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Opinion Paper

First international meeting of early career investigators: Current opportunities, challenges and horizon in critical care nutrition research

Christian Stoppe [a, *], Robert van Gassel [b, c], Joop Jonckheer [d], Maria Eloisa Garcia Velasquez [e], Filippo Giorgio Di Girolamo [f], Sebastian Pablo Chapela [g, h], Sanit Wichansawakun [i], Albert Albay Jr. [j], Tim Friede [k], Robert Martindale [l], Mette M. Berger [m]

[a] Department of Anesthesiology, Intensive Medicine and Pain Therapy, University Hospital Würzburg, Germany
[b] Department of Intensive Care Medicine and Surgery, Maastricht University Medical Centre, Maastricht, the Netherlands
[c] NUTRIM School for Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, the Netherlands
[d] Department of Intensive Care Medicine, University Hospital of Brussels, Brussels, Belgium
[e] Department of Clinical Nutrition, San Francisco Clinic Hospital, Guayaquil, Ecuador
[f] Department of Medical Surgical and Heath Science, Cattinara Teaching Hospital, University of Trieste, Italy
[g] Universidad de Buenos Aires, Facultad de Medicina, Departamento de Bioquímica Humana, Argentina
[h] Hospital Británico de Buenos Aires, Servicio de Terapia Intensiva, Argentina
[i] Division of Clinical Nutrition, Department of Internal Medicine, Faculty of Medicine, Thammasat University, Pathumthani, Thailand
[j] Division of Pulmonary Medicine, Department of Medicine, Philippine General Hospital, University of the Philippines Manila, Philippines
[k] Department of Medical Statistics, University Medical Center Göttingen, Göttingen, Germany
[l] Department of Surgery, Oregon Health and Science University, Portland, OR, USA
[m] Department of Adult Intensive Care Medicine and Burns, Lausanne University Hospital CHUV, Lausanne, Switzerland

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SUMMARY

Background: Appropriate nutritional support is a key component of care for critically ill patients. While malnutrition increases complications, impacting long term outcomes and healthcare-related costs, uncertainties persist regarding optimal provision of nutritional support in this setting.
Methods: An international group of healthcare providers (HCPs) from critical care specialties and nutrition researchers convened to identify knowledge gaps and learnings from studies in critical care nutrition. Clinical research needs were identified in order to better inform future nutrition practices.
Results: Challenges in critical care nutrition arise, in part, from inconsistent outcomes in several large-scale studies regarding the optimal amount of calories and protein to prescribe, the optimal time to initiate nutritional support and the role of parental nutrition to support critically ill patients. Furthermore, there is uncertainty on how best to identify patients at nutritional risk, and the appropriate outcome measures for ICU nutrition studies. Given HCPs have a suboptimal evidence base to inform the nutritional management of critically ill patients, further well-designed clinical trials capturing clinically relevant endpoints are needed to address these knowledge gaps.
Conclusions: The identified aspects for future research could be addressed in studies designed and conducted in collaboration with an international team of interdisciplinary nutrition experts. The aim of this collaboration is to address the unmet need for robust clinical data needed to develop high-quality

Abbreviations: EE, energy expenditure; EN, enteral nutrition; HCP, healthcare provider; ICU, intensive care unit; MNA, Mini Nutritional Assessment (MNA); MST, Malnutrition Screening Tool; MUST, Malnutrition Universal Screening Tool; NRS-2002, Nutrition Risk Screening; PN, parenteral nutrition; RCT, randomized controlled trial; SGA, Subjective Global Assessment; SNAQ, Short Nutritional Assessment Questionnaire.

* Corresponding author. Departement of Anesthesiology, Intensive Medicine and Pain Therapy University Hospital Würzburg, Germany.
E-mail address: christian.stoppe@gmail.com (C. Stoppe).

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evidence-based nutritional intervention recommendations to better inform the future management of critically ill patients.

1. Introduction

Despite nutrition support being captured in basic care bundles as a crucial component of critical care, many critically ill patients fail to receive adequate nutritional intake [1]. Protein and energy deficiencies are reported in 43–88% of critically ill patients [2,3], and malnutrition is associated with increased rates of complications, prolonged stay in the intensive care unit (ICU) and negatively impacts mortality [4–8]. It stands to reason that improving the nutritional care of ICU patients can lead to improved clinical outcomes. Indeed, adequate nutritional support has been shown to result in more patients being discharged to home rather than transferred to rehabilitation or nursing facilities [9].

However, uncertainty persists regarding the optimal nutritional support for critically ill patients [10–12]. For example, it remains unclear how best to identify patients likely to benefit from artificial feeding. Further clarification is also required on the role of parenteral nutrition (PN) as well as the optimal time to start enteral nutrition (EN) or PN support in this setting. These uncertainties are due, in part, to heterogeneous results from small numbers of large-scale randomized controlled trials (RCTs) which limit interpretation for nutrition guidelines in this setting. Furthermore, guideline recommendations are frequently based on outcomes from individual clinical studies of varying quality, which impacts the strength of evidence [11,12]. Indeed, limited high quality data underscores the need for new, well designed multicentre studies that accurately capture the medical needs and perspectives of critically ill patients in order to address the nutritional knowledge gaps and optimize care. Given the substantial cost and time associated with clinical trials, improved understanding of the challenges and limitations associated with previous studies may provide insight for planning future study protocols. The aim of this paper is to summarize the outcomes of these discussions, focussing on how the identified knowledge gaps can best addressed in future studies, and the challenges and opportunities facing researchers in critical care nutrition.

2. Methods

An international group of 23 multidisciplinary healthcare providers (HCPs) and nutrition researchers from Europe, North America, South America, Asia and South Africa convened during a 4-day meeting focussed on clinical controversies in critical care nutrition (Fig. 1). Participants of this focus group were involved in the care of critically ill patients and comprised early career intensivists, anaesthesiologists and dieticians, as well as senior experts and researchers in critical care nutrition, statistics and clinical trial design. The participants of this open meeting were selected based on their applications which underwent a rigorous review process by an independent international committee of senior experts in the field.

Knowledge gaps in critical care nutritional support and learnings from studies in this setting were identified in an open exchange during the first day of the meeting based on the participants' day-to-day clinical experiences and a non-systematic search of PubMed for relevant English-language publications (clinical studies in critical care nutrition and international guidelines on critical care nutrition).

3. Key areas of uncertainty: limitations in current clinical studies

The focus group identified several areas of uncertainty regarding the provision of nutritional support to ICU patients. These include how best to accurately assess the nutritional needs of clinically diverse patients, and clarification of the energy and protein requirements of these individuals. Knowledge gaps also exist regarding the optimal time to initiate nutritional support with consideration of the endogenous energy production, the complex clinical requirements of critically ill patients, and lack of clarity on the role of PN in this setting. These uncertainties largely stem from insufficient clinical evidence, and potential opportunities to address these points to better inform clinical practice are discussed.

3.1. How should nutrition risk be assessed?

Although recommended in nutrition guidelines as key components of care for critically ill patients, nutrition screening and assessment are largely under-recognized and not standardized in clinical practice, world-wide [11,12]. Measuring the patient's current nutritional status using established nutrition scores may identify undernourished individuals. However, identifying patients who may benefit from nutritional support due to anticipated changes in their nutritional status as well as situations where nutritional intervention may be deleterious, are challenging. While numerous nutritional assessment and screening tools are available, such as the Malnutrition Universal Screening Tool (MUST), Mini Nutritional Assessment (MNA), the Short Nutritional Assessment Questionnaire (SNAQ), the Malnutrition Screening Tool (MST), and the Subjective Global Assessment (SGA), many are excessively complex and time consuming to perform, and therefore difficult to implement during routine clinical practice. Furthermore, no nutritional screening tools have been validated for use in critically ill patients [13]. However, while nutritional risk determined in Nutrition Risk Screening (NRS-2002) and NUTRIC scores largely depends on disease severity, suggesting all ICU patients would be categorized as having high nutritional risk [14–17], NRS-2002 scores were recently shown to identify long-stay critically ill patients at highest risk of poor outcome when exposed to underfeeding [18]. Notably, the NUTRIC score has been criticized for not including nutritional parameters, and a recent explorative *post hoc* analysis failed to confirm its value: among patients identified with high and low nutritional risk, permissive underfeeding with full protein demonstrated similar outcomes as standard low feeding [19]. In contrast, two prospective nonrandomized studies demonstrated that patients with high nutrition risk (assessed using NRS-2002 and NUTRIC) significantly benefit from an early enteral nutrition (EN), resulting in improved outcome and reduced nosocomial infection compared with patients at low nutrition risk [16,20]. Further studies are needed to understand the clinical utility of the NUTRIC Score by evaluating additional outcomes.

Fig. 1. HCPs involved in the nutritional care of critically ill patients who contributed to this analysis.

As an alternative to nutrition risk assessment tools, the prediction of prolonged ICU stay may be a promising approach to identify patients at risk for underfeeding. Faisy et al. demonstrated that negative energy balance increases with duration of ICU stay, being particularly relevant during prolonged mechanical ventilation, in patients fed according to a standard nutritional management protocol [21]. In the absence of validated screening tools for use in the ICU, ESPEN guidelines recommend a pragmatic approach to classify critically ill patients at risk of malnutrition using the NRS-2002, including individuals staying in the ICU for more than 48 h, as well as those receiving mechanical ventilation, with infection, underfed for more than 5 days, and/or presenting with a severe chronic disease [12].

The investigators agreed that prospectively validated nutrition assessment tools are urgently needed to identify ICU patients who may either benefit from nutrition support, may show neutral effects or for whom intensive nutrition support may be detrimental.

3.2. *What are the energy and protein requirements of critically ill patients?*

The gold standard to determine resting energy expenditure for nutritional therapy is indirect calorimetry [12]. Predictive equations have shown to be inaccurate leading to important over- and underestimation of REE [22,23]. This is probably due to the fact that intensive care patients are a heterogeneous group. For an example, different therapies such as hypothermia or CRRT can have an influence on metabolism [24–26]. This suggests that weight is not the only parameter that has to be taken into account when building formula to predict energy need. However the evidence to support a beneficial effect of using IC over predictive equations is scarce [22]. Therefore, nutrition guidelines based on available data and expert opinion indicate that in the absence of IC, simple body weight-based equations (20-25 kcal/kg/d) or predictive equations can be used to calculate the caloric targets [11,12].

Carbon dioxide consumption (VCO_2) data obtained from mechanical ventilators has also been suggested as a tool to calculate resting energy expenditure (EE) in critically ill patients. However, prospective trials examining VCO_2 and resting EE are needed, given poor agreement between these parameters was reported in a retrospective observational study [27]. While resting EE tends to be higher in critically ill patients compared with healthy individuals, guidelines recommend that nutrition support should be gradually increased during acute illness in order to prevent overfeeding, with the aim of reaching no more than 70% of EE in the early phase, increasing to 80–100% of EE after day 3 [12]. While under- and overfeeding have both been associated with delayed recovery and increased mortality [28,29], further clarification is required, given a systematic review found overfeeding did not increase mortality in enterally fed, critically ill patients [30]. However, as this review included an unusual definition of overfeeding (energy delivery > 2000 kcal/day, > 25 kcal/kg/day, or ≥ 110% of energy prescription) these results need to be interpreted cautiously and the clinical significance of both under- and overfeeding should to be clearly evaluated in well designed clinical studies.

Clarification is also needed regarding the use of body weight to calculate resting EE in equations. For example, it is not known if body weight considerations should differ for underweight and overweight critically ill patients and take into account body composition, including the contributions of muscle and fat mass to energy requirements. Data from well-designed RCTs are needed to further inform the time-dependent caloric needs of diverse critically ill patients during the different phases of critical illness and enable a more individualized, flexible and precise caloric delivery.

In critically ill patients, bed-rest and inflammation are key factors altering protein catabolism, defined by low protein synthesis and high protein breakdown [31–34]. While protein catabolism is an adaptive metabolic response to meet the demands of severe injury or physical stress, it can lead to negative outcomes including loss of total body protein, sustained weakness persisting up to a

year following hospital discharge and higher risk of morbidity and mortality [10,32–34]. Consequently, there is considerable attention on protein goals in nutritional support. Elevated amino acid requirement observed in ICU patients is largely due to anabolic resistance and higher protein synthesis rates supporting tissue repair and the acute-phase response [31–34]. However, only limited data are available from prospective, randomized interventional trials evaluating the clinical benefits of protein delivery on outcomes in critically ill patients.

Clinical guidelines for ICU care suggest patients receive a protein intake in the range of 1.2–2.0 g/kg/day [11,12], with the aim of improving clinical outcomes and lowering mortality rates [35–38]. In RCTs, administration of amino acids or protein (in mixed-nutrient supplements with fixed protein/energy ratios) above the recommended levels was strongly associated with unfavourable outcomes including increased duration of hospitalization and consequently greater muscle wasting [10,39–41]. Moreover, it is speculated that higher nutrient intake may counteract autophagy, which facilitates clearance of damaged sub-cellular particles and pathogens in patients with sepsis [10,42]. Of note, a prospective study of 843 critically ill medical and surgical patients on prolonged mechanical ventilation (>72 h) found the impact of protein and energy provision (Day 4 of ICU admission) on outcomes was influenced by the patients' clinical condition [38]. High protein intake was associated with lower mortality rates in non-septic, non-overfed (ratio energy intake: EE < 1.1) patients. In contrast, in patients with sepsis and those who were energy overfed, higher protein intake did not appear to impact mortality rates [38]. While this study provides useful insight, adequate evidence is lacking to inform protein requirement in specific patient subgroups, for example for critically ill patients who are underweight and overweight patient with low skeletal muscle mass. Nevertheless, despite uncertainty regarding the optimal dose of protein in ICU patients, recent guideline updates advocate higher protein goals, compared with previous recommendations, underscoring the importance of adequate protein delivery in this setting [11,12].

The investigators agreed that further studies are urgently needed to clarify which patient subgroups may benefit from high protein intake along with the timeframe to achieve protein goals. Furthermore, the impact of protein type/nutritional support **product on clinical outcomes requires further investigation**.

3.3. What is the optimal time to start nutrition support?

Identifying the optimal timing to commence nutrition support in critically ill patients is clearly of high priority. Guidelines define the different phases of critical illness as 'ebb' and 'flow', reflecting the hyperacute early phase of hemodynamic instability and the subsequent post-acute period of improvement and rehabilitation or stabilized catabolic state [12] However, the mechanisms underlying these phases in critically ill patients remains poorly defined and require further investigation. Guidelines recommend that critically ill patients should receive early feeding (within 24–48 h) via the enteral route when feasible [11], as this is associated with reduced risk of complications, resulting in a decreased length of stay and mortality [28]. Current guidelines also recommend delaying EN in patients with hemodynamic instability [11], although this may result in increased infectious complications, underfeeding, muscle wasting and ultimately worse outcomes. As both rapid and delayed initiation of nutritional support have been associated with poor outcome, it remains controversial whether early nutritional intervention may have beneficial or deleterious effects in the acute phase of critically ill patients [43,44].

Future studies are needed to identify the optimal timing for nutritional support provision, the optimal route (EN vs. PN or combined concepts), which should take into consideration the clinical condition of critically ill patients.

3.4. What is the role of PN within the nutritional tool box for critically ill patients?

Current international guidelines uniformly recommend EN as the preferred route of feeding ICU patients as this may promote the gut mucosal proliferation, maintain gastrointestinal integrity, attenuate inflammatory stress, promote microbiome stability and reduce the occurrence of infectious complications [11,12]. These effects may ultimately lead to a shorter duration of stay in ICU and hospital, as well as a reduced overall mortality [45,46]. Nevertheless, studies indicate that EN is often withheld or initiated following a significant delay after ICU admission [47–49]. This may lead to significant protein and calorie deficits and negatively impact clinical outcomes, particularly during the patient's first week in ICU [50,51]. Importantly, EN alone often cannot achieve nutrition targets within the recommended timeframe, often due to hemodynamic instability during the initial phase of acute illness or gastrointestinal intolerance [52,53]. Furthermore, while several smaller studies have reported the safety and feasibility of EN, it is contraindicated in patients requiring high levels of vasopressor support, as it may alter intestinal perfusion and increase the risk of gastrointestinal complications such as bowel ischemia [54].

Two large, multicentre RCTs, CALORIES and NUTRIREA-2, challenge the paradigm that EN is superior to PN with respect to clinical outcomes in critically ill patients. In CALORIES, a pragmatic RCT, over 2,300 patients were randomized to receive either total PN or EN (25 kcal/kg per day) within 36 h of ICU admission for up to 5 days [55]. No significant differences in 90-day mortality or infectious complications were reported between PN- and EN-fed patients, supporting the safety of PN in critically ill patients [55]. The NUTRIREA-2 trial included 2410 critically ill ICU patients receiving invasive mechanical ventilation and requiring vasopressor support for shock who were randomly assigned to receive PN or EN (20–25 kcal/kg per day) within 24 h after intubation [56]. Similarly, in this study EN did not reduce 28-day mortality or the risk of secondary infections compared with PN. However, early isotonic EN was associated with an increased risk of digestive complications such as vomiting, diarrhoea and colonic pseudo-obstruction compared with early isocaloric PN [56]. Furthermore, in the extension phase of NUTRIREA-2, a statistically significant increase in mild gastrointestinal complications (bowel ischemia not requiring surgery) was observed in patients who received early EN versus PN. While no difference in rates of bowel ischemia was observed between EN and PN groups in the CALORIES trial, which included a cohort of less severely ill patients compared with NUTRIREA-2, a significant reduction in hypoglycaemic events was noted in the PN group [55]. Together, data from these large-scale RCTs support the use of PN in ICU patients, including individuals receiving ventilator and vasopressor support, and suggest a potential for clinically meaningful safety advantages compared with EN. Importantly, given data from NUTRIREA-2 indicated PN was more effective than EN for achieving nutrition goals, this calls into question clinical guideline recommendation of EN as the first-line nutritional intervention for ICU patients unable to eat [11,12].

PN is increasingly considered a promising bridging strategy to provide adequate nutritional support when full dose EN is administered progressively. Indeed, progression of EN to full dose can often take several days due to intestinal intolerance and require interruptions [52,53]. This highlights an important role for PN in reducing protein-calorie deficits in critically ill patients. Guidelines

advocate PN is initiated in combination with EN in patients for whom nutritional goals cannot be achieved with EN alone [11,12]. This is supported by several RCTs which found supplemental PN and combined PN and EN to be clinically useful interventions for critically ill patients [40,57–59].

The investigators identified the need to clarify the roles of EN, PN and combined EN and PN across different subgroups of critically ill patients. This will facilitate specific guidance on how route of administration of nutritional support should be tailored for individual patients.

4. Selecting optimal outcomes in nutrition studies

Selecting the optimal outcome measure is an essential component of all clinical research. However, this can be particularly challenging when designing clinical nutrition studies, demonstrated by the heterogeneous outcomes used in recent RCTs examining nutritional interventions in critically ill patients [60]. While a broad array of outcome measures are available (Table 1), the majority of RCTs in critical care nutrition focus on 'hard' clinical outcomes such as mortality, length of hospital stay and rates of infection and/or complications [40,61]. While 'hard' clinical outcomes are relatively easy to measure and clearly defined, few studies of critically ill patients utilizing these endpoints have been able to detect a significant impact of nutritional interventions [40]. This is likely because the large sample size required to demonstrate statistical significance with such endpoints is often unfeasible in this setting. Furthermore, 'hard' clinical endpoints may not represent the most biologically meaningful outcomes for nutritional interventions in the ICU [62].

Physiological and metabolic outcome measures, such as plasma metabolites or metabolic fluxes measured using stable isotope tracers, have also been used to investigate the effects of nutritional interventions in critically ill patients [63–65]. While a key advantage of these endpoints is the relatively small sample size required to detect an effect, a positive effect on a metabolic outcome measure may not necessarily translate into a clinical benefit and therefore confirmation in a larger follow-up study may be required. Indeed, physiological and metabolic endpoints are often used to demonstrate the physiological rationale or mechanism of an intervention [63–66]. Of note, muscle-related outcome measures are emerging which may, in part, bridge the gap between physiological and 'hard' clinical endpoints [62]. Based on the physiological rationale that adequate nutrition can potentially ameliorate muscle wasting [67], these endpoints measure different aspects of muscle quantity and quality including muscle imaging or biopsies to determine muscle mass and structure [68,69], standardized tests for muscle strength and condition [70], and questionnaires on physical function [71]. Although muscle-related outcomes show promise, their use in prospective nutritional trials so far is limited [71–73]. Furthermore, these outcomes are more labour intensive than most clinical endpoints and are not routinely measured in clinical practice. For muscle-related endpoints to be applied to clinical studies, further understanding of their relationship to harder, clinically relevant endpoints and the potential role as surrogate endpoints is needed [65,74]. This will require outcomes not only to be correlated at the patient level but also an understanding of how the effects of an intervention translate from muscle-related outcomes to clinical endpoints.

Recognizing that many measurements used in clinical trials fail to capture patients' perspectives following discharge from hospital [75], increasing attention is directed towards evaluating patient-reported outcome measures following hospital discharge [76–78]. However, similar to muscle-related outcomes, there is limited experience on these outcome measures in prospective, randomized studies in critically ill patients. Nevertheless, measurement of traditional ICU outcomes should always be considered in clinical trials of nutritional interventions in critically ill patients, including duration of mechanical ventilation, ICU-acquired infections, ICU re-admission, re-intubation, duration of ICU and hospital stay, time to hospital discharge, mortality rates at different time points, and resumption of prior activities.

While the optimal outcome measure for clinical studies investigating nutritional support in ICU settings may vary depending on the study objective, phase (proof-of-concept to confirmatory trial), methodology, type of intervention and study population, heterogeneous outcome measures used in nutritional trials can limit comparisons between different studies. The creation of a 'core

Table 1
Potential outcome measure for studies of nutritional interventions in critically ill patients.

	Outcome type			
	Physiological/metabolic	Clinical	Functional/muscle	PROMs
Examples of endpoints	• Plasma biomarkers or metabolites • Stable isotope tracers	• Mortality • Infection rate • Duration of hospital stay	• Handgrip strength • 6-Minute walk test • Muscle mass (assessed by imaging)	• HRQoL • Time to return to work • Time to independent living
Anticipated sample size	Small	Large/very large	Medium	Unknown
Strengths	• Requires small sample size • May detect small(er) effects	• May demonstrate clinical value • Potential impact on clinical practice	• May detect more subtle effects than clinical endpoints • Closer alignment with clinical effect than metabolic endpoints	• Relevant for patients and HCPs
Limitations	• Does not demonstrate clinical effectiveness or superiority	• Requires large sample sizes • Multi-factorial endpoint, not only affected by nutrition	• Labour intensive data collection • Limited experience • Lack of 'clinically relevant' cut-off values	• Limited experience in intervention studies • Subjective measure
Anticipated timing of assessment	During intervention	During ICU/hospital stay	After intervention	Long term (months/years following intervention)

HCPs, healthcare providers; HRQoL, health-related quality of life; ICU, intensive care unit; PROMs, patient-reported outcome measures.

outcome set' with an accompanying endpoint instruments may help to address this issue. For example, in acute respiratory failure, a core outcome set is available which includes clinical, functional and patient-reported outcome measures [79]. More research is needed to determine the utility and robustness of a core outcome set for nutritional intervention studies.

Finally, there are challenges regarding the access to equipment to measure physiological and metabolic outcomes as well as identifying the optimal timing to assess the primary outcome in clinical trials of ICU nutritional interventions, particularly in early phase clinical trials. While assessment immediately after ICU discharge, when the patient has recovered from acute aspects of critical illness, may facilitate the effects of an ICU-based intervention to be detected, outcomes capturing the patient-perspective outcomes are suited to a longer time frame which presents logistical challenges. For the latter scenario, endpoint assessment after ICU discharge but prior to hospital discharge would avoid some practical challenges.

The investigators agreed that validated, standardized endpoints to assess the impact of nutritional interventions in critically ill patients are needed, which are illustrated in Table 1. Such outcome measures should be patient-centric, reliable, accurate and simple to undertake in order to minimize bias. Interventions should also have a positive impact on quality of life following critical illness, which needs to be assessed adequately.

5. Further lessons from critical care nutrition studies

Due to the ever growing number of studies in critical care nutrition, HCPs are faced with an overwhelming task of sorting through available literature to find quality evidence to inform their clinical decisions. While national and international guidelines provide helpful direction, these can be limited by the timing of publication, as well as heterogeneity among the populations studied and the definitions of illness severity in the RCTs on which recommendations are based [11,12]. Furthermore, inconsistencies and heterogeneity in reporting outcomes can also limit the ability to interpret existing data, as highlighted by a meta-analysis [80], which is relevant for the development of treatment guidelines [80].

Methodological weakness among many studies also limits the generalization of available data to routine clinical practice. This is illustrated by EPaNIC, a RCT comparing early and late PN to supplement insufficient EN in ICU patients [81]. In this study, patients randomized to early PN group received intravenous (IV) glucose (20% solution) on ICU days 1 and 2, with PN initiated on day 3 (100% caloric targets through combined EN and PN) while the late PN group received IV glucose (5% solution) on day 1, EN on day 2, with PN initiated on day 8 if deemed necessary to reach caloric goals [81]. Of note, blood glucose was tightly controlled in all patients in this study using a protocol based on intensive insulin therapy [82], which has since been shown to have poor efficacy and increase mortality [83], and is not part of current clinical practice worldwide, so that the results obtained from this study should be interpreted cautiously [81]. Standardized protocols or clear recommendations on the control of metabolic tolerance are needed to guide clinical practice based on data from large-scale confirmatory multicentre trials [84].

The Early PN Trial investigating the effects of early PN ($\leq$24 h following ICU admission) in critically ill patients with short-term contraindications to EN was also associated with methodological challenges [39]. While this study did not demonstrate a significant impact of early PN versus standard care on 60-day mortality rate (primary endpoint), early PN was associated with reduced duration of ventilation as well as reduced muscle wasting and fat loss [39]. However, non-protocolized use of PN in some control group patients may have impacted outcomes, while early termination of the study due to slow recruitment may have increased the chance of a false positive result [39].

Although few clinical studies demonstrate neutral or harmful effects of nutritional interventions in critical care, methodological weaknesses limit the interpretation of some data. Consequently, further well designed studies are needed, including pragmatic trials with outcomes that can be generalized and applied as established procedures in routine practice settings worldwide.

5.1. What can we learn from the statistician?

Randomization and blinding are key techniques to minimize the risk of bias in clinical trials, with RCTs being the gold standard for evaluating interventions. Randomly allocating patients to the interventions being compared minimizes bias due to differences in demographic and clinical characteristics. Stratification of the randomization for important prognostic factors should also be considered, and typically includes the study site in multicentre trials. By blinding (or masking) the treatment allocation, bias related to the perceived impact of treatment on outcome assessments can also be avoided. Blinding can be applied on different levels, including patient (single blinding) or patients and HCPs (double blinding). With the latter, typically the trial management team is also unaware of the treatment allocations while the study is ongoing (sometimes referred to as triple blinding).

Appropriate study design can reduce the risk of study results being inconclusive. Such planning typically includes power and sample size calculations which are generally straightforward to carry out using specialized software. Critical aspects in determining the population size required for a trial include the size of a clinically relevant effect on the primary endpoint, variability of the endpoint and the anticipated rate of the outcome in the control group. Inaccurate determination of these factors can result in inappropriately sized trials. However, adaptive trial designs, including group sequential designs or designs with sample size re-estimation, can mitigate these risks to some extent [85]. As the follow-up time of individual patients in critical care nutrition studies is often relatively short compared with the recruitment period, studies in this setting lend themselves very well to adaptive designs.

Heterogeneity of the patient population can also be challenging in nutrition trials and identifying patients who are most likely to benefit from a particular intervention is highly relevant. Therefore, selecting appropriate inclusion and exclusion criteria is another key aspect in the design of an ICU clinical nutrition study. If eligibility criteria are set too wide, considerable patient variability may making it difficult to detect an effect of the study intervention, while narrow eligibility criteria may prevent the generalizability of the results to wider patient populations. Adaptive enrichment designs can sometimes provide a useful middle ground. These studies allow for flexibility, enabling patient recruitment to be refined if the intervention effects appear to be more pronounced in prespecified subgroups. However, adaptive designs require careful planning including trial simulations [86]. Input from experienced trialists and statisticians is important to achieve the most appropriate trial design to permit adequate development of an adaptive clinical trial.

6. International, multidisciplinary collaboration to facilitate interventional and pragmatic studies

In order to maximise the clinical utility of the recommendations identified during the 4-day educational meeting, the investigators agreed to establish a communication platform to facilitate knowledge exchange, communication and collaboration for future

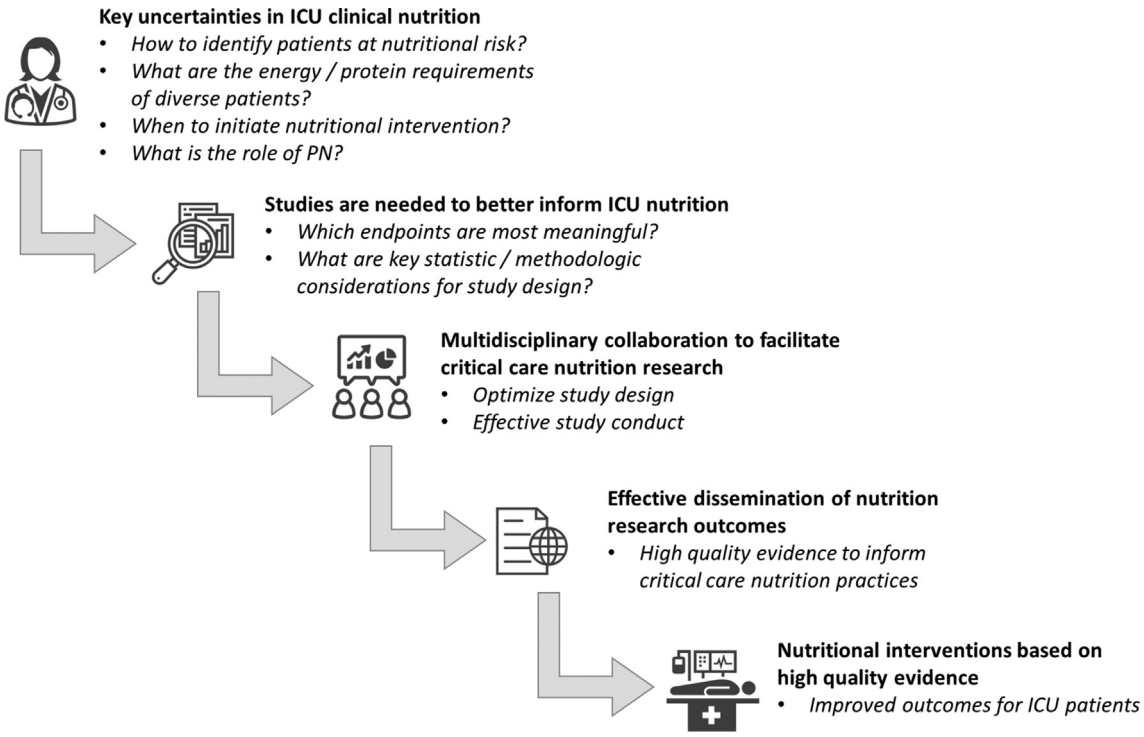

Fig. 2. Roadmap for generating robust evidence-based guidance to inform critical care nutrition. ICU, intensive care unit, PN, parenteral nutrition.

interventional and pragmatic studies in critical care nutrition. It was proposed that a coordinating committee be established to provide technical assistance and practical advice on how to conduct multinational clinical studies in the most effective way. Nominated national coordinating investigators would be responsible for disseminating planned activities in line with national guidelines and liaise with authorities to ensure national regulations are met. The investigators also agreed that study proposals should be presented and critically reviewed during annual meetings with input from leading experts, including statisticians, to optimize the design of these studies.

The investigators agreed an overall key mid-to long-term goal is to establish an international network of critical care nutrition experts to facilitate the development of future interventional studies with the aim of providing high-quality evidence for future critical care nutrition guidelines.

7. Conclusion

This paper describes outcomes from an international focus group of early career multidisciplinary HCPs caring for ICU patients and senior research specialists in critical care nutrition, statistics and focussed on controversies in critical care nutrition. Key areas for clinical research were identified which need to be addressed in order to better inform the nutrition care of critically ill patients. The areas of unmet need focussed on how to identify patient groups in whom nutritional support would be beneficial and detrimental, the optimal time to initiate nutritional support, and the role of PN for critically ill patients (Fig. 2). Based on learnings from studies in this setting, the design of future clinical trials to address these questions needs to be refined and include endpoints which are most relevant to nutritional interventions in critical care. Such studies should be designed in collaboration with multidisciplinary HCPs, including internationally recognized experts in the field. To achieve this goal, the investigators identified the need to establish a critical care nutrition trial group with expertise in design and conduct of high-quality clinical trials in this setting. The studies designed by this collaborative effort would aim to address the identified controversies and unanswered questions in critical care nutrition, thereby generating robust clinical data to inform evidence-based nutrition practice and ultimately improve outcomes for critically ill patients.

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Authors' contributions

CS designed the concept of this manuscript and figure and wrote the initial draft. All authors (CS, RvG, JJ, MGV, FGDG, SC, SW, AA, TF, RM, MB) participated in the focus group meeting on which this paper is based, critically reviewed each draft of the manuscript for important intellectual content and approved the final version.

Declaration of Competing Interest

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