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Protocol

The impact of high versus standard enteral protein provision on functional recovery following intensive care admission: Protocol for a pre-planned secondary Bayesian analysis of the PRECISe trial

Samuel Heuts [a, b, 1], Pieter de Heer [c, 1], Andrea Gabrio [d], Julia L.M. Bels [c, e], Zheng-Yii Lee [f, g], Christian Stoppe [g, h], Sander van Kuijk [i], Albertus Beishuizen [j], Ashley de Bie-Dekker [k], Vincent Fraipont [l], Stoffel Lamote [m], Didier Ledoux [n, o], Clarissa Scheeren [p], Elisabeth De Waele [q], Arthur van Zanten [r, s], Dieter Mesotten [t, u, 2], Marcel C.G. van de Poll [c, e, v, *, 2], on behalf of the PRECISe investigators[†]

[a] Department of Cardiothoracic Surgery, Maastricht University Medical Center+, Maastricht, the Netherlands
[b] Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, Maastricht, the Netherlands
[c] Department of Intensive Care Medicine, Maastricht University Medical Center+, Maastricht, the Netherlands
[d] Department of Methodology and Statistics, Maastricht University, Maastricht, the Netherlands
[e] School for Nutrition and Translational Research in Metabolism (NUTRIM), Maastricht University, Maastricht, the Netherlands
[f] Department of Anaesthesiology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia
[g] Department of Cardiac Anesthesiology & Intensive Care Medicine, Charité Berlin, Germany
[h] University Hospital Würzburg, Department of Anaesthesiology, Intensive Care, Emergency and Pain Medicine, Würzburg, Germany
[i] Department of Clinical Epidemiology and Medical Technology Assessment (KEMTA), Maastricht University Medical Center+, Maastricht, the Netherlands
[j] Intensive Care Center, Medisch Spectrum Twente, Enschede, the Netherlands
[k] Department of Intensive Care Medicine, Catharina Ziekenhuis Eindhoven, Eindhoven, the Netherlands
[l] Intensive Care Unit, Citadelle Hospital, Liège, Belgium
[m] Department of Intensive Care Medicine, Academisch Ziekenhuis Groeninge, Kortijk, Belgium
[n] Sensation and Perception Research Group, GIGA Consciousness, University of Liège, Liège, Belgium
[o] Intensive Care Units, University Hospital of Liège, Liège, Belgium
[p] Department of Intensive Care Medicine, Zuyderland Medisch Centrum, Heerlen, the Netherlands
[q] Department of Nutrition, Universitair Ziekenhuis Brussel, Jette, Belgium
[r] Department of Intensive Care Medicine, Gelderse Vallei Ziekenhuis, Ede, the Netherlands
[s] Division of Human Nutrition & Health, Wageningen University & Research, Wageningen, the Netherlands
[t] Department of Intensive Care Medicine, Ziekenhuis Oost-Limburg, Genk, Belgium
[u] Faculty of Medicine and Life Sciences, UHasselt, Diepenbeek, Belgium
[v] Department of Surgery, Maastricht University Medical Center+, Maastricht, the Netherlands

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SUMMARY

Background: The PRECISe trial is a pragmatic, multicenter randomized controlled trial that evaluates the effect of high versus standard enteral protein provision on functional recovery in adult, mechanically ventilated critically ill patients. The current protocol presents the rationale and analysis plan for an evaluation of the primary and secondary outcomes under the Bayesian framework, with an emphasis on clinically important effect sizes.

Methods: This protocol was drafted in agreement with the ROBUST-statement, and is submitted for publication before database lock and primary data analysis. The primary outcome is health-related quality of life as measured by the EQ-5D-5L health utility score and is longitudinally assessed. Secondary outcomes comprise the 6-min walking test and handgrip strength over the entire follow-up period

* Corresponding author. Department of Intensive Care Medicine, Maastricht University Medical Center+ (MUMC+), P. Debyelaan 25, 6229HX, Maastricht, the Netherlands.
E-mail address: marcel.vande.poll@mumc.nl (M.C.G. van de Poll).
[1] Shared first authorship.
[2] Shared senior authorship.
[†] Please see Supplementary Material 1 for the full list of the PRECISe investigators.

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(longitudinal analyses), and 60-day mortality, duration of mechanical ventilation, and EQ-5D-5L health utility scores at 30, 90 and 180 days (cross-sectional). All analyses will primarily be performed under weakly informative priors. When available, informative priors elicited from contemporary literature will also be incorporated under alternative scenarios. In all other cases, objectively formulated skeptical and enthusiastic priors will be defined to assess the robustness of our results. Relevant identified subgroups were: patients with acute kidney injury, severe multi-organ failure and patients with or without sepsis. Results will be presented as absolute risk differences, mean differences, and odds ratios, with accompanying 95% credible intervals. Posterior probabilities will be estimated for clinically important benefit and harm.

Discussion: The proposed secondary, pre-planned Bayesian analysis of the PRECISe trial will provide additional information on the effects of high protein on functional and clinical outcomes in critically ill patients, such as probabilistic interpretation, probabilities of clinically important effect sizes, and the integration of prior evidence. As such, it will complement the interpretation of the primary outcome as well as several secondary and subgroup analyses.

1. Introduction

Loss of muscle mass and function are important risk factors for disability and reduced quality of life in post intensive care unit (ICU) recovery [1]. The optimization of nutritional support and protein provision during ICU stay is a promising and easily applicable approach, that is hypothesized to preserve muscle mass and may improve functional outcomes after ICU discharge. However, high-quality prospective evidence for optimal protein provision in critically ill patients is scarce [2]. Therefore, we performed the *Impact of high versus standard enteral protein provision on functional recovery following intensive care admissio*n (PRECISe) trial, which is a pragmatic, multicenter randomized controlled trial that evaluates the effect of high versus standard enteral protein provision on functional recovery in adult, mechanically ventilated critically ill patients [3]. To complement the primary analysis that is performed under the frequentist framework, we aim to perform a secondary Bayesian analysis of the PRECISe trial.

Bayesian inference is increasingly used to complement primary analyses of randomized trials in critical care [4–6]. In contrast to the frequentist framework - that provides a mere dichotomous assessment of a null hypothesis - Bayesian inference estimates the posterior probability of any given effect size, therefore facilitating clinical interpretation of results from studies or secondary analyses that may not be powered to detect a minimal clinically important difference (MCID) by frequentist inference [7].

Here, we present the protocol for the secondary Bayesian analysis of the PRECISe trial, assessing the posterior probabilities of a minimal clinically important difference for the primary endpoint in the intention-to-treat population, and in relevant subgroups and various secondary endpoints. Outcome measures and subgroups, prior distributions, and minimal clinically important differences that will be used in this analysis are specified prospectively.

2. Methods

2.1. Study design and conduct

The PRECISe trial is an investigator-initiated pragmatic, bi-national multi-center, randomized controlled, quadruple-blinded study, designed to assess the effect of high protein enteral nutrition (target 2.0 g/kg/day) vs standard protein enteral nutrition (target 1.3 g/kg/day) on functional recovery at 30 days, 60 days, and 180 days following ICU admission, including health-related quality of life, measures of muscle strength, physical function, and mental health. The trial's primary endpoint is health-related quality of life as measured by the Euro-QoL-5D-5-level (EQ-5D-5L) questionnaire Health Utility Score. Between-group differences of the primary and other sequential endpoints will be assessed over the three time points using linear mixed-effects models. The published primary study protocol presents details on trial design, patient recruitment, and methodology [3]. This secondary Bayesian analysis protocol was announced in this primary protocol paper, and was prepared according to the Reporting Of Bayes Used in Clinical Studies (ROBUST) guideline [8] (Supplementary Material 2).

The current Bayesian analysis protocol was finalized and submitted for publication before the completion of the follow-up of the last patient and before database lock. As such, all formulated endpoints, priors, and MCIDs were elicited in an unbiased manner, before trial results are known.

2.2. Trial pragmatism

Randomized clinical trials may differ in pragmatism across a continuum from *explanatory* to *pragmatic* [9]. Explanatory trials are aimed to evaluate the efficacy of an intervention in highly standardized circumstances. Such an approach may have high internal validity, but results of these trials are often not immediately generalizable to the real-world. The PRECISE-trial was designed as a pragmatic trial. To ensure external validity and generalizability, pragmatic trials aim to minimize adjustments to regular clinical practice within the study protocol when evaluating the clinical effectiveness of an intervention. Particular pragmatic characteristics of the PRECISe-trial are the broad inclusion criteria, the multicentre, transnational setting, the inelaborate delivery of the intervention and the relevance of the primary outcome to the participants.

2.3. Approvals and reporting

The PRECISe trial is conducted in five Dutch and five Belgian hospitals. The study was approved for the Belgian sites by the Belgian leading ethics committee of the University Hospital of Brussels (2020/223) and for the Dutch sites by the Medical Ethics committee of Maastricht University (METC azM/MUMC+, METC20-039). The informed consent procedure differs between the two involved countries, and has been extensively described elsewhere [3]. In short, for Dutch centers, a deferred consent procedure was applied (METC azM/MUMC+, METC20-039) [10]. As informed consent is not always feasible in incapacitated patients,

the concept of deferred consent allows the inclusion of incapacitated patients in trials with a potential advantage, when the trial fulfills specific criteria as formulated by the World Medical Association, and evaluated by local Institutional Review Boards [11]. In line with these, written informed consent was obtained as soon as possible from a patient's proxy, or the patient after regaining consciousness. In Belgium centers, permission to apply deferred consent was not granted and written informed consent was obtained from the patient's proxy, prior to the inclusion in the study (Ethical Committee of the University Hospital Brussels - 2020/223). Finally, the trial is registered at ClinicalTrials.gov (NCT04633421).

2.4. Enrolment criteria

Adult patients 18 years and above with an unplanned admission to the ICU, being mechanically ventilated within 24 h following ICU admission, and with an expected duration of mechanical ventilation of at least 3 days (i.e., indication for enteral nutrition support) were included. Exclusion criteria are; contraindication for enteral nutrition at the discretion of the treating physician, moribund or expected withholding of treatment, kidney failure without the possibility of dialysis, hepatic encephalopathy West Haven criteria 3–4, or a body mass index <18 kg/m^2.

2.5. Interventions

Patients were 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 groups. One group received enteral nutrition with a high protein content of 8g/100 kcal (expected intake 1,6–2,0 g/kg/day), and the other group received enteral nutrition with a standard protein content of 5g/100 kcal (expected intake 0,8–1,25 g/kg/day). Only the protein content differed between the two groups. Total energy content and volume of the enteral nutrition across both groups were similar (i.e., isocaloric and isovolumetric). The study nutrition was continued throughout the entire ICU stay as long as enteral nutrition was required with a maximum of 90 days.

2.6. Sample size and trial status

Detailed sample size justifications for the frequentist analyses are available in the primary protocol [3]. In short, the initial sample size was 824 patients, which was calculated to provide 80% power to detect a difference of 0.06 (SD 0.3) on the EQ-5D-5L healthy utility score scale during the follow-up, with an alpha of 0.05. During a pre-planned interim safety analysis, it became apparent that the mortality rate in the trial (39%) was higher than anticipated (30%), leading to a higher SD for the primary endpoint. To adjust for this finding, a new power analysis was performed, leading to an updated sample size of 935 patients. The first patient was enrolled on November 19th, 2020, and the 935th and final participant was included on 17 April 2023, with the last visit planned for October 2023 [3].

2.7. Principles of Bayesian analyses

A cornerstone of Bayesian inference is the incorporation of prior beliefs about an effect estimate (the prior) into the calculation of the posterior probability of that effect estimate (the posterior), following the emergence of novel evidence (the likelihood). This methodology resembles clinical reasoning, where one's strong belief (either enthusiastic or skeptical) towards a certain treatment, based on solid evidence or convincing clinical experience is less likely to be affected by new evidence than one's neutral attitude towards a specific treatment. In Bayesian inference, prior beliefs are either informative (based on evidence or clinical experience) or non-/weakly informative. Such a weakly informative prior aims to yield posterior probabilities that are influenced almost exclusively by the actual trial data. Given the potential influence of informed priors on posterior probability distributions, it is essential to define priors realistically and before trial results become available [12].

2.8. Rationale for the implementation of Bayesian inference

Historically, clinical trials have been evaluated by the use of frequentist inference, by which the probability of the data is tested, assuming the null hypothesis (no difference). Such an approach heavily depends on the trial's power, which in turn is the result of the included sample size and the treatment effect. Clinical trials are often time- and resource-consuming, which has led investigators to base their sample size calculation on an (optimistic) expected treatment effect, rather than a clinically important treatment effect. When the null hypothesis is not rejected in these cases, this may be the consequence of a reduced power, and this might cause critical care physicians to abandon therapies that have a potentially clinically important benefit [4]. In contrast, the Bayesian frameworks allows the direct estimation of the posterior probability of any treatment effect, including the MCID. Finally, the incorporation of prior data may facilitate a more feasible sample size calculation, while the use of reference priors (such as enthusiastic and skeptical priors) can assess the robustness of the findings.

2.9. Outcomes and subgroups

This secondary analysis will assess several outcomes and subgroups that were deemed most relevant to the overall study aim. The following outcomes will be assessed: EQ-5D-5L health utility score (longitudinal analysis), 6-min walking test and handgrip strength over the entire follow-up period (longitudinal analyses), 60-day mortality, duration of mechanical ventilation as well as EQ-5D-5L health utility scores at 30, 90 and 180 days (cross-sectional analyses). Based on the available literature, patients with acute renal failure, sepsis and non-sepsis, and severe multi-organ failure at ICU admission were identified as relevant subgroups [13,14]. Acute renal failure is determined using the Kidney Disease: Improving Global Outcome (KDIGO) criteria for acute kidney injury (AKI) as stage I or higher [15]. Sepsis is defined according to the Sepsis III criteria [16]. Severe multi-organ failure is assessed using the Sequential Organ Failure Assessment (SOFA) score [17], for which we will use the median value of the SOFA score in our patient population to dichotomize patients with severe multi-organ failure (severe multi-organ failure will be defined as patients with $\geq$ median SOFA score). Finally, Non-surviving patients will be assigned an EQ-5D-5L health utility score of 0, in agreement with the trial protocol [3].

2.10. Statistical analysis

The Bayesian analyses will be performed using dedicated software, including R (R Core Team, R Foundation, Vienna, Austria, version 4.3.1 – *R2jags* package [18,19]) and JASP (JASP team 2023, version 0.17.3, Amsterdam, the Netherlands [20]). Baseline data will be presented in the primary trial publication as specified elsewhere [3]. If prior data from previous randomized trials is available to formulate an informative (literature-based) prior, such a prior will be incorporated. When no prior trial data are available, analyses will be performed under a weakly informative prior. In addition, skeptical and enthusiastic priors will be used to assess the robustness of the results. In the following sections, the components of the Bayesian analyses will be outlined.

2.11. Priors

For each endpoint, an MCID is derived from the literature (Table 1). For all analyses, we will use weakly informative priors centered around 'no effect' (for example a mean difference [MD] of 0, or an odds ratio [OR] of 1 [0 on the log OR scale]). For the binary outcomes (ORs, denoted as the log of the OR), a mean of 0 will be applied for the weakly informative prior, while the standard deviation (SD) will be set to 3 on the log OR scale, to capture all credible effect sizes. For the continuous outcomes (on the MD scale), we aim to be consistent and reproducible, but will also allow the distributions to capture all plausible effect sizes. As such, the standard deviation (SD) will be based on a multiplication of the MCID (x100). Table 1 presents the numerical values of these weakly informative priors. Skeptical and enthusiastic priors are defined following a modification of the approach suggested by de Grooth and Elbers [21]. Skeptical priors will be centered at a mean difference (MD) or log OR of 0. The distribution will incorporate a <10% probability that the estimated treatment effect will exceed+1 MCID. Conversely, the enthusiastic priors are centered around an effect of +2 MCID, and will follow a similar distribution with a probability of <10% that estimated effect size will be lower than +1 MCID (Fig. 1).

For the cross-sectional endpoints "60-day mortality" and "duration of mechanical ventilation", informative priors could be derived from a meta-analysis of randomized trials addressing the clinical effectiveness of high protein nutrition in critical illness [22], which has recently been updated by the same authors after the publication of the EFFORT Protein trial [13]. Data from this updated meta-analysis that are relevant to the current Bayesian analysis protocol were kindly shared with us by the authors prior to publication. This meta-analysis also contains one study that reports on EQ-5D-5L [23], albeit on a survivors-only analysis. Since the PRECISe trial uses a complete-case analysis (including non-survivors), these data could not be used to formulate a reasonable literature-based prior for the estimation of the treatment effect on this outcome. Therefore, cross-sectional and longitudinal analyses of EQ-5D-5L will be performed under weakly informative priors, skeptical priors, and enthusiastic priors.

The MCIDs and informative priors for all analyses are presented in Table 1. These parameters are also included in the overarching Statistical Analysis Plan of the trial [3]. Finally, as all analyses will be performed with adjustment for the random center effect, a prior for this effect is uniformly formulated as well. These models incorporate random intercepts and the prior for these random effects follow a normal distribution with an effect centered around a mean of 0 and a large standard deviation, similar to the other priors.

If evidence from additional relevant randomized trials on high protein provision will be published before the execution of this

Table 1
Prior probability distributions and MCIDs.

Outcome	Effect size and approach	Weakly informative	Literature-based[a] (mean, SD)	MCID	Ref.
Primary outcome					
EQ-5D-5L HUI (>0)	MD, longitudinal	(0, 6.0)	NA	0.06	[3]
EQ-5D-5L HUI (0)	OR, longitudinal	(0, 3.0)	NA	0.06	[3]
Secondary outcomes					
6MWT (m)	MD, longitudinal	(0, 1900)	NA	19 m	[28]
HGS (kg)	MD, longitudinal	(0, 500)	NA	5.0 kg	[29]
Duration of MV (days)	MD, cross-sectional	(0, 100)	(-0.42, 0.30) days	1.0 days	[30]
60-day mortality	OR, cross-sectional	(0, 3.0) Log-scale, OR	(-0.02, 0.09) Log-scale, OR	5% ARD	[31]
EQ-5D-5L HUI 30 days (>0)	MD, cross-sectional	(0, 6.0)	NA	0.06	[3]
EQ-5D-5L HUI 30 days (0)	OR, longitudinal	(0, 3.0)	NA	0.06	[3]
EQ-5D-5L HUI 90 days (>0)	MD, cross-sectional	(0, 6.0)	NA	0.06	[3]
EQ-5D-5L HUI 90 days (0)	OR, longitudinal	(0, 3.0)	NA	0.06	[3]
EQ-5D-5L HUI 180 days (>0)	MD, cross-sectional	(0, 6.0)	NA	0.06	[3]
EQ-5D-5L HUI 180 days (0)	OR, longitudinal	(0, 3.0)	NA	0.06	[3]
Subgroup analyses					
EQ-5D-5L HUI Sepsis (>0)	MD, longitudinal	(0, 6.0)	NA	0.06	[3]
EQ-5D-5L HUI Sepsis (0)	OR, longitudinal	(0, 3.0)	NA	0.06	[3]
EQ-5D-5L HUI Non-sepsis (>0)	MD, longitudinal	(0, 6.0)	NA	0.06	[3,14]
EQ-5D-5L HUI Non-sepsis (0)	OR, longitudinal	(0, 3.0)	NA	0.06	[3,14]
EQ-5D-5L HUI AKI (>0)	MD, longitudinal	(0, 6.0)	NA	0.06	[3,13]
EQ-5D-5L HUI AKI (0)	OR, longitudinal	(0, 3.0)	NA	0.06	[3,13]
EQ-5D-5L HUI Severe multi-organ failure (>0)	MD, longitudinal	(0, 6.0)	NA	0.06	[3,13]
EQ-5D-5L HUI Severe multi-organ failure (0)	OR, longitudinal	(0, 3.0)	NA	0.06	[3,13]

6MWT: 6-min walking test, AKI: acute kidney injury, HGS: hand grip strength, HUI: health utility index, MCID: minimal clinically important difference, MD: mean difference, MV: mechanical ventilation, NA: not applicable, OR: odds ratio, Ref: reference, SD: standard deviation.

[a] Literature based priors are derived from an updated version of the meta-analysis of Lee et al. [22], particularly containing data from the recently published EFFORT-protein trial [13]. This update was unpublished at the time of submission of the current Bayesian protocol.

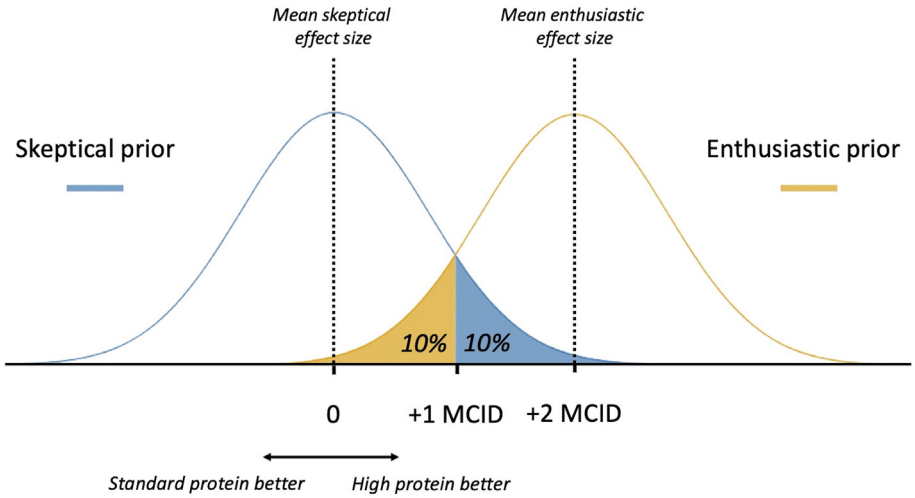

Fig. 1. Distributions of prior probabilities under a skeptical prior belief (blue) and an enthusiastic prior belief (yellow), in relation to the minimal clinically important difference (MCID).

Bayesian analysis, we will consider incorporating these data in the literature-based priors.

2.12. Presentation of results and summary statistics

Posterior distributions will be presented as MDs or mean ARDs and median OR, accompanied by 95% credible intervals (CrI), and reference to the used priors (Tables 2 and 3). Furthermore, full posterior probability distributions will be presented in dedicated grid plots, as visualized in Fig. 2.

2.13. Analysis of the primary outcome

The primary outcome is the EQ-5D-5L health utility score over the first 180 days following ICU admission. A pre-planned interim safety analysis revealed a bimodal distribution for EQ-5D-5L since non-survivors (39% during interim analysis) were attributed with a health utility score of zero. Given this mixture distribution (the component of zero, and the component other than 0) we will specify separate priors per longitudinally assessed outcome. Consequently, we will specify a prior for the mean difference with an EQ-5D-5L other than 0, and a prior for the proportion of patients who have an EQ-5D-5L score of 0 (i.e., deceased patients). This longitudinal analysis will be performed with adjustment for center as a random effect. The results of the analyses for the components will be presented separately and as weighted averages.

2.14. Analysis of longitudinally assessed secondary outcomes

Secondary outcomes for which no prior evidence was available are the 6-min walking test and hand grip strength. As such, the posterior probabilities of these outcomes will be estimated under a weakly informative prior, in a model similar to the longitudinally assessed primary outcome, with adjustment for the random effect of center. Based on these probability distributions, the probability

Table 2
Endpoints and Bayesian analyses under weakly informative priors.

	Standard protein group	High protein group	Mean Posterior ARD/MD (95% CrI)	Median Odds ratio (95% CrI)	Posterior probability of any benefit[a]	Posterior probability of clinically important benefit[b]	Posterior probability of clinically important harm[c]
EQ-5D-5L HUI[d]	##.# (#.#)	##.# (#.#)	##.# (##.#-##.#)	#.# (#.#-#.#)	##%	##%	##%
6MWT[d]	## (#) m	## (#) m	##.# (##.#-##.#)	#.# (#.#-#.#)	##%	##%	##%
HGS[d]	## (#) kg	## (#) kg	##.# (##.#-##.#)	#.# (#.#-#.#)	##%	##%	##%
Duration of mechanical ventilation	##.# (#) days	##.# (#) days	##.# (##.#-##.#)	#.# (#.#-#.#)	##%	##%	##%
60-day mortality	#.#%	#.#%	#.#% (#.#%-#.#%)	#.# (#.#-#.#)	##%	##%	##%
EQ-5D-5L HUI 30 days	##.# (#.#)	##.# (#.#)	##.# (##.#-##.#)	#.# (#.#-#.#)	##%	##%	##%
EQ-5D-5L HUI 90 days	##.# (#.#)	##.# (#.#)	##.# (##.#-##.#)	#.# (#.#-#.#)	##%	##%	##%
EQ-5D-5L HUI 180 days	##.# (#.#)	##.# (#.#)	##.# (##.#-##.#)	#.# (#.#-#.#)	##%	##%	##%
EQ-5D-5L HUI Sepsis[d]	##.# (#.#)	##.# (#.#)	##.# (##.#-##.#)	#.# (#.#-#.#)	##%	##%	##%
EQ-5D-5L HUI Non-sepsis[d]	##.# (#.#)	##.# (#.#)	##.# (##.#-##.#)	#.# (#.#-#.#)	##%	##%	##%
EQ-5D-5L HUI AKI[d]	##.# (#.#)	##.# (#.#)	##.# (##.#-##.#)	#.# (#.#-#.#)	##%	##%	##%
EQ-5D-5L HUI Severe multi-organ failure[d]	##.# (#.#)	##.# (#.#)	##.# (##.#-##.#)	#.# (#.#-#.#)	##%	##%	##%

6MWT: 6-min walking test, AKI: acute kidney injury, HGS: hand grip strength, HUI: health utility index, MD: mean difference, MV: mechanical ventilation, NA: not applicable, OR: odds ratio, Ref: reference, SD: standard deviation.

[a] ARD/MD > 0.
[b] ARD/MD > MCID.
[c] ARD/MD < -MCID.
[d] Longitudinal assessment at 30, 90 and 180 days following ICU admission.

Table 3
Bayesian sensitivity analyses under skeptical, enthusiastic, and informed priors.

Priors	Skeptical prior			Enthusiastic prior			Literature based prior		
	Mean Posterior ARD/MD (95% CrI)	Posterior probability clinically important benefit[a]	Posterior probability clinically important harm[b]	Mean Posterior ARD/MD (95% CrI)	Posterior probability clinically important benefit[a]	Posterior probability clinically important harm[b]	Mean Posterior ARD/MD (95% CrI)	Posterior probability clinically important benefit[a]	Posterior probability clinically important harm[b]
EQ-5D-5L HUI[c]	##.# (##.#-##.#)	##%	##%	##.# (##.#-##.#)	##%	##%	NA	NA	NA
6MWT[c]	##.# (##.#-##.#)	##%	##%	##.# (##.#-##.#)	##%	##%	NA	NA	NA
HGS[c]	##.# (##.#-##.#)	##%	##%	##.# (##.#-##.#)	##%	##%	NA	NA	NA
Duration of mechanical ventilation	##.# (##.#-##.#)	##%	##%	##.# (##.#-##.#)	##%	##%	##.# (##.#-##.#)	##%	##%
60-day mortality	#.#% (#.#%-#.#%)	##%	##%	#.#% (#.#%-#.#%)	##%	##%	##.# (##.#-##.#)	##%	##%
EQ-5D-5L HUI 30 days	##.# (##.#-##.#)	##%	##%	##.# (##.#-##.#)	##%	##%	NA	NA	NA
EQ-5D-5L HUI 90 days	##.# (##.#-##.#)	##%	##%	##.# (##.#-##.#)	##%	##%	##.# (##.#-##.#)	##%	##%
EQ-5D-5L HUI 180 days	##.# (##.#-##.#)	##%	##%	##.# (##.#-##.#)	##%	##%	NA	NA	NA
EQ-5D-5L HUI Sepsis[c]	##.# (##.#-##.#)	##%	##%	##.# (##.#-##.#)	##%	##%	NA	NA	NA
EQ-5D-5L HUI Non-sepsis[c]	##.# (##.#-##.#)	##%	##%	##.# (##.#-##.#)	##%	##%	NA	NA	NA
EQ-5D-5L HUI	##.# (##.#-##.#)	##%	##%	##.# (##.#-##.#)	##%	##%	NA	NA	NA
AKI[c]									
EQ-5D-5L HUI	##.# (##.#-##.#)	##%	##%	##.# (##.#-##.#)	##%	##%	NA	NA	NA
Severe multi-organ failure[c]									

6MWT: 6-min walking test, AKI: acute kidney injury, HGS: hand grip strength, HUI: health utility index, MD: mean difference, MV: mechanical ventilation, NA: not applicable, OR: odds ratio, Ref: reference, SD: standard deviation.

[a] ARD/MD > 0.

[b] ARD/MD > MCID. ***ARD/MD < -MCID.

[c] Longitudinal assessment at 30, 90 and 180 days following ICU admission.

of clinically important benefit and harm will be estimated (Tables 2 and 3).

2.15. Analysis of outcomes at one given timepoint

Secondary binary outcomes, such as 60-day mortality, will be expressed in ORs and absolute risk differences (ARD). These binary outcomes will be analyzed in a binary mixed regression model (Bernoulli distribution) with an adjustment for the random center effect. Priors for these binary outcomes are presented on the log OR scale in Table 1. Other secondary continuous outcomes, such as the duration of mechanical ventilation, will be reported in mean difference (MD) for the specific units of that endpoint. Also for these analyses, the posterior probabilities of a clinically meaningful benefit and clinically important harm will be estimated (Tables 2 and 3). Finally, the same mixture distribution (the component of zero, and the component other than 0) will be used for the EQ-5D-5L assessment at the cross-sectional timepoints, and separate priors will be formulated, similar to the primary outcome assessment.

2.16. Handling of missing data

As the missingness of data is assumed to be missing at random (MAR), the linear mixed effects model will be appropriate to handle missing data, in agreement with the protocol for the frequentist analysis of our study [3].

2.17. Model settings and diagnostics

The models for our analysis will be implemented in *JAGS* using Markov Chain Monte Carlo (MCMC) algorithms, through the *R2jags* package [18,19]. Assessment of model convergence will be performed for key model parameters via potential scale reduction factors (Rhat) effective sample size (ESS), and other diagnostics such as density and trace plots. Model fit will be assessed in relative terms through the deviance information criterion (DIC and other criteria alike), and in absolute terms by use of posterior prediction checks (PPCs).

3. Discussion

The clinical effectiveness of high protein nutrition in critically ill patients is unclear. Observational data suggest a strong association between enhanced protein intake and improved outcome [24,25]. Still, a recent meta-analysis of RCTs showed that higher protein had no statistically significant effect on clinical and functional outcomes [22]. A subsequently published multicenter RCT - the EFFORT protein trial - also failed to show a positive effect of high protein nutrition on clinical outcomes, and even suggested potential harm in patients with acute kidney injury - without dialysis - and in patients with very severe multi-organ failure [13]. The PRECISe trial differs in several aspects from the EFFORT protein trial. Protein targets are covered by a specific enteral formula, whereas the mode of protein administration was left at the discretion of treating clinicians in the EFFORT protein trial. In addition, the EFFORT protein trial used a registry based, clinical primary endpoint, while the PRECISe trial applies individual prospective follow-up and uses a functional outcome measure, as the primary endpoint [3]. The TARGET protein trial, performed by the ANZICS group is another large study addressing high protein nutrition in critical ill patients, and uses formula based study feeds that are identical to the PRECISe trial, but also apply registry based outcome assessment [26]. The current protocol provides the possibility to incorporate results from the TARGET protein trial into the literature-based priors of the

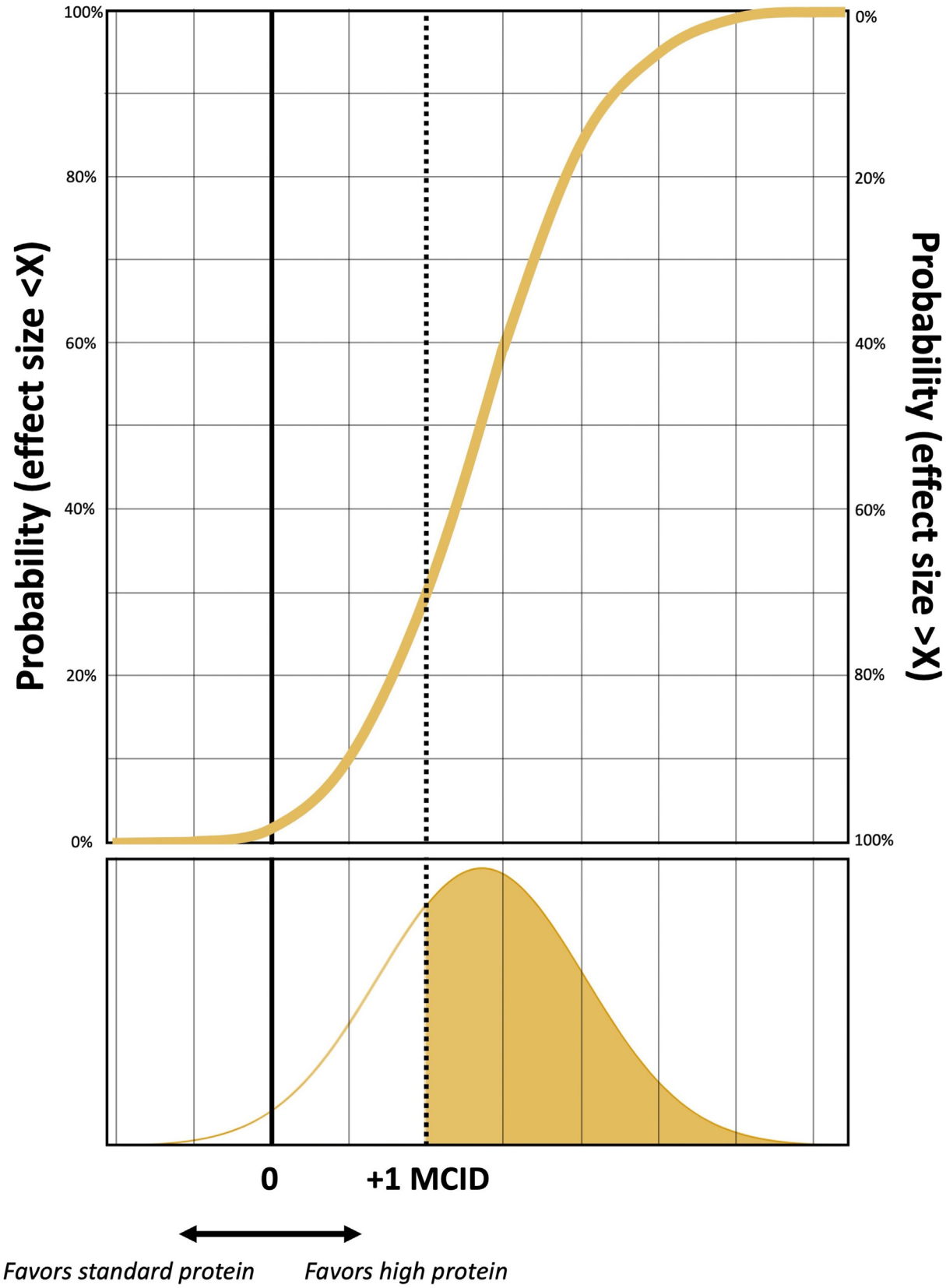

Fig. 2. Mock figure for graphic representation of full posterior probability distributions.

Bayesian analysis of the PRECISe trial, if published before the execution of this Bayesian analysis.

The PRECISe trial is powered to detect a minimum clinically important difference using frequentist statistics. The outlined, pre-planned, secondary Bayesian analysis will therefore complement the primary analysis, particularly by facilitating the probabilistic interpretation of secondary outcomes and subgroup analyses. These analyses frequently lack statistical power to detect clinically meaningful treatment effects using frequentist inference. As such, Bayesian analyses may help clinicians and researchers to more clinically intuitively interpret the results, and further guide clinical practice and future research.

Apart from the possibility to facilitate interpretation of small and potentially underpowered datasets, Bayesian inference incorporates prior knowledge, thereby integrating new and existing evidence, and can estimate the posterior probability of a given effect size. In this particular case, we have planned to integrate the knowledge of an updated meta-analysis, incorporating topical trial data with the results from the PRECISe trial. These integrated data will shed further light on the role of high protein in nutrition on functional outcomes in critical illness, and on the risks and benefits of high protein nutrition in patients with acute kidney injury, sepsis, and severe multi-organ failure.

In addition to the incorporation of informative literature-based priors, enthusiastic and skeptical priors will be incorporated to evaluate the robustness of our trial's results. These theoretical priors represent a physician's belief with either an enthusiastic or a skeptical attitude towards the effectiveness of an intervention. We defined skeptical priors that resemble the attitude of skeptical physician who beliefs that there is probably no effect of a certain treatment, and no more than 10% probability of a clinically important clinical benefit [21]. This skeptical prior estimates that there is a 50% prior probability that there is any harm (not necessarily clinically meaningful) related to the intervention, which is in line with the suggestion by some investigators that high protein may not be beneficial and even be harmful in critical illness [2,27]. Conversely, we hypothesized that an enthusiastic physician holds a belief that there is a >90% probability that the effect size of an intervention exceeds the threshold for clinicalmeaningfulness.

3.1. Strengths and limitations

The proposed study has several strengths in addition to the general strengths of the PRECISe trial, that are outlined in the primary protocol [3]. Secondary Bayesian analyses of randomized trials are at risk of confirmation bias, as many of these analyses are conducted after trial results are known. Therefore, the current protocol was drafted and submitted prior to the database lock of the study, and results were therefore not yet available. This approach provides the least biased method to propose the protocol for a secondary Bayesian analysis of a trial. Consequently, the endpoints, priors, and MCIDs were defined in an objective fashion. To avoid multiplicity, a limited number of outcome parameters were selected for this Bayesian post-hoc analysis. Apart from the primary endpoint (EQ-5D-5L over time) and a breakdown of EQ-5D-5L at the various follow-up moments, we selected relevant physical tests (6 min walking test, and handgrip strength) that are prone to type II error in the frequentist analysis. In addition we selected several relevant and frequently reported clinical outcome measures (duration of mechanical ventilation, 60 day mortality) to make optimal use of prior knowledge, in line with the principles of Bayesian inference.

A limitation of our approach is the scarcity of high-quality data that can be used to inform priors. Consequently, informative priors are only used to assess the results for a limited number of outcome parameters. Due to heterogeneity in the data underlying these priors, the comparability with the current study - and hence the appropriateness of the informative priors - may be reduced.

3.2. Conclusion

The proposed secondary, pre-planned Bayesian analysis of the PRECISe trial will provide additional information on the effects of high-dose dietary protein on functional and clinical outcomes in critically ill patients. It will complement the interpretation of primary and secondary endpoints, and of prespecified subgroup analyses. Finally, the incorporation of informative data will lead to an integration of all available evidence.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2023.10.040.

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