapeutic study, which can provide a clinically relevant effect.

As such, if a patient fulfills the in- and exclusion criteria for the study, the subject can be included in the study using deferred consent, provided that:

1. The patient has not previously objected to participation in medical research
2. The patient's legal representative will be informed and asked for consent as soon as this is possible

11.2.2 *Consent after inclusion from legal representative*

Once a subject is included in the study using deferred consent, but still unable to provide consent, the legal representative will have to be informed and asked for consent as soon as this is possible, taking into account the time family members may need to orientate and get used to the situation in which the subject concerned finds him- or herself. The legal representative will have a reflection period of 48 hours, before having to decide whether he/she gives consent.

If a legal representative is not present, or if a legal representative is present but unable to be informed or provide informed consent, the study will be continued until informed consent by a legal representative is possible.
If the patient dies before consent from the legal representative is obtained, the data collected can be used without additional consent, but the legal representative will be informed about the study participation.
If the legal representative is informed about the study but refuses consent, the data collection will be discontinued and the legal representative will be informed about the right to resist the use of already collected data. If the legal representative provides consent, the study can be continued.

11.2.3 *Consent after inclusion from patient regaining capacity*

If the patient regains capacity to provide informed consent during their stay in ICU, patients will be informed about the study by a member of the local study team and asked to provide written informed consent. The patient will have a reflection period of 48 hours, before having to decide whether he/she gives consent. If the patient regains capacity to provide informed consent after ICU discharge (for instance because of a post-sedative state or delirium), patients will be contacted by a member of the local study team (in person or by phone) for the upcoming follow-up moment (either 30, 90, or 180 days) and will then be asked to provide written informed consent. The patient information letter (including the informed consent document) will be presented to the patient. The patient will have the opportunity to ask any questions and will have a reflection period of 48 hours, before having to decide whether he/she gives consent. If the patient refuses consent, participation in the study will be terminated and the patient will be informed about the right to resist the use of already collected data.
If the patient does not regain capacity to provide informed consent (i.e. because of death, severe neurological deficit, or other cause), or if the patient regains capacity for informed consent after ICU discharge but cannot be contacted anymore, previously obtained consent by the legal representative will be deemed sufficient to use the collected data during the study.

11.2.4 *Regulation statement on informed consent*

The Principal Investigator (PI) retains overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorized, trained, and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki. If delegation

of consent is acceptable then details should be provided and recorded in the local Trial Master File (TMF).

Informed consent can be obtained from the patient or a legal representative as described in the previous paragraph. Acting as legal representative for the patient can be (in descending order) 1) A legally appointed legal representative, 2) a by the patient written authorized legal representative, 3) a husband/wife, 4) a registered partner or other life companion, 5) parents, 6) reasonably reachable children of the patient that are of age or finally 7) brothers or sisters that are of age and can reasonably be reached.

The process of obtaining informed consent should be documented in the patient source documents.

11.2.5 *Refusal or withdrawal of consent*

The right of a participant or legal representative to refuse participation without giving reasons must be respected.

The participant or legal representative must remain free to withdraw at any time from the trial without giving reasons and without prejudging his/her further treatment and will be provided with a contact point where he/she may obtain further information about the trial. When a participant is required to re-consent or new information is required to be provided to a participant it is the responsibility of the PI to ensure this is done in a timely manner.

The PI takes responsibility for ensuring that all vulnerable patients are protected and participate voluntarily in an environment free from coercion or undue influence.

11.3 Recruitment

Patients can be enrolled after admission to the ICU if they fulfill all of the inclusion criteria and none of the exclusion criteria. Patients will be recruited over an expected period of approximately 24 months.

11.3.1 *Patient identification*

Patients eligible for study participation will be identified by the medical team, who will have first contact with potential study subjects. Only a member of the patient's existing clinical care team should have access to patient's records before inclusion of the patient and check whether they meet the eligibility criteria.

11.3.2 *Screening*

All unplanned admissions to the ICU, where invasive mechanical ventilation is initiated within 24 hours of admission will be screened for study participation by the treating physicians. The BMI parameters weight and length are necessary to assess eligibility as they are part of the exclusion criteria. During the trial, all ICU patients screened for participation (including the reasons for excluding patients from participation) will be logged on a screening log.

11.3.3 *Patient recruitment*

If the patient meets the eligibility criteria, the patient can be included into the study using a 'deferred consent' procedure as described above in the paragraph 'Consent'.

It is highly recommended to inform and discuss eligible patients with the local study team before inclusion. However, inclusions can happen at any time of the day or week and a study team member might not always be present. Therefore, the medical team is authorized to include an eligible patient in the study using deferred consent.

Following the conditions of the deferred consent procedure as described previously, if the patient is unable to provide consent, the patients legal representative should be informed as soon as this is possible under the conditions specified above. A member of the medical team will always be the first to approach the legal representative to ask them if they agree to be informed about the study.

It is preferred that a member of the local study team then informs the representative about the study and completes the informed consent procedure. However, due to the nature of the study population and continuing care 24/7, it is possible that a member of the study team cannot be present when the legal representative is able to provide consent. Only if waiting for a member of the local study team will cause a long or unreasonable delay in informing the legal representative, the treating physician is allowed to complete the informed consent procedure. The legal representative will have a reflection period of 48 hours, before having to decide whether he/she gives consent.

11.4 Randomization

A computer algorithm will be used to generate the random allocation sequence. Patients will be randomized in a 1:1 ratio, using permuted block randomization with varying blocks of 4-6 patients per center, into one of the two intervention parallel groups. Randomization will be done centrally by an interactive web response system (IWRS). Due to the combination of central randomization and varying blocks, sites will not be able to guess the treatment assignment based on the block size. Randomization

of patients will be stratified by center to account for systematic differences in routine practice between the participating centers.

Once the patient is found eligible for the trial, the patient can be randomized via the IWRS by the PI or qualified person to whom he/she has delegated this study task. This will generate a unique study randomization number and the feeding label (A, B, C, or D) to which the patient is randomized. The generated feeding label will correspond to either a high or standard enteral formula depending on the patient allocation. Thus, while randomization occurs between two intervention groups (high or standard protein), each intervention group has two representing feeding labels, to prevent complete unblinding of the study in the case an unblinding occurs (e.g. A and C might correspond to standard protein and B and D to high protein).

An accountability log with the number of bottles provided to the patient and the corresponding feeding label will be kept by the PI or delegated person to ensure that allocation of nutrition was successfully performed.

11.5 Blinding

This is a triple-blinded study; meaning that patients and physicians are blinded for the assigned intervention but also that outcome assessment will be performed without knowledge of subject group allocation.

Once a patient is assigned to a study group (standard or high protein nutrition), he/she will remain in that arm and all efforts will be made to provide the optimal nutrition specified for that treatment assignment. In the unforeseen circumstance that this is clinically not feasible, the patient will remain in the assigned treatment arm for statistical analysis based on the intention-to-treat principle, as it represents a normal medical situation of success and failure of delivering the planned medical therapy.

11.5.1 *Study nutrition blinding*

Each feeding bottle contains either high or standard protein content feeds. Except for the feeding label (A, B, C, D), the high and standard protein feeding bottles are completely similar in color, weight, packaging, and odor. This ensures that patients and care providers are blinded for the assigned intervention. The key for the latter coding will not be disclosed to those assessing outcomes and performing data analyses, leading to adequate blinding of them.

11.6 Unblinding

Blinding of the study nutrition will be maintained from the time of randomization until database lock. For assessment of the primary outcome, the groups will remain blinded for the trial statistician. Although we do not foresee serious adverse events (SAE) related to the study nutrition, the study code should **only** be broken for valid medical or safety reasons, e.g. in the case of a severe adverse event where it is necessary for the investigator or treating health care professional to know which treatment the patient is receiving before the participant can be treated. It is not mandatory but strongly encouraged to contact the chief investigator before unblinding any patient's treatment assignment. Patients and members of the research team should remain blinded.

The following rules apply for unblinding;

- Rapid unblinding of a patient can be performed by the treating physician. Detailed information concerning the unblinding procedures is provided in the Manual of Operations.
- On receipt of the treatment allocation details, the PI or treating health care professional will continue to deal with the participant's medical emergency as appropriate.
- The PI/Investigation team documents the breaking of the code and the reasons for doing so on the medical notes and in the eCRF. It will also be documented at the end of the trial in any final study report and/or statistical report.

Unblinded data are to be kept strictly confidential until the time of unblinding of the trial and will not be accessible by anyone else involved in the trial with the following exceptions: (1) the Product Manager of the company responsible for the labelling and packaging of the nutritional product; (2) the Interactive Response Technologies system programmers who work on the randomization and drug management system; and (3) the data manager who prepares reports required for regulatory reporting. These individuals will not be involved in the day-to-day running of the study.

11.7 Visit schedule

Following enrollment into the study after admission to the ICU, participation in the study will last until the final follow-up visit at 180 (±4) days after ICU admission.

The visit schedule for this study can be divided into 3 phases:

1. **Screening phase**: starting from identifying a study subject until the first nutrition will be given.
2. **Treatment phase**: starting from the first nutrition until ICU discharge or a maximum of 90 days of ICU admission.

3. **Follow-up phase**: starting when the treatment phase ends or at 30 days after ICU admission (whichever comes first) until 180 (±4) days after ICU admission.

Note: The treatment phase can overlap with the follow-up phase in case the patient still receives study nutrition 30 days after ICU admission. In that case, the assessments applicable to both phases need to be performed.

11.7.1 *Screening phase assessments*

- Obtain written informed consent (according to deferred consent procedure)
- Check inclusion and exclusion criteria
- Collect height and body weight
- Perform randomization via IWRS (*see section 11.4 Randomization*)
- Collect demographics (i.e. age, sex)
- Collect medical history (i.e. comorbidities including the Charlson Comorbidity index)
- Collect admission information (i.e. reason of admission and admission diagnosis)
- Perform the Glasgow Coma Scale
- Collect vital signs to calculate ICU scores
- Collect fluid balance
- Collect results from standard of care local laboratory assessment:

Haematocrit	CRP	Potassium	ALT	pH	PaO2/FiO2 ratio
White blood cells	Urea	Phosphate	AST	bicarbonate	Haemoglobin
Platelets	Creatinine	Albumin	GGT	Magnesium	
Sodium	Bilirubin	ALP	Lactate	glucose	

- Collect Nutritional Risk Score (NRS)
- Have the pre-hospital functional status of the subject assessed by the (legal) representative (proxy) by asking to complete the EQ5D-5L questionnaire (= primary outcome measure)
- Complete the Rockwood Clinical Frailty Scale in cooperation with the (legal) representative (proxy) (if necessary)
- Collect concomitant medication (antibiotics, prokinetics, noradrenaline, adrenaline, dobutamine, dopamine and chronic use of glucocorticoids)

Note: In the PRECISe study, *day 1* refers to the day the patient is admitted to the ICU. Every consecutive calendar day needs to be referred to as *day 2, day 3*, etc. The day the patient receives study nutrition

the first time refers *to treatment day 1*. Every consecutive calendar day need to be referred to as *treatment day 2, treatment day 3,* etc.

11.7.2 *Treatment phase assessments*

First day of nutrition (Treatment Day 1)

- Plan the nutritional protocol for the patient (*see section 12.3 Feeding protocol).*
- Initiate the enteral study feed at the calculated rate.

Daily until ICU discharge or until 90 Days of admission at ICU

- Collect the volume of study nutrition received in the past 24 hours via enteral study feeding
- Adjust the rate of enteral nutrition according to the nutrition guidance protocol *(see section 12.3 Feeding protocol)*
- Collect the mobilization treatment: passive/active in bed, passive/active on bed bicycle, out of bed
- Collect ventilation status
- Collect concomitant intravenous medication: glucocorticoids, antibiotics, prokinetics, muscle relaxants, and medication/infusions with substantial non-nutritional calories (e.g. propofol, insulin, etc.).
- Collect and assess events of special interest including all-cause mortality, life-threatening event(s) caused by the nutrition, hepatic dysfunction (i.e. cholestasis and liver dysfunction), index ICU acquired infections, ventilator acquired pneumonia (VAP), Extracorporeal membrane oxygenation (ECMO), renal replacement therapy, refeeding hypophosphatemia, and gastrointestinal events (i.e. vomiting, ischaemia, diarrhoea, abdominal distension, gastric paresis, bleeding/ulcer)

Only on treatment days 1, 3, 5, 7, 9, 11 and 13

- Collect results from standard of care local laboratory assessment:

Hematocrit	CRP	Potassium	Albumin	ALT
White blood cells	Urea	Phosphate	PaO2/FiO2 ratio	ALP
Platelets	Creatinine	Glucose	Bilirubin	GGT
Magnesium	Haemoglobin	pH	AST	

- Collect vital signs to calculate SOFA score
- Collect fluid balance
- Perform the Glasgow Coma Scale

- Collect additional concomitant medication (noradrenaline, adrenaline, dobutamine, and dopamine).

The study nutrition will be continued until ICU discharge as long as enteral nutrition is required or 90 days of ICU admission. Due to variations in length of ICU stay, the duration of this visit schedule per patient is estimated to vary between 3 and 90 days.

11.7.3 *Discharge*

The day the patient is discharged from the ICU (or transferred to the ICU of another hospital) and the day the patient is discharged from the hospital (or transferred to another hospital) will need to be collected. In addition, the location where the patient is discharged to (home, rehabilitation home, other hospital ward, nursing home, etc.) will also be collected.

11.7.4 *ICU re-admissions*

If a patient is re-admitted to the ICU within 48 hours of discharge from the index ICU, this will be regarded as one ICU stay. Thereafter, any re-admission to the ICU within the same index hospitalization will be regarded as a new ICU stay and only these ICU readmissions will need to be collected

11.7.5 *Follow-up phase assessments*

Follow-up visits will take place at 30 days, 90 days, and 180 days (± 4 days) after the index ICU admission.

Irrespective of the patient's location (ICU, hospital ward, nursing home, home, etc.), the following questionnaires will need to be completed by the patient:

- EQ-5D-5L (primary outcome measure, if patient isn't capable of completing the questionnaire the (legal) representative of the patient can complete this questionnaire)
- HADS
- IES-R
- SF-36

During the follow-up visits, the following information will need to be collected and the assessments will need to be performed:

- Handgrip strength (using a dynamometer)
- 6-minute walk test
- MRC-SUM score

- Destination after hospital discharge (if applicable)
- Length of stay at a rehabilitation facility (if applicable)
- Work activity re-started (if applicable)
- Rockwood Clinical Frailty Scale
- Event of special interest: all-cause mortality

11.8 Table of trial procedures

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[j]				
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^+, PO_4, magnesium, albumin, bilirubin, ALT, AST, GGT, ALP, pH, bicarbonate, lactate, glucose, PaO2/FiO2 ratio

[h] Haemoglobin, haematocrit, WBC, platelets, CRP, urea, creatinine, K^+, PO_4, 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 (i.e. cholestasis and liver dysfunction), 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

11.9 Withdrawal criteria

All subjects will be encouraged to remain on treatment and under observation for the full duration of the study. However, at any time during the study and without giving reasons, subjects may withdraw from the study at their own request or at the request of their (legal) representative. The subject will not suffer any disadvantage as a result.

It is important to note that discontinuation of study treatment is not equivalent to withdrawal of informed consent. Whenever subjects indicate they do not want to "continue", investigators must determine whether this refers to discontinuation of study treatment (the most common expected scenario), unwillingness to attend the follow-up visit, unwillingness to have telephone contact, unwillingness to have any contact with study personnel, or unwillingness to allow contact with a third party (e.g. family member, doctor). Every effort must be made to continue to follow the subject until the end of the study.

In all cases, the reason for discontinuation (including "at the subject's request") must be recorded in the eCRF and in the subject's medical records. Data gathered before withdrawal of consent will not be deleted.

No subject replacements are permitted in the study.

11.10 Administrative aspects

11.10.1 *Amendments*

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

11.10.2 *Annual progress report*

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

11.10.3 *Temporary halt and (prematurely) end of study report*

The sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit. The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12. TRIAL INTERVENTION/NUTRITION

12.1 Name and description of intervention

The intervention is a high protein enteral feeding formula (8g protein/100 kcal). The comparator is a standard protein enteral feeding formula (5g protein/100 kcal). Both formulae are commercially available from Nutricia Advanced Medical Nutrition (Nutrison Protein Intense (high protein) and Nutrison Protein Plus (standard protein)) but will be supplied in blinded identical packages by Nutricia Advanced Medical Nutrition (Utrecht, the Netherlands). Both feeds are isocaloric and isovolemic and identical in terms of color, odor and consistency, enabling a triple blind design. In addition, the side effect profile (gastrointestinal tolerance) for both products is identical [28].

Since dosing of tube feeding is based upon calories, the rate of administration (ml/h) will be identical for both products. When the final energy target of 25 kcal/kg/day is met, patients in the interventional arm will have received 2.0g protein/kg/day versus 1.25g protein/kg/day in the comparator arm. Using this pragmatic approach, the difference in protein delivery between both groups is based on the composition rather than on the dosing of the feeds, independent of whether predefined nutritional targets are reached.

12.2 Rationale of the intervention

Even when protein targets are not fully met, a clinically relevant effect of higher protein administration is to be expected. The recent TARGET-trial used a similar approach to separate groups in calorie provision using feeds with two different caloric compositions (1 vs 1.5 kcal/ml). This study was successful in separating the groups based upon the calories received [29].

The protein difference between the comparator and intervention is 60% and will amount to up to 0.8 g/kg/day when nutritional targets are fully met. The cumulative difference in proteins received will gradually increase over time for the duration of the intervention (Figure 3). For example, based on an average patient weighing 80 kg, the absolute difference in provision is 64 grams of protein per day, which can accumulate up to over 500 grams over the expected median admission duration of 10 days.

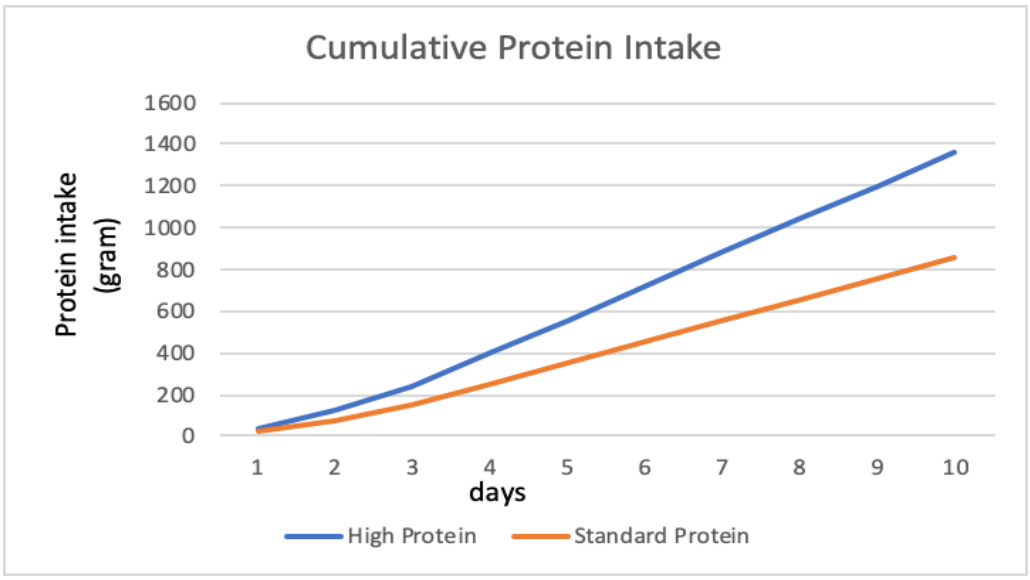

Figure 3. Projection of cumulative protein intake during the first 10 days of ICU stay for a patient with a weight of 80kg.

It is expected that this difference in cumulative protein intake is sufficient to show a potential, clinically relevant and statistically detectable effect based on currently available literature. For instance, the difference between the intervention and comparator is larger than those in the various retrospective studies (0,8 vs 1,2 g/kg/day [8]) and prospective studies (0,75 vs 1,2 g/kg/day [30]) that found improved outcomes in the higher protein groups. In addition, retrospective analyses describe a directly proportional, relationship between higher protein provision and better ICU outcome. The linear relation between protein provision and outcome is in contrast with the "U-shaped" relation between energy provision and ICU outcome that clearly suggests an optimum of calorie provision and describes the risk of both caloric "underfeeding" and "overfeeding"[31].

12.3 Feeding protocol

12.3.1 *Caloric target and initiation of enteral nutrition*

Once the patient is eligible for the trial, subjects will be randomized to either the high or standard protein arm.

The feeding protocol will be in line with recently updated guidelines of the European Society for Enteral and Parenteral Nutrition [27], which are the leading guidelines for enteral nutrition in critical illness in Western Europe. Key points of these guidelines are initiation of enteral nutrition within 48 hours after ICU admission and restriction of energy provision to <80% of the estimated energy expenditure during the first 3 days of ICU admission, followed by a full coverage of energy expenditure from day 4

onwards. According to these guidelines, energy expenditure can be measured by indirect calorimetry or estimated by a simple weight-based equation (20-25 kcal/kg/day). Since indirect calorimetry is not fully implemented in all ICUs and is not available in all participating centers, a simple weight-based equation (25 kcal/kg/day) will be used to estimate energy expenditure. Nutrition dosing will be based on pre-admission weight since fluid accumulation in the acute phase of critical illness frequently leads to a rapid increase of body weight. To avoid overfeeding in patients with extreme overweight, the BMI cap for feeding targets will be set at a BMI of 27 kg/m^2 . This means that for patients with a BMI > 27 kg/m^2, ideal body weight (with recalculation of weight with given height and BMI set at 27 kg/m^2) will be used to calculate caloric targets. This is based on the recommendations in the current ESPEN guidelines on clinical nutrition in the Intensive Care [27].

Enteral nutrition will be started within 24 hours after endotracheal intubation at a rate of 6,25 kcal/kg/day which comes down to a pump rate of 0,21 ml/kg/h (figure 4). The rate will incrementally be increased daily with 25% of the eventual target until 100% of the estimated energy expenditure is covered on day 4. For all patients and treatment days, standard methods of calculation will be provided to calculate the correct weight (in case of overweight) as well as the correct nutritional targets and accompanied pump rates based on the imputed body weight.

The study nutrition will be continued throughout the entire ICU stay as long as enteral nutrition is required or with a maximum of 90 days. During the first 7 days after ICU admission it is not allowed to provide parenteral nutrition to the patient (cfr. Section 12.3.2, section 4: parenteral nutrition). If after 7 days, a patient's daily nutritional targets cannot be met via enteral nutrition (due to severe gastro-intestinal dysfunction), it is permitted to use (supplemental) parenteral nutrition. However, enteral nutrition remains the preferred mode of nutrition and all efforts should be made to switch to full enteral nutrition and wean from parenteral nutrition as soon as possible. Whenever the study enteral nutrition is stopped (e.g. diagnostic intervention, therapeutic intervention, change in mode of nutrition) and re-started, the patient should receive study enteral nutrition under the condition that the re-start of enteral feeding falls within the 90 days period after the index ICU admission.

	High protein		**Standard protein**	
	Per 100 kcal	*% of energy*	*Per 100 kcal*	*% of energy*
Protein	8.0 g	32 %	5.0 g	20 %

Carbohydrate	8.2 g	33 %	11.4 g	45 %
Fat	3.9 g	35%	3.9 g	35 %
Volume	80 ml		80 ml	

Figure 4. Nutrition composition (*adapted from van Zanten et al. Crit Care 2018 [28]*)

12.3.2 *Nutritional adequacy*

In clinical practice there is often a mismatch between the amount of calories that have been prescribed and the amount of calories actually delivered to critically ill patients. The degree to which set nutritional targets are actually reached is referred to as nutritional adequacy. There are three important threats to nutritional adequacy.

1. Inattention to adjust pump rates

It has been shown that a dedicated dietician or nurse, or a nurse-driven protocol can virtually eliminate nutritional inadequacy due to inattention. At all participating sites, dedicated study nurses will supervise protocol adherence.

2. Feeding interruptions due to diagnostic or therapeutic interventions

Enteral nutrition is often interrupted in critically ill patients during surgical procedures or during transport to e.g. the radiology department. Several strategies can be applied to "catch up" for the lag in nutritional adequacy. The most intensive is to adjust pump rate after every feeding interruption, with the goal to end each 24 hour period with a closed balance. This can result in multiple adjustments of pump rate per day, which is laborious and can lead to very high pump rates during short periods of time. In the PRECISe study, a more gradual approach to correct for feeding interruptions will be applied by calculating the caloric deficit once per 24 hours and by adjusting nutritional targets for this deficit for the following 24 hours. The daily energy target, including the deficit to be catched-up is calculated based on the total volume of nutrition administered in the preceding 24 hours. The desired pump rate will be calculated and adjusted only once per 24 hours.

3. Gastric Residues

Historically, gastric residual volumes are determined in critically ill patients every 6-8 hours even in the absence of signs of gastrointestinal intolerance. This practice is accompanied by protocols that prohibit

increasing or dictate decreasing the administration rate of enteral nutrition when certain thresholds of gastric residual volumes are exceeded. Some of these protocols also describe whether gastric aspirates should be reinfused or discarded based upon certain volume thresholds. This practice often leads to long periods with low pump rates and considerable wasting of aspired nutrition that was already administered. There is increasing evidence that measuring gastric residual volumes does not decrease complications such as vomiting, gastrointestinal intolerance or aspiration pneumonia whereas it significantly impairs nutritional adequacy. Omitting the assessment of gastric residues nowadays is proven to be safe and is increasingly applied in clinical practice. To optimize nutritional adequacy we recommend not to perform routine measurements of gastric residual volume in this study.

4. Parenteral Nutrition

During the first 7 days after ICU admission it is not allowed to provide parenteral nutrition to the patient. This restriction has been based on the following:

A. The current recommendations of the European Society for Clinical Nutrition and Metabolism (2019):
   - Recommendation 5:
     If oral intake is not possible, early enteral nutrition (within 48h) shall be performed/initiated in critically ill adult patients rather than early parenteral nutrition.
   - Recommendation 6:
     In case of contraindications to oral and enteral nutrition, parenteral nutrition should be implemented within three to seven days.

B. The use of parenteral nutrition within 7 days of ICU admission could have a masking effect on the enteral nutrition (i.e. study intervention) the patient is receiving.

If parenteral nutrition is provided to the patient (after day 7 after ICU admission), no catch-up feeding is required and the target study nutrition feeding will be 100% of the nutrition target.

12.3.3 *Nutritional guidance protocol*

First day of study feeding (Treatment Day 1)

- Start enteral nutrition within 24 hours after endotracheal intubation and from the moment the patient is hemodynamic and respiratory stable.
- Set pump rate at 0.21 ml/kg/h (= daily targeted volume: 5 ml/kg)

Second day of study feeding (Treatment Day 2)

- Register administered volume of nutrition given to the patient between start of enteral nutrition until the morning of treatment day 2 (approximately between 6:00 a.m. and 10:00 a.m.)
- Set pump rate at 0.42 ml/kg/h (= daily targeted volume: 10 ml/kg)

Third day of study feeding (Treatment Day 3)

- Register administered volume of nutrition given to the patient in the past 24 hours
- Set pump rate at 0.63 ml/kg/h (= daily targeted volume: 15 ml/kg)

Fourth day of study feeding (Treatment Day 4)

- Register administered volume of nutrition given to the patient in the past 24 hours
- Set pump rate at 0.83 ml/kg/h) (= daily targeted volume: 20 ml/kg)

Fifth day of study feeding (Treatment Day 5) **and further** (Treatment Day X)

- Register administered volume of nutrition given to the patient in the past 24 hours
- Calculate deficit (= targeted volume – administered volume)
- Calculate daily targeted volume (=20 ml/kg + deficit)
- Calculate pump rate (daily targeted volume/24h) and adjust pump rate accordingly

In case the study enteral nutrition has been stopped during the index ICU admission (e.g. due to a diagnostic or therapeutic intervention or due to changes in mode of nutrition) and is restarted, the applied pump rate at the moment of restart can be determined at the discretion of the treating physician.

12.3.4 *Refeeding hypophosphatemia*

Refeeding syndrome represents a potentially life-threatening shift in fluids and electrolytes in malnourished patients receiving artificial nutrition. Hypophosphatemia typically has 2 peaks during ICU stay: during the first 12 hours and on day 3-5 after starting nutritional support [32]. In line with the recommendations from the current ESPEN guidelines on clinical nutrition in the ICU, several measures will be taken to minimize risk of refeeding [27]. This includes early caloric restriction (i.e. gradual build-up of enteral nutrition over the first 4 days), which reduces the risk of refeeding syndrome [32]. Furthermore, following initiation of enteral nutrition, repeated measurements of

phosphate, potassium and magnesium will be performed on at least at treatment day 1, 3, 5, 7, 9, 11, and 13 to monitor occurrence of refeeding hypophosphatemia.

If refeeding hypophosphatemia does occur (phosphate levels below <0.65 mmol/l, a drop >0.16 mmol/L from previous level in ICU and no other explanation for hypophosphatemia), it is recommended that electrolytes are measured twice daily and supplementation of phosphate and electrolyte levels should be performed accordingly [27, 32]. The occurrence of refeeding hypophosphatemia will be recorded into the eCRF as an event of special interest.

12.4 Nutrition storage and supply

All study feeds will be produced and packaged in a blinded form by Nutricia Advanced Medical Nutrition (Utrecht, the Netherlands). The study products will be delivered to the individual participating sites in several 'batches', where they will be delivered to the local hospital kitchen or pharmacy depending on local agreements. Study products will be handled and stored similar to other enteral nutrition solution in accordance with local regulations. All products can be stored at room temperature.

12.5 Non-nutritional care

Routine clinical care and treatment for all subjects will continue undisturbed during study participation. As enteral nutrition is the standard of care for all eligible patients, no additional procedures (i.e. enteral tube placement) have to be performed for study participation. Only the composition of the nutrition received will be altered. Furthermore, early onset of passive and active (cycling) mobilization will be applied in both study arms, which is the current standard of care.

13. SAFETY REPORTING

13.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal/nutritional product has been administered, including occurrences which are not necessarily caused by or related to that product.

Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: ● results in death ● is life-threatening ● requires in-patient hospitalization or prolongation of existing hospitalization ● results in persistent or significant disability/incapacity ● consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardize the participant or require an intervention to prevent one of the above consequences. NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

13.2 Recording and reporting safety information

Due to the nature of the patient population (i.e. critically ill patients), all study subjects will enter the study in a state of life-threatening illness and are likely to experience many events that could be classified as an (S)AE. This is part of the normal disease course of ICU patients and not related to participation in the study. In addition, both study interventions (either high or standard protein formulas) are part of current routine care within the ICU and known to be safe. Therefore, only the SAEs which result in death or life-threatening situations due to complications with nutritional support will need to be reported.

In order to assess safety, several additional blood parameters will be regularly assessed (cfr. *Section 11.7.2*) and will be collected in the eCRF. These blood parameters fall under standard of care laboratory blood analyses.

The following events of special interest that occur during the index ICU stay will be collected in the eCRF:

- ICU-acquired infection
- Ventilator acquired pneumonia (VAP)
- Extracorporeal membrane oxygenation (ECMO)
- Acute Kidney Injury, defined as creatinine level higher than 2 times baseline level (including the use of renal replacement therapy)

- Refeeding hypophosphatemia (defined as phosphate levels below <0.65 mmol/l, a drop >0.16 mmol/L from previous level in ICU and no other explanation for hypophosphatemia)
- Hepatic dysfunction (cholestasis and liver dysfunction)
- Gastrointestinal events (i.e. vomiting, ischaemia, diarrhoea, abdominal distension, gastric paresis, bleeding/ulcer)

The following event of special interest that occurs between index ICU discharge and end of the study (follow-up visit at 180 days) admission will be collected in the eCRF:

- All-cause mortality

The Principal Investigator or the qualified person to whom this task has been delegated should ***assess causal relationship between an event of special interest and the study nutrition on the basis of his/her clinical judgment and the following definitions.*** The causality assessment must be made based on the available information and can be updated as new information becomes available.

Related:

The Event of Special Interest follows a reasonable temporal sequence from administration of study nutrition and cannot be reasonably explained by the subject's clinical state or other factors (e.g. current disease during the study, concurrent diseases, and concomitant medications).

or

The Event of Special Interest follows a reasonable temporal sequence from administration of study nutrition and is a known reaction to the nutrition under study or is predicted by known pharmacology.

Not Related:

The Event of Special Interest does not follow a reasonable sequence from administration of study nutrition or can be reasonably explained by the subject's clinical state or other factors (e.g. current disease during the study, concurrent diseases, and concomitant medications).

Recovery of the event of special interest will be followed until resolution, medically stabilized or until study completion/termination visit, whichever comes first.

13.3 Responsibilities

Principal Investigator (PI):

Checking for events of special interest when participants attend for treatment / follow-up.

1. Ensuring that these events of special interest are recorded and reported to the Sponsor and the Chief Investigator in line with the requirements of the protocol.

Chief Investigator (CI) / delegate or independent clinical reviewer:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk/benefit.
2. Review of specific events of special interest in accordance with the trial risk assessment and protocol.

Sponsor:

1. Central data collection and verification of events of special interest according to the trial protocol.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk/benefit.
3. Checking for (annually) and notifying PIs of updates to the Safety Information for the trial and if needed amend the protocol.
4. Preparing standard tables and other relevant information in collaboration with the CI and ensuring timely submission to the DSMB and EC.

Data Safety Monitoring Board:

In accordance with the Charter for the DSMB, periodically reviewing safety data.

13.4 Notification of deaths and life-threating situations

As we investigate critically ill patients, the expectation is that many SAEs will occur, since mortality and serious morbidity is high among ICU patients and part of the disease course. Therefore, SAEs that result in death but not related to nutrition, will not be reported to the regulatory authorities in the

Netherlands and Belgium. Only death or life-threatening situations due to complications with nutritional support will need to be reported by the sponsor to ToetsingOnline (in the Netherlands) and Federal Agency for safety of the food chain (in Belgium). These events need to be reported within 48 hours of awareness of the event by the PI or delegated person. Therefore, the PI or delegated person need to report these events as soon as possible via e-mail to the sponsor.
The sponsor will report these SAEs, within 7 days of first knowledge followed by a period of maximum 8 days to complete the initial preliminary report.
These SAEs will be recorded and reported until the end of the study in all participating countries.

13.5 Reporting urgent safety measures

If any urgent safety measures are taken, the CI/Sponsor shall immediately give written notice to the relevant EC of the measures taken and the circumstances giving rise to those measures.

13.6 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the Ethical Committee without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the Ethical Committee. The investigator will take care that all subjects are kept informed.

13.7 Data Safety Monitoring Board (DSMB)

Due to the size of the study and nature of the patient population, a formal DSMB will be instituted for the PRECISe trial.

13.7.1 *Composition of the DSMB*

Membership will consist of four (4) members, including one clinician experienced in the clinical area and one statistician. The additional members are experienced in clinical trials.

Members of the DSMB are:

- Dr. Liesbeth Bruckers (Statistican)
- Drs. R. Smets (Intensivist, experienced in clinical area)
- Prof. Dr. C.H.C. Dejong (Surgeon, experienced in clinical trials, experienced in clinical area)
- Dr. Sofie Van Cromphaut (Intensivist, experienced in statistics, experienced in clinical trials)

13.7.2 *Tasks and responsibilities*

The overall aim of the committee is to protect and serve the participants' safety, to monitor the overall conduct of the clinical trial and to protect the validity and credibility of the trial.

The DSMB should receive and review the progress and collected data of this trial and provide advice on the conduct of the trial to the Trial Steering Committee (TSC).
The DSMB should inform the Chair of the TSC if, in their view, the results are likely to convince a broad range of clinicians, including those supporting the trial and the general clinical community, that one trial arm is clearly contraindicated, and there was a reasonable expectation that this new evidence would materially influence patient management.

Interim review of the trial's progress includes the review of updated figures on recruitment, data quality, missing data, and safety data.

Specifically, this includes:

- assess data quality, including completeness (and by so doing encourage collection of high quality data)
- monitor recruitment figures and losses to follow-up
- monitor compliance with the protocol by participants and investigators
- decide whether to recommend that the trial continues to recruit participants or whether recruitment should be terminated only for safety reasons
- monitor continuing appropriateness of patient information
- considering the ethical implications of any recommendations made by the DSMB
- assess the impact and relevance of external evidence provided by the TSC whenever such evidence becomes available

13.7.3 *Criteria for premature study termination*

Following inclusion of 50% of patients, the DSMB will perform an interim analysis on safety data. The safety data will be:

- ICU and in-hospital mortality

Between group differences on these safety data will be analysed by the DSMB statistician, and subsequently interpreted by all DSMB members.

The DSMB can provide one of 3 possible recommendations:

1) No action needed; trial continues as planned
2) Early study discontinuation due to clear harm of a treatment, or external evidence
3) Sanctioning and/or proposing protocol changes

The DSMB will try to reach a unanimous decision. If the DSMB cannot achieve this, a vote will be taken. The deliberation process will not be communicated in the open sessions of the DSMB meetings. In the decision-making process ethical, statistical, practical, financial, and other implications will be considered before any recommendation is made.

More detailed and specific information on the role and responsibilities of the DSMB can be found in the DSMB charter.

The advice(s) of the DSMB will only be sent to the sponsor of the study. Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing Ethical Committee, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

14. STATISTICS AND DATA ANALYSIS

14.1 Sample size calculation

The primary endpoint of the PRECISe trial is the overall between group-differences in EQ-5D single summary index during the first 180 days after ICU admission. However, as longitudinal data on functional outcomes in ICU trials are not available, the power calculation is based on a published point-measurement of the EQ-5D single summary index at 180 days following ICU admission [33]. Using this point-measurement for the sample size calculation rather than using an estimate of the actual primary endpoint is justified since the expected difference in health-related quality of life after an ICU admission between both groups is likely to decrease over time. Therefore, the difference between data for the entire period of 180 days is presumably larger than the difference of the point-measurement at 180 days.

Reported instrument-defined minimally important difference estimates for the EQ-5D-3L index scores are 0.040 and 0.082 for the US and UK scoring algorithms, respectively; and for the EQ-5D-5L index

scores are between 0.037 and 0.069 for Canada, China, Spain, Japan, England, and Uruguay scoring algorithms, respectively [34, 35]. Therefore we consider a minimum difference of 0.06 points on the single summary index of the EQ-5D as being clinically important [34].

Based on these data the PRECISe trial is powered as follows: with an EQ-5D single summary index reported mean of 0.6 and standard deviation (SD) of 0.3 at 180 days, considering a type I error rate α=0.05 and a type II error rate β=0.20 (yielding a statistical power of 80%), 392 patients per intervention group will be required to detect the minimal clinically relevant difference of 0.06 EQ-5D single summary index points. In line with other critical care trials, final sample size will be adjusted for an estimated 5% loss to follow-up for the primary endpoint [29]. After this adjustment, the final calculated sample size for the PRECISe trial targets 824 participants [36].

14.2 Statistical analysis plan

14.2.1 *Primary endpoint analysis*

The treatment effect for the primary endpoint (i.e. overall between group-differences in EQ-5D summary index) is calculated using a linear mixed model for longitudinal data analysis. The between-group difference at each follow-up moment (i.e. 30, 90, and 180 days) is calculated by adding time as a categorical variable with a time-by-treatment interaction to the model. The model has a 3-level structure, i.e. the repeated measurements of the primary endpoint will be clustered within participants and participants will be clustered within participating centers. Therefore, the model includes a fixed effect for treatment, a random effect for center, and a random effect for participants (intercept, slope) [36]. Regression coefficients β with 95% confidence intervals will be reported that indicate between-group differences [37].

After reporting the crude mixed model above, the mixed model is first adjusted for baseline EQ-5D summary index. Second, the model is adjusted for the following potential confounders: sex, age, anthropometrics (body height and weight), lean body mass, lactate concentration, chronic use of glucocorticoids, pre-admission comorbidity (Charlson comorbidity index), severity of illness (APACHE II score), Nutrition Risk Score, and pre-admission frailty (Rockwood Clinical Frailty Scale). Finally, as a sensitivity analysis for the applied intervention, the model is adjusted for the total amount calories delivered (including medication-related calories) and the difference between total targeted-study feeding minus total delivered-study feeding. Confounders will be retained in the model either if there is evidence of confounding, if they explain significant variation in the outcome, or if they improve the precision of the estimated treatment effect.

The missing data mechanism assumed for the primary endpoint is missing at random and the proposed mixed model for longitudinal data analysis is robust with regard to this missing data mechanism. Nevertheless, to investigate the sensitivity of the conclusions with regard to this assumption a sensitivity analysis using multiple imputations will be used.

14.2.2 *Secondary endpoint analysis*

With regard to the main **secondary endpoints**: the treatment effects for functional (SF-36, HADS, revised Impact of Events scale, EQ-5D-5L (EQ-VAS and pain question), 6-minute walk test, MRC-SUM, and handgrip strength) secondary endpoints are also assessed using linear mixed models. The calculation of between group differences, the 3-level model structure (with fixed treatment effect, random center effect and random effect for participants), reporting of effect size and the adjustment for potential confounders is similar as described for the primary endpoint analysis.

For the clinical secondary endpoint mortality, first, survival curves for both treatment arms will be constructed using the Kaplan-Meier method. Then, a mixed-effect Cox proportional hazard model, with a 2-level structure, i.e. participants clustered within centers, is used to investigate a treatment effect on this secondary endpoint. The model, therefore, includes a fixed effect for treatment and a random effect for center. The adjustment for potential confounders is similar as described for the primary endpoint analysis. Hazard ratios will be reported with a 95% confidence interval. The proportional hazard assumption will be examined.

The missing data mechanism for the main secondary endpoints cannot be assumed to be missing at random. In particular when the intervention affects mortality, data cannot be assumed missing at random. To investigate the sensitivity of the conclusions with regard to the missing data mechanisms, a modified multiple imputation method is applied that uses weighting on the imputed data in two ways; one with imputed data in favor of the intervention; another with imputed data against the intervention; in addition to an unweighted multiple imputation analysis similarly proposed for the primary endpoint.

14.2.3 *General considerations*

Transformation will be used when model assumptions, such as normality, are violated. Population characteristics are presented as means +/- SD, medians [IQRs], or proportions. Variables will be compared between intervention groups for continuous data using independent Student's t-test or Mann-Whitney U test for skewed data and Chi-squared test for proportions.

Effect sizes with 95% confidence intervals will be reported and a 2-sided P-value <0.05 and P-interaction <0.10 will be considered as statistically significant.

For the primary and secondary endpoints, exploratory subgroup analyses will be performed for patients with infection on index ICU admission versus patients with no infection on index ICU admission, for severe brain injury versus others, patients with prolonged ICU stay (>1 week) vs others, high versus low nutritional risk (NRS-score) and medical versus surgical admission.

14.2.4 *Missing data*

Throughout the trial, reasons for missing data after randomization will be registered. Missing data patterns will be defined and analyzed with regard to the multiple imputations for primary and secondary outcome analyses. Several reasons for missing data are foreseeable such as drop-out due to truncation by death and dropout due to surviving in an unconsciousness state. However, lost to follow-up or missing intermittent data will also occur [38]. Truncation by death and its consequences for analyses have extensively been addressed in the statistical analyses section. In addition, unconsciousness could cause similar missing data as truncation by death for secondary outcomes. Both of these sources of missing data could be informative missing, and this will be handled with multiple imputation and sensitivity analyses. Other reasons for lost to follow-up will be registered, which enables to define other not foreseeable patterns of missing data. Linear mixed models have the particular advantage of handling random (and thus intermittent) missing data robustly [36].

14.3 Data collection for economic evaluation by the funders and similar healthcare research institutes in Europe

If a health-economic analysis is performed after the completion of the sponsor, the data could be retrieved from the PRECISe database or administrative databases.

Accordingly, the Sponsor will transfer the pseudonymized study data set to funder(s) upon request. The funder will request approval from the competent chamber of the Information Security Committee to have the relevant study data linked with an administrative database (e.g. InterMutualistisch Agentschap (IMA)) by a trusted third party using the patient national number.

In addition, the patient information and consent form includes wording that the national number will be recorded on site by the investigator for later data linkage. The patient information and consent form will also include that in case the patient is randomized, it is planned that a trusted third party will receive and use the national number to link with an administrative database (e.g. IMA). This data

linkage is required to obtain a more complete data set that will be used for the analysis of effectiveness and cost-effectiveness of the intervention by the funders.

For the cost-utility analysis, a quality of life questionnaire, the EQ-5D-5L, will be used in order to calculate the incremental costs per Quality Adjusted Life year (QALY).
The friction cost method will be used to calculate the productivity costs according to the Dutch guidelines and Belgian guidelines.

14.3.1 *Economic evaluations analysis*

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 healthcare payer and societal perspective since costs both in and outside (i.e. productivity loss) health care are assumed to be relevant.
For the analysis of the economic evaluation, QALYs for each patient will be calculated as the area under the curve following the trapezium rule which assumes linear interpolation between follow-up points [39]. 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. Bootstrap analysis will be used to quantify the uncertainty surrounding the incremental cost-effectiveness ratio. Results of this analysis will be presented in cost-effectiveness planes and acceptability curves. Overall, the trial based cost-effectiveness analysis will follow the ISPOR guidelines [40].

15. DATA HANDLING

15.1 Data collection tools and source document identification

It is the responsibility of the Principal Investigator at each site to maintain adequate and accurate source data, source documentation and CRFs to record all observations and other data pertinent to the clinical investigation in a timely manner.
Patient's personal data, which are included in the Investigator Sites Files (ISF) shall be treated in compliance with all applicable laws and regulations. The data collected and stored will be pseudonymized and the data will only be used for the purpose(s) of this trial.
Source Data are defined as "All information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction

and evaluation of the trial. Source data are contained in source documents (original records or certified copies)."

Source Documents are defined as "Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial)."

Case report form **(CRF)** is a form on which individual patient data required by the trial protocol are recorded.

All data relating to the trial must be recorded in the eCRF (electronic CRF) prepared by the Sponsor. Data reported in the eCRF should be in English, consistent with the source data and discrepancies should be explained. If information is not known, this must be clearly indicated in the eCRF. All missing and ambiguous data will be queried.

The study data will be transcribed by study personnel from the source documents into an eCRF, within 5 working days of the subject's visit.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subjects' source documentation.

Every effort should be made to ensure that all subjective assessments to be recorded in the eCRF are performed by the same individual who made the initial screening assessment.

The Investigator must verify that all data entries in the eCRF are accurate and correct. All eCRF entries, corrections, and alterations must be made by the Investigator or other authorized study-site personnel. The Investigator or an authorized member of the investigational staff must adjust the eCRF (if applicable) and complete the query.

PRECISe uses an eCRF which will be used to perform statistical analysis for the trial. The CRF will be constructed to ensure:

- adequate data collection
- structured flow and execution of the trial procedures
- proper trails will be kept to demonstrate the validity of the trial (both during and after the trial)
- that only the data required by the protocol are captured in the CRF

An annotated CRF is developed with coding conventions that will be used in the database.

The Principal investigator is responsible to keep records of all participating patients (sufficient information to link records e.g., CRFs, hospital records, and samples), all original signed informed consent forms, and copies of the CRF pages and store them in the investigator site file (ISF).

15.2 Data handling and record keeping

All collected study data will be recorded and stored in the CRF created with the CASTOR© software. To protect the privacy of the participants, all collected data will be encoded. Following the creation of a new study record in the eCRF, a study specific patient code will be created. The code will consist of a code specific for the site of recruitment (i.e. 01, 02 etc), the abbreviation of the study (PRECISe), and an incremental 3-digit number per centre (starting from 001 in order of inclusion). Examples of study codes could be 01-PRECISe-023 or 02-PRECISe-008.

CASTOR© complies with all applicable medical data privacy laws and regulations: GCP, 21 CFR Part 11, EU Annex 11, the European Data Protection Directive, ISO9001, and ISO27001/NEN7510.

All other data collected that is not/cannot be stored in the eCRF (i.e. paper notes, signed ICFs etc.) are stored in the local TMF binder, which is stored behind a locked environment which is only accessible by the local PI or local delegated study person.

Once the PI and delegated member(s) of the investigational staff have been trained, they will receive the link of the eCRF together with a log-in account and password. Detailed information regarding the eCRF is provided in the CRF completion guidelines.

All handling of data will be in agreement with the 'EU General Data Protection Regulation' and in the Netherlands in agreement with the 'Uitvoeringswet AVG (UAVG; the Dutch Act on Implementation of the General Data Protection Regulation)'.

15.3 Access to data

Direct access to the eCRF and encoded data will be granted to authorized representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits, and inspections.

Only the local PI and local delegated study person have access to the key linking the individual patient to the study patient code. At no point will the key leave the local study site.

Access to the decoded data can be necessary to for controlling and monitoring purposes. Access to the decoded data is restricted to the safety commission, monitors working on behalf of the sponsor and national and international supervising authorities (i.e. IGJ in the Netherlands).

Data will not be shared with parties outside of the EU. Pseudonymized data will be shared with KCE in order to perform a health-economic analysis to inform national governments about reimbursement of the study intervention.

15.4 Archiving

- Archiving of the Trial Master File will be authorized by the Sponsor following submission of the clinical study report.
- It is the responsibility of the Principal Investigator at each site to ensure all essential trial documentation and source records (e.g. signed Informed Consent Forms, Investigator Site Files, patients' hospital notes, etc.) at their site are securely retained for as long as required according to the current national legislation (e.g. 15 years in the Netherlands) or according to any amendments of this legislation if they become applicable before the study completion.
- The sponsor will be responsible for archiving all CRF documents and trial database for at least as long as required according to the current national legislation (e.g. 15 years in the Netherlands, 20 years in Belgium) or according to any amendments of this legislation if they become applicable before the study completion.
- Therefore, all essential documents will be archived for a minimum period after completion of trial as required by the applicable legislation.
- In addition to legal requirements, data are stored for the purposes of 1) re-analysis and new analysis aimed at answering questions in line with the aims of the current study and 2) to use for other scientific research regarding nutrition and intensive care medicine.

16. MONITORING, AUDIT & INSPECTION

A Trial Monitoring Plan will be developed based on the trial risk assessment which will be done by exploring the trial dataset or performing site visits.

The Sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study center visit log. The visit log will be kept at the site. The first post-initiation visit will be made as soon as possible after enrollment at the center has begun. Monitoring might be initially conducted across all sites, and subsequently conducted using a risk-based approach that focuses, for example, on sites that have the highest enrollment rates, large numbers of withdrawals, or atypical (low or high) numbers of reported events of special interest. At these visits, the monitor will compare the data entered into the eCRF with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original

data, required to complete the eCRF, are known to the Sponsor, Chief Investigator and investigational staff and are accessible for verification by the Sponsor site contact. If electronic records are maintained at the investigational site, the method of verification must be discussed with the investigational staff. The processes reviewed can relate to participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions and policies to protect participants, including reporting of harm and completeness, accuracy, and timeliness of data collection.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data, patients informed consent will be obtained hereto. Findings from this review of eCRFs and source documents will be discussed with the investigational staff. The Sponsor expects that, during monitoring visits, the relevant investigational staff will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the Investigator on a regular basis during the study to provide feedback on the study conduct.

17. ETHICAL AND REGULATORY CONSIDERATIONS

17.1 Ethical considerations

17.1.1 *Group relatedness and benefits*

For this study, mechanically ventilated patients admitted to the ICU will be studied. This is a vulnerable patient group that, due to the nature of their condition, will not able to give informed consent before start of the study. However, alternative models or patients are not able to answer our research question, as it is specific for this patient group, making it necessary to perform this study in a vulnerable population. Critical illness (for which mechanical ventilator support is necessary for an undetermined period) is a severe, life-threatening disease with unique and detrimental metabolic derangement resulting in a spectacularly rapid loss of muscle mass and strength unlike any other disease state. Therefore, previous work on the effectiveness of protein provision on function recovery in healthy or less severe disease conditions cannot simply be extrapolated to ICU patients. However, the increased protein catabolism and impaired anabolic response during ICU admission has a severe impact on the recovery and functional outcome in critically ill patients, both in the short and long-term.

The PRECISe study aims to investigate whether the enteral protein administration is able to improve functional recovery following ICU admission. If the study is able to show a benefit of one treatment arm over the other, the results will be implemented in daily practice where they will lead to better treatment of critically ill patients. Therefore, this study has the potential to improve care for this patient population and therefore outweighs the objection that it requires the study to be performed in a study population unable to give informed consent by themselves.

17.1.2 *Benefits and risks assessment*

No additional risks are involved in the study. The study compares nutritional strategies that are currently used in daily ICU practice and both strategies have proven to be safe, well tolerated, and without any additional side effects [28].

In summary, critical illness is a life-threatening condition with severe impact on muscle mass and function. This translates into a detrimental impact on patient's physical state and impaired quality of life for patients following ICU admission. The current study compares the effect of two nutritional compositions on functional recovery following ICU admission. It is currently unknown which intervention is better at improving recovery of patients. As muscle wasting and increased protein requirements occur especially during the early phase of critical illness, the intervention has to be initiated at this stage, meaning that patients will be unable to provide consent themselves. Since no associated risk are involved for both interventions, and the potential to improve care for ICU patients

if the study is able to show a benefit of one treatment over the other, we believe it is both ethical and justified to perform the study in this patient group.

17.2 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

1. € 650.000,-- (i.e. six hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 5.000.000,-- (i.e. five million Euro) for death or injury for all subjects who participate in the Research;
3. € 7.500.000,-- (i.e. seven million five hundred thousand Euro) for the total damage incurred by the organization for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

17.3 Incentives

Subjects will receive € 12,50 for travel expense for each follow-up visit attended (at 1, 3 and 6 months). If travel expense exceeds € 12,50, the extra expense will be supplemented by the sponsor.

17.4 Ethics committee review & reports

- Before the start of the trial, approval will be sought from an EC for this trial protocol, informed consent forms, and other relevant documents e.g. insurance documents, advertisements, and GP information letters.
- Substantial amendments that require review by EC will not be implemented until the EC grants a favorable opinion for the study.
- All correspondence with the EC will be retained in the Trial Master File/Investigator Site File.

- An annual progress report will be submitted to the EC within 30 days of the anniversary date on which the favorable opinion was given, and annually until the trial is declared ended.
- It is the Chief Investigator's responsibility to produce the annual reports as required.
- The Chief Investigator will notify the EC of the end of the study.
- If the study is ended prematurely, the Chief Investigator will notify the EC, including the reasons for the premature termination.
- Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the EC.

17.5 Peer review

The protocol has been reviewed by KCE and ZonMw (the funders). In addition, PRECISe has undergone a high quality peer review by experts who have knowledge of the relevant discipline to consider the clinical and/or service based aspects of the protocol, and/or have the expertise to assess the methodological and statistical aspects of the study.

17.6 Public and patient involvement

In an early stage of the proposal, (former) ICU patients, representatives from patient organizations as well as family members of (former) patients have been involved in the development of the proposal. In the Netherlands, patients and family members are joined via the FCIC (Family and patient Centered Intensive Care), a Dutch patient organization that is active on the subject of post-ICU survivorship and its impact on patients and family. Unfortunately, a similar organization is not active in Belgium. To assure input from both the Dutch and Belgian side we have set up a patient advisory group, consisting of 2 members from the FCIC, 1 individual Flemish and 1 individual Wallonian former ICU patient. This group has met 2 members of the project group to discuss the design of the study and to define meaningful and patient relevant outcomes.

17.6.1 *Patient involvement plan*

Involvement by patient representatives throughout the project is guaranteed through two instruments: 1) participation in the trial steering committee and 2) the formation and consultation of the patient advisory group.

1. Trial steering committee

The trial steering committee (TSC) will oversee the execution of the study and involves not only the primary project members, but also several independent experts including a nutritional scientist, health economist and statistician.

2) Patient advisory group

For this project a patient advisory group has been formed with 3 former ICU patients and 1 family member, representing all three of the national/language regions. The patient advisory group will be regularly updated with the progress of the study and can be consulted to provide input from the patient perspective. Aside from the possibility to ask for advice in between, we will organize a meeting on at least the following set moments:

1. Design of the project and patient relevant outcomes

This first meeting to involve the patient perspective in the design of the project and outcomes took place on 20 September 2018. A short summary report and the advice on patient relevant outcomes are discussed below.

2. Pre EC submission of the protocol

Pending approval of the project, a meeting will be organized to involve patients in the practical execution of the trial. This includes amongst others review of the informed consent procedure, the patient/family information documentation and the final study protocol.

3. Study end

Following inclusion of the final participant, a final meeting will be organized with the patient advisory group. This meeting will not only discuss the final evaluation of the study and its execution, but also discuss how to disseminate the results of the study to the participants, patients, relatives, patient organizations and other important public stakeholders.

17.6.2 *Input on design and patient-relevant outcomes*

During a first meeting, the experience-experts shared the impact that their ICU stay has had on their lives afterwards. All patients had in common that they had a dramatic, enduring and disabling loss of physical strength following their ICU admission. In this light the patient advisory group unanimously agreed that muscle strength should be one of the main parameters to be evaluated. Out of several scientifically validated methods to assess muscle strength, the assessment of handgrip strength was considered to be the most appealing to use as a primary outcome measure. One patient mentioned: ‘After I woke up, my hands were so weak I couldn’t even hold on to a glass of water. Another stated “I still remember myself in the bed struggling to hold a popsicle I was given’.

The lack of strength did not only affect them on the physical level: 'If you feel that weak and lack the strength to do anything, it also impacts your mental state. It felt incredibly frustrating'. One patient mentioned: 'It had a big impact on how our family live was organized. I was not able to return to work for quite some time, while my partner had a full-time job. Being used to a two-income household with children, this was quite a challenging time'. This sentiment was echoed by the other experience experts, who underlined the big impact of the inability to work on the ability to participate in society. Therefore, time to return to work was also recommended to include as an outcome measure by the patient advisory group.
The panel further recommended to also evaluate the ability to walk (6-minute walk test) and ability to resume daily activities (SF-36 questionnaire) as additional secondary endpoints.

The consensus from the first patient advisory group meeting was to recommend handgrip strength as the primary outcome. However, following the review process by several independent experts, the robustness and relevance to health-care decision makers of this measure was doubted. Following several discussions within the study team, it was put forward to change the primary outcome to HRQL, measured by the EQ-5D-5L. The patient panel supports this change, especially considering that their recommended outcomes (strength and physical functioning) will still be recorded as part of the extended core outcome measures set in the secondary outcomes.

17.7 Regulatory compliance

The trial will not commence until approval is obtained from the Ethics Committee. The protocol and trial conduct shall be governed and construed in accordance to the principles of the Declaration of Helsinki as revised most recently in Brazil, 2013 and in accordance with the law of Belgium and the Netherlands. The Trial will for instance comply with the Belgian law of May 7th, 2004 regarding experiments on the human person and the Dutch law 'Wet Medisch-wetenschappelijk Onderzoek met Mensen' (WMO).

17.8 Protocol compliance

Protocol deviations, non-compliances, or breaches are departures from the approved protocol.

- Prospective, planned deviations or waivers to the protocol are not allowed and must not be used. For example, it is not acceptable to enroll a subject if he/she does not meet the eligibility criteria or restrictions specified in the trial protocol.

- Accidental protocol deviations can happen at any time. They must be adequately documented and explained on the relevant forms and reported to the Chief Investigator and Sponsor immediately.
- Deviations from the protocol which recur frequently are not acceptable, will require immediate action and could potentially be classified as a serious breach.

17.9 Notification and serious breaches to GCP and/or the protocol

A "serious breach" is a breach which is likely to effect to a significant degree

- the safety or physical or mental integrity of the subjects of the trial; or
- the scientific value of the trial

The sponsor and the Chief Investigator will be notified immediately of any case where the above definition applies during the trial conduct phase.

The sponsor of the clinical trial will notify the Ethical Committees in writing of any serious breach of the conditions and principles of GCP in connection with that trial; or the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.

17.10 Data protection and patient confidentiality

All investigators and trial site staff must comply with the requirements of the Regulation (EU) 2016/679 of April 27, 2016 of the European Parliament and the Council Concerning the protection of individuals with regard to the processing of personal data and the free movement of such data and repealing Directive 95/46 / EC (General Data Protection Regulation), the European Privacy Act of 8 December 1992 on the protection of privacy in relation to the processing of personal data and, as of the 5th of September 2018 the Law of 30 July 2018 related to the protection of natural persons with regard to the processing of personal data, the Law of 22 August 2002 related to the rights of patients, including their respective Royal Decrees), with regards to the collection, storage, processing, and disclosure of personal information and will uphold the Act's core principles. Data from the Netherlands will be treated according to the Dutch Act on Implementation of the General Data Protection Regulation (UAVG).

Therefore:

- personal information will be collected, kept secure, and maintained in a way that is conform all regulation concerning privacy;

- the creation of coded, depersonalized data where the participant's identifying information is replaced by an unrelated sequence of characters;
- secure maintenance of the data and the linking code in separate locations using encrypted digital files within password protected folders and storage media;
- limiting access to the minimum number of individuals necessary for quality control, audit, and analysis with a list of persons who have access to data, and all this conform the regulation concerning privacy;
- the confidentiality of data will be preserved when the data are transmitted to sponsors and co-investigators;
- the data will be stored for as long as required according to the current national legislation (e.g. 15 years in the Netherlands, 20 years in Belgium) or according to any amendments of this legislation if they become applicable before the study completion.

17.11 Financial and other competing interests for the principal investigators

Since both nutritional products are regular, commercially available products, no competing interests that might influence trial design, conduct, or reporting are present neither for the Chief Investigator nor for the PIs at each site and committee members and this during the overall trial management.

17.12 Indemnity

1. The Sponsor will ensure appropriate insurance to meet the potential legal liability of the Sponsor(s) for harm to participants arising from the design or management of the research. Before the start of the trial, approval will be sought from the EC.

2. The participating sites will ensure appropriate insurance to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research.

17.13 Access to the final trial dataset

Only the managing steering group has access to the full trial dataset in order to ensure that the overall results are not disclosed by an individual trial site prior to the main publication.

However, site investigators will be allowed to access the full dataset if a formal request describing their plans is approved by the TSC.

18. DISSEMINATION POLICY

18.1 Dissemination policy

Upon completion,

- The data arising from the trial will be owned by the sponsor;
- The data will be analyzed and tabulated and a Final Study Report prepared;
- The full study report can be accessed online as well as on ClinicalTrials.gov;
- Participating investigators will have rights to publish any of the trial data upon approval of the steering committee;
- The publication containing the primary study results should be finalized within 6 months of the statistical analysis. There are no time limits or review requirements on the additional publications;
- Funding by KCE and ZonMw will be acknowledged within the publications;
- The participants of the trial will be notified by a letter containing the outcome of the trial by provision of the publication and/or via a specifically designed newsletter;
- The participants might specifically request results from their PI upon completion of the trial, which might be provided once the results have been published;
- It is foreseen that at the latest at publication, a machine-readable electronic copy of the published version or final peer-reviewed manuscript accepted for publication in a repository for scientific publications will be deposited (preferably open access). The research data needed to validate the results presented in the scientific publications will be deposited.

Upon completion, the study will also be submitted for presentation at the annual International Symposium on Intensive Care and Emergency Medicine (ISICEM), the annual European Society of Intensive Care Medicine (ESICM) meeting, and the annual ESPEN conference (European Society of Clinical Nutrition and Metabolism).

The primary study results of the PRECISe study will be reported fully and made publicly available when the research has been completed. All researchers shall ensure that the outcome of the research is prepared as a research paper for publication in a suitable peer-reviewed, preferably open-access, journal. In addition, the database of the PRECISe study will be available for further sub-analysis per request of any of the sub-investigators. The Consort Guidelines and checklist will be reviewed prior to generating any publications for the trial to ensure they meet the standards required for submission to high quality peer reviewed journals etc. http://www.consort-statement.org/).

All participating investigators will also try to disseminate their research findings to the broader public as well as to the research participants when the study has completed.

The study topic, design and endpoints were meticulously chosen based on consensus of all participating investigators, the involvement of the patient panel and is considered the highest priority study to be performed by the most recent research agenda published within the field [11]. Furthermore, the principal investigators represent several internationally renowned experts in the field also represented in several society and guideline committees. Therefore, a positive result will also have the potential to be adopted soon in the national and international guidelines for nutritional support of ICU patients.

In conclusion, it is felt that a positive endpoint might lead to a fast adoption of the use of high-protein enteral nutrition in the treatment of critically ill patients because of:

1. Publication in top ranked (intensive care) medical journal
2. Presentation of study results in national and international intensive care and clinical nutrition meetings
3. Adoption in guidelines
4. Internationally recognized expert study team

18.2 Authorship eligibility guidelines

For PRECISe, the TSC will manage study publications with the goal of publishing findings from the data. The TSC will develop the final Publication Plan as a separate document. In addition, the committee will apply and reinforce the authorship guidelines set forth in the Publication Plan. Membership in the TSC does not guarantee authorship. The committee will meet at regular intervals.

Publications will adhere to authorship criteria defined by the International Committee of Medical Journal Editors (ICMJE, Uniform requirements for manuscripts submitted to biomedical journals, www.icmje.org). Individual authorship criteria defined by the target journal or conference will be followed when it differs from ICMJE criteria. Authors, including KCE representatives, must at a minimum meet all of the conditions below:

- Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data; AND
- Drafting the article or revising it critically for important intellectual content; AND

- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Decisions regarding author- and contributorship will be made by the committee. The selected authors will be responsible for drafting the publication. All selected authors must fulfill the authorship conditions stated above to be listed as authors, and all contributors who fulfill the conditions must be listed as authors.

All investigators not listed as co-authors will be acknowledged as the “PRECISe Study Investigators” and will be individually listed according to the guidelines of the applicable scientific journal when possible. Any other contributors will be acknowledged by name with their specific contribution indicated. Based on the recruitment, site investigators can also be part of the authorship.

A methods paper describing the PRECISe study, the statistical analysis plan, as well as the publication containing the primary study results will be drafted and submitted for publication after approval of the members of the TSC.

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