<PE-AT>Quantifying response to nutritional therapy during critical illness: implications for clinical practice and research? A narrative review

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Conflicts of interest

Fetterplace K. has received conference grants or honoraria from Baxter, Fresenius Kabi, Nutricia, Abbott and Nestle Health Science (not related to this study), Deane A.M. has received honoraria or project grant funding from Baxter, Fresenius Kabi, GSK, Medtronic and Takeda (not related to this study) and Ridley E.J has unrestricted research funding from Baxter Healthcare Corporation and has received honorarium from Baxter Healthcare Corporation (United States and Australia) and Nutrica (not related to this research).

Financial disclosure: None declared

Abstract:

Critical illness causes substantial muscle loss that adversely impacts recovery and health related quality of life. Treatments are therefore needed that reduce mortality and/or improve the quality of survivorship. The purpose of this review is to describe both patient centered and surrogate outcomes that quantify responses to nutrition therapy in critically ill patients. The use of these outcomes in randomized clinical trials will be described, and the strengths and limitations of these outcomes detailed. Outcomes used to quantify the response of nutrition therapy must have a plausible mechanistic relationship to nutrition

therapy, and either be an accepted measure for the quality of survivorship or highly likely to lead to improvements in survivorship. This review identified that previous trials have utilized diverse outcomes. The variety of outcomes observed is probably due to a lack of consensus as to the most appropriate surrogate outcomes to quantify response to nutrition therapy during research or clinical practice. Recent studies have used, with some success, measures of muscle mass to evaluate and monitor nutritional interventions administered to critically ill patients. <PE-FRONTEND>

Background

Why is nutrition therapy important?

Critical illness activates a 'stress' response that is characterized by secretion of neuroendocrine hormones and inflammatory mediators (1). Such messaging induces catabolism and resistance to anabolism, with significant changes in protein, glucose and lipid metabolism (1). The consequence of these physiological changes in critical illness includes substantial muscle wasting, which occurs to a much greater degree than is seen with bed rest alone (2). Muscle loss has been associated with less favorable outcomes from critical illness, such as increased mortality rates and complications, muscle weakness, delayed recovery of physical function and reduced quality of life (3-6). Given these consequences of critical illness, some therapies such as nutrition and early rehabilitation, are administered in the intensive care unit (ICU) to attenuate deterioration in functional ability and enhance recovery (7, 8). Intuitively, optimal nutrition therapy may reduce mortality and improve the

quality of survivorship with a reduction in disability; however, this remains to be determined.

The optimal nutrition therapy for critically ill patients remains unknown (9, 10). Recent large randomized clinical trials (RCTs) have challenged the orthodoxy that greater calorie provision during the early phase of critical illness improves outcomes (11-14). This has resulted in a shifting focus from the study of calorie provision to other aspects of the composition of nutrition formula, in particular the provision of protein (15). There is also considerable interest in the timing of nutrition therapy and the challenge to align nutrition therapy with the 'phase of illness', with speculation that excessive nutrition during the early phase of critical illness may alter adaptive processes, such as autophagy, which may exacerbate rather than attenuate the impact of critical illness (9). Furthermore many trials of nutrition therapy have focused only on the early period of critical illness, where interventions are generally implemented for a relatively shorter period, and therefore the potential impact of such limited intervention on long term outcomes needs to be considered (16, 17). In a recent systematic review it was identified that there is heterogeneity of outcomes reported in nutrition trials, with limited use of outcomes, other than mortality, that are likely to be important to patients (17). All of these factors make it difficult to assess the effect of nutrition interventions in a confounded environment of complex critical illness and highlights the importance of identifying appropriate outcomes to evaluate nutrition therapy (18).

The purpose of this review was to describe outcomes available to quantify the response to nutrition therapy provided to the critically ill (19). While mortality is clearly of extreme

importance to seriously ill patients, this review will focus on other outcomes that are relevant to the quality of survivorship. The objectives were to detail the outcomes used, and the strengths and limitations of each of these outcomes. An evaluation of outcomes that are aligned to health service efficiency, such as duration of ventilation and admission, are beyond the scope of this review.

Methods

A literature review was undertaken to identify RCTs of nutrition therapy in critically ill patients which included at least one of the following outcomes: quality of life, physical function, muscle strength, muscle mass or nutrition related anthropometric measurements. These outcomes were selected as they have a possible mechanistic link to nutrition therapy and they are likely to be important to patients or a surrogate to an important patient outcome. The MEDLINE database (Ovid SP, from 1948 to current) was searched in December 2019, using the following subject headings and key search terms: variations of critically ill, intensive care, critical care, nutrition support, enteral nutrition, nasogastric, nasojejunal, parenteral nutrition, dietary protein, muscle strength, muscle mass, body composition, quality of life, activities of daily living and physical functional performance (Appendix 1). The search was limited to adult patients and papers written in English. All titles and abstracts were reviewed for relevance and reference lists of previous review papers were examined to maximize the likelihood that all relevant RCTs were included (10, 17, 20-23). Seventeen nutrition therapy RCTs in critically ill patients were identified and subsequently one additional paper was added with an updated search in January 2020 (13, 24-40).

Outcomes and methods available to assess the response to nutrition therapy

Mortality

Mortality is generally considered to be the gold standard for assessing the effects of all treatments, including nutritional therapy, for critically ill patients. This is because the outcome is unequivocally important to patients, it is relatively easy and inexpensive to quantify, and it is not subject to ascertainment bias. For these reasons it is one of the most frequently utilized outcomes in nutrition therapy RCTs (17, 19). However, over time ICU mortality rates have reduced. The subsequent reduction in the baseline mortality rates necessitates a larger sample population in order to detect an effect (7, 41). This is particularly pertinent for nutrition, which is a low-cost therapy administered to a large number of heterogeneous patients. Population-level effects may be relatively modest, because some groups may benefit to a great degree and others may not. To date the largest sample populations included in critical care nutritional trials have been powered to detect a 3 to 4% absolute reduction in mortality, however, considering the very large numbers who are treated with nutrition therapy, a benefit (or harm) of a 1% reduction (or increase) in mortality would be an important and cost-effective outcome for individuals, populations and healthcare services (12, 25, 42). Furthermore, to detect the true effect of nutrition therapy on mortality in a heterogeneous population of critically ill patients, a trial in the tens of thousands of participants may be required or, at the very least, an enriched cohort of several thousand, who are highly likely to respond (41). Therefore, the search for appropriate surrogate markers is necessary, unless very large studies can be undertaken.

Other outcomes

Quality of life following critical illness is an extremely important outcome to patients and care givers (7, 17). However the effect of nutrition therapy on this outcome remains uncertain and quality of life is unlikely to be useful in quantifying the effect of nutrition therapy in short term interventions (43).

Other outcomes may also be relevant even if not immediately considered by patients as crucial to a better survival; these outcomes may be termed 'surrogate outcomes'. A surrogate outcome is defined as an outcome that, while not directly important to patients, is strongly related, either proven or plausible, to an outcome that is important to patients (44, 45). For an outcome to be identified as a suitable primary outcome for a trial, the outcome must be considered as important to patients, feasible to measure, subject to minimal bias, and there must be a plausible mechanism linking the intervention to an improvement in the outcome (45). It is important to recognize that surrogate outcomes facilitate conduct of 'proof of principle studies' in smaller cohorts prior to studies in larger cohorts. Additionally, the inclusion of surrogate outcomes in trials provides mechanistic understanding of why an intervention might improve a patient-centered outcome (17, 45).

The patient centered and surrogate outcomes, other than mortality, which have been used in RCTs include: health related quality of life, functional capacity, muscle strength, muscle mass, nutritional status and biochemical markers (17, 18, 22). Not all of these measurements will be directly important to patients; Figure 1 outlines outcomes that nutrition therapy may impact and the likely level of importance to patients (17, 46). Additionally, there are substantial limitations when trying to use some of these parameters

as the primary outcome for a RCT. Figure 2 provides suggested criteria for outcomes that may be of use in RCTs of nutrition therapy (7, 43, 45-49).

Figure 1. Patient centered and surrogate outcomes which have a mechanistic link to nutrition therapy and level of importance to patients

*Level of importance is based on our opinion and available data (17, 46)

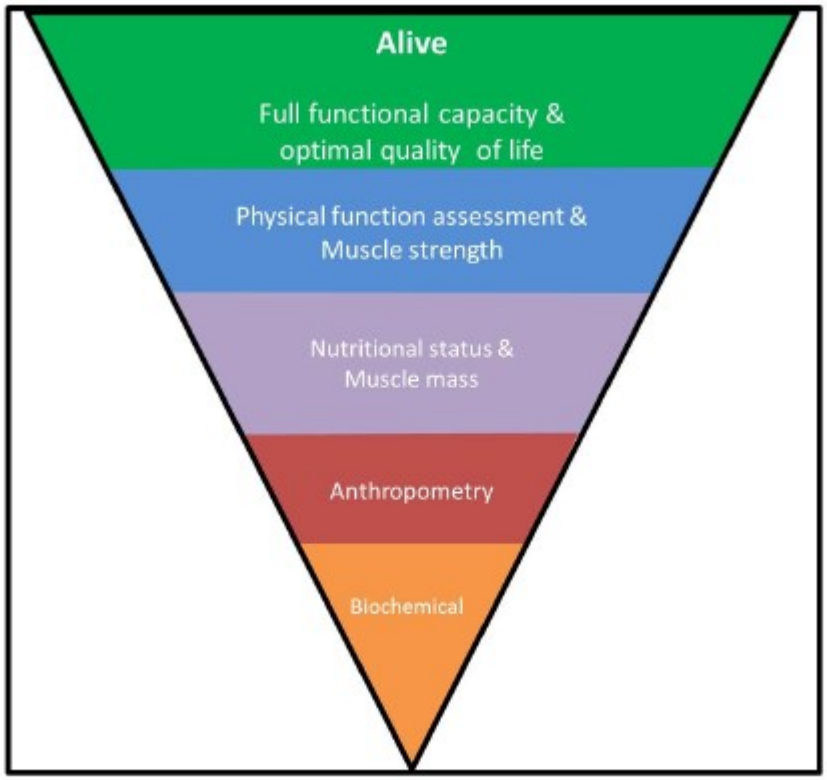


Figure 2. Important features of outcomes and degree to which the selected outcomes meet these criteria (7, 43-49)

Legend:

+ = the outcome clearly meets the criteria,

– = the outcome somewhat meets the criteria

? = it is unclear if the outcome meets the criteria

× = the outcome does not meet the criteria

Features	Outcomes						
	Mortality	Health related quality of life	Physical function	Muscle strength	Muscle mass	Nutritional status	Anthropo-metry
Important to patients	+	+	+	–	–	?	–
Easy to measure	+	×	–	–	?	–	–
Reliability	+	?	–	–	?	?	?
Limited ascertainment bias	+	×	×	×	+	?	?
Mechanism	?	?	?	?	+	+	+

The tools to quantify these patient centered and surrogate outcomes, which were utilized in the included studies are provided in Table 1, this is not an exhaustive list of all available tools. A limitation of many of these outcomes is that they can only be used in survivors who are awake and able to participate in the assessment. This means that if death, loss to follow up, or an inability to participate is not randomly distributed between groups, spurious associations maybe made and therefore the validity of the results will be diminished. This is of particular concern in critically patients due to the nature of their presenting conditions

and the requirement for mechanical ventilation. For this reason, measurements that are independent of patient participation, such as muscle mass, and those that have less loss to follow up, have considerable appeal. It should be emphasized that improvements in surrogate outcomes, such as muscle mass, do not currently have any causal link with improved patient centered outcomes, such as survival and quality of life (50).

Table 1. Tools to measure patient centered and surrogate outcomes and strength and limitations

Abbreviations: BMI, Body mass index; iADLs, SF-BIA, Single frequency Bioimpedance analysis; MF-BIA, Multi-frequency Bioimpedance analysis; BIS, Bioimpedance spectroscopy; Instrumental Activities of Daily Living; SGA, Subjective Global Assessment; WHODAS, World health organization disability assessment schedule.

There is variability in the methodology used to quantify outcomes and the time points at which these outcomes are measured (Table 2). Across the studies reviewed, the most commonly reported outcome was physical function (13/18 studies), however over ten different tools have been utilized. This variability makes comparisons between studies challenging. The study characteristics of nutrition therapy RCTs are summarized (Table 3) and the impact on surrogate outcomes are also shown (Figure 3). The studies included mostly heterogeneous critically ill patients, the intervention were not consistent across the studies and in the majority of studies (13/18) the intervention period was for 10 days or less and limited to the ICU and therefore this limits the interpretation of these results.

Table 2. Summary of tools used to measure patient centered and surrogate outcomes in nutritional therapy randomized control trials

Abbreviations: BMI, Body mass index; ECOG, Eastern Cooperative Oncology Group (ECOG) performance status; EQ-5D, EuroQol-5D; ICU, Intensive care unit; MUAC, Mid Upper Arm Circumference; MRC-ss, Medical research Council-sum score; SF-36, Short Form-36; SGA, Subjective Global Assessment; WHODAS, World health organization Disability assessment schedule.

*Bioimpedance analysis devise - Nutriguard-MS analyzer (Data Input GmbH, Darmstadt, Germany)

Table 3. Characteristics of critical care nutrition therapy RCTs which include at least 1 of the selected outcomes, not including mortality

Abbreviations: CT, Computed tomography, LOS, Length of stay; MUAC, Mid Upper Arm Circumference; RCT, Randomized control trial; PN, Parenteral Nutrition; US, Ultrasound.

Legend: ND = No statistically significant different between the groups, ↓ = the outcome was worsened with the nutrition intervention, ↑ = the outcome was improved with the nutrition intervention

[a]g/kg was not available, therefore results reported as gram per day

[b]energy and protein in kcal/kg and g/kg were not provided; therefore data is presented as percentage of requirements met

[c]Analysed data was not available, therefore this was estimated for mean daily nutrition delivery graph

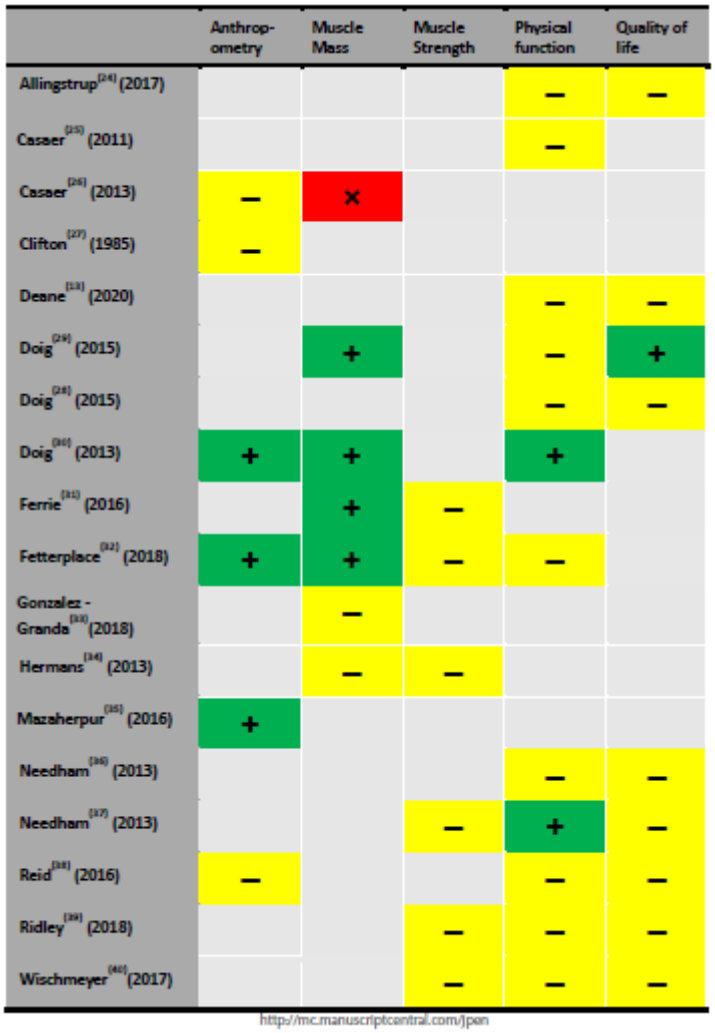
Figure 3. Effect of nutrition therapy on selected outcomes according to RCTs

Legend:

+ = Nutritional intervention being studied reported to have a beneficial effect on the outcome measured

– = Nutritional intervention being studied reported to have no significant difference on the outcome measured

× = Nutritional intervention being studied reported to have a detrimental effect on the outcome measured



Utility of each outcome based on available evidence from nutrition RCTs

Biochemical or other biomarkers

Many studies of nutrition therapy have included biochemical measurement to assess the impact of nutrition therapy, including albumin, pre-albumin and nitrogen balance. Albumin and pre-albumin concentrations dramatically reduce during the acute onset of critical illness making interpretation problematic. Likewise, nitrogen balance is affected by the catabolic processes of critical illness and is significantly altered with renal impairment (51). Moreover, there is little evidence that these measurements have a causal relationship with improved nutrition status or, more importantly, overall outcome in critical illness (52). The ideal biochemical measure would be independent of severity of illness and have a clear causal relationship to better outcomes that patients care about. As such, analysis of muscle tissue to determine changes in muscle quality and the assessment of whole-body protein turnover and muscle protein metabolism are appealing but these are impractical for routine clinical care or larger RCTs (53-56).

Standard anthropometry

Anthropometric measurements can be used to estimate baseline lean body mass and nutritional status. These measurements include weight, mid upper arm circumference (MUAC) and skin fold assessments (57).

Weight loss is a frequently used outcome in clinical practice to assess the effectiveness of nutrition therapy and has been proposed as a criterion to assess nutritional status (58). However, substantial fluid shifts due to resuscitation during the acute phase, 'de-resuscitation' in the recovery phase and muscle loss due to bed rest, all limit the utility of weight as an outcome. Observational data suggests that mean loss of body weight is between 3 to 5 kg or approximately 5% of body weight over an intensive care admission (59, 60). Whilst there are associations between cumulative calorie deficit and weight loss in critical illness, when confounding variables are incorporated into models, associations are either diminished or no longer present suggesting these may not be causal associations (60). Whilst smaller single-center RCTs have included weight loss as an outcome (32, 35, 61), larger multi-center RCTs of nutritional therapy have rarely reported change in weight.

Mid upper arm circumference (MUAC) or Mid Arm Muscle Circumference (MAMC) are bedside anthropometric measurements that have been used in observational studies and RCTs. The techniques used to obtain these measurements are described elsewhere (62). In four RCTs of nutrition interventions in critical care, there have been no significant differences in MUAC or MAMC reported as a result of the intervention (30-32, 39). Based on the available data it appears that anthropometric measurements probably lack precision to appropriately quantify the impact of nutrition therapy in critical illness (62, 63) or the impact of critical illness is not reversed with current nutrition interventions.

Nutritional status

The Subjective Global Assessment (SGA) is used in clinical practice to identify nutritional risk on admission to ICU (64, 65). Whilst there are limitations to this technique, the SGA classification correlates with handgrip strength, muscle thickness measurements, hospital length of stay and ventilated days in the critical care setting (31, 66). Deterioration in SGA scores is also associated with greater nutritional deficits in observational datasets of critically ill patients (60, 67) . Whether change in SGA is sufficiently sensitive or specific to be useful outcome in RCTs is unknown. A small single center pilot RCT reported attenuated reduction in SGA categories with greater protein provision (32). However, in a large multi-center open-label RCT early parenteral nutrition that increased nutrition provision also attenuated the worsening of SGA scores but had no effect on any patient-centered outcome (30). The latter observation suggests that assessing effect of nutritional intervention using the SGA requires circumspect interpretation.

The NUTRIC score has been suggested as a tool to assess nutrition risk on admission to ICU and to identify who will benefit the most from nutrition therapy (68). There are, however, limitations to NUTRIC as a screening tool, and post-hoc analyses of RCTs, the NUTRIC score has not identified any subgroups who benefitted from the nutritional intervention (66, 69). Moreover, the NUTRIC score was not designed to be repeatedly used to assess the impact of nutrition provision.

Muscle mass

Loss of muscle mass during ICU admission has been associated with increased mortality, longer length of stay, increased requirement for rehabilitation, poor physical function and quality of life (4). Given that it is plausible that a nutritional intervention will attenuate loss of muscle mass, and increased muscle loss is associated with worse patient-centered outcomes, this is an appealing surrogate outcome (22). However, the use of muscle mass does rely on the assumption that greater muscle mass will improve physical function and quality of life (50).

Dual-energy X-Ray Absorptiometry (DXA) is widely accepted as the 'reference' method for the assessment of body composition (70) (4). DXA has been used in observational studies in the critically ill (59, 71) but its use remains limited, as it necessitates transfer out of the ICU, is costly and exposes the patient to radiation. Several other methodologies have been used to quantify skeletal muscle mass during an ICU admission, including computed tomography (CT), multi-frequency bioimpedance analysis (MF-BIA), bioimpedance spectroscopy (BIS) and ultrasound (22, 55, 72).

In ambulant patients with cancer, skeletal muscle cross sectional area at the third lumber vertebra (single slice CT image) is strongly associated with whole-body skeletal muscle measured using DXA (Pearson's linear correlation coefficient r = 0.94) (70). Observational studies in the ICU using repeated CT images have suggested that greater energy provision diminishes skeletal muscle loss (73) but this technique has been rarely used in RCTs. Due to radiation dose the majority of studies make use of opportunistic imaging, which increases

the risk of selection bias. In a cohort study nested within the EPaNIC trial (25), authors reported data from 15 patients who had a CT scan soon after admission and a repeat scan one week later (26). All patients lost substantial muscle volume during the 1 week period and there was no strong evidence of a difference in muscle volume according to study treatment, however, there was an increase in the femoral intramuscular lipid and water content observed in the early PN group (26). Repeated CT imaging is unlikely to be feasible in clinical practice or larger trials unless radiation dose and the need for transfer out of ICU are addressed.

In healthy populations bioimpedance techniques are considered relatively accurate methods to estimate fat free mass, however in critically ill these techniques are prone to greater errors, particularly when single frequency BIA devices are utilized (55). MF-BIA and BIS have been used to provide estimates for extracellular, intracellular water and total body fluid, these devices utilize prediction equations which are population specific or algorithms with different resistive constants, respectively to estimate fat-free mass and fat mass (72, 74, 75) . In observational studies of critically ill patients, raw bioimpedance values have been associated with nutritional status, skeletal muscle mass (CT measurements, $r \approx 0.6$), sarcopenia and mortality (72, 76-78). Additionally, in critically ill cohorts calorie deficit has been associated with a reduction in fat-free mass (60) and impedance raw values (lower phase angle and higher impedance ratio), were reported to be predictive of lower muscle strength scores (both using the SFB7 BIS device (ImpediMed^{TM}, Pinkenba, Australia) (79). The MF-BIA device (Nutriguard-MS analyzer, Data Input GmbH, Darmstadt, Germany) has only been incorporated as an outcome assessment in one single-center nutrition RCT in the ICU (33). The authors reported that in 40 critically ill patients allocated to nutrition support

directed by indirect calorimetry with 1.2g/kg protein or usual care, there were no significant differences in any bioimpedance analysis measurements (including fat-free mass and phase angle) between the groups (33). However, this study was limited by a small sample and the energy and protein provision were similar across the two groups. Bioimpedance techniques are promising, but they require further validation in the critically ill.

Ultrasound also overcomes some of the limitations of CT scans, being a portable and non-invasive methodology (72). It is, however, operator-dependent, and there is lack of consensus on the most appropriate ultrasound protocol to use and which muscle site to measure (80). In several ICU studies a four-point protocol has been described to measure quadriceps mass (bilateral quadriceps muscle layer thickness (QMLT) (81). QMLT was reported to be strongly associated with site-specific DXA measures of lean tissue mass in healthy individuals (r-squared = 0.82)(82). In observational studies conducted in the critically ill, moderate associations have been reported between QMLT and DXA total lean mass (Pearson linear correlation coefficient r = 0.74) (59) and QMLT and CT abdominal skeletal muscle cross sectional area (Pearson's linear correlation coefficient r = 0.45) (83). Ultrasound techniques appear to have very good intra-observer agreement but inter-observer agreement is not as strong (84). Alternatives to QMLT include muscle cross sectional area or protocols which incorporate other muscle groups such as the biceps, abdominal muscles and forearm have been suggested to improve prediction of total skeletal muscle mass (85, 86).

Observational studies using ultrasound have reported that critically ill patients lose approximately 1-2% of muscle thickness per day in ICU (2, 87), however the precision of

these estimates is unknown and in other studies intra- and interrater variability has been reported to be larger than this change (2, 84). Greater muscle mass at ICU discharge, assessed with ultrasound, has been associated with improved quality of life and functional outcomes (59, 85). Two RCTs have utilized ultrasound to assess change in muscle mass in response to a specific nutritional therapy (31, 32). In a single center RCT greater parenteral protein administration was associated with greater forearm (mean (SD), 3.2 (0.4) vs 2.8 (0.4) cm, $p < .0001$) and quadriceps muscle thickness (mean (SD) 6.8 (2.1) vs 5.8 (1.9), $p = 0.02$) at day 7 of ICU, but not biceps thickness (31). In another single-center RCT a high protein volume based enteral feeding protocol was associated with attenuated loss of QMLT thickness (0.22cm (95%CI 0.06 -0.38, $p = 0.01$) (32). These results support the concept that ultrasound may be a useful modality to assess muscle mass in response to nutritional therapy, however consensus on an optimal protocol is required to improve the precision of this technique, and the high interrater variability needs to be overcome or minimized in order for this methodology to be utilized in multi-centered studies (88).

Muscle strength

The Medical Research Council sum score (MRC-ss) can be used to assess muscle strength and diagnose ICU acquired weakness (score <48/60) (89, 90). In observational studies cumulative calorie deficit during critical illness has been associated with greater odds of developing ICU-acquired weakness at ICU discharge (Odds Ration (OR) 2.1, 95%CI 1.4–3.3, P = 0.001) (60). The MRC-ss has been used in at least three RCTs. In a sub-group of EPaNIC participants (25) who were able to cooperate at various assessment points, ICU acquired weakness was diagnosed on day 8 in 127/294 (43%) patients randomized to early PN and

105/305 (34%) patients allocated to late PN (mean difference 9% (95%CI 1 to 16, p =0.03) (34). However this difference was not observed at the final assessment at ICU discharge (34). In the other two RCTs no significant differences in MRC-ss were observed with the nutrition interventions (32, 37).

Handgrip dynamometry is a measure of volitional force, which quantifies distal muscle strength of the upper limb, and it is easy to perform in patients who are awake and able to follow instructions (47) (91, 92). In the critically ill, weaker handgrip strength is associated with greater mortality (OR 4.5, 95%CI 1.5-13.6, p = 0.007) (93) but the mechanistic relationship between weakness of distal muscle groups and mortality is not fully understood. Handgrip strength has been reported in several RCTs of nutritional interventions at various time points including ICU discharge, hospital discharge and 6 months after discharge (31, 32, 39, 40). Ferrie and colleagues reported handgrip was higher in the group that received greater protein provision via parenteral nutrition (mean SD 21.1 (10.1) vs 18.5 (11.8) kg, p = 0.03) at day 7, however there was less strength of evidence that there was a different at ICU discharge (31). Other RCTs have been limited by a substantial amount of missing data, ranging from 57%-69% of the study population and therefore it is difficult to assess if there was any effect from the nutrition intervention (32, 39, 40). Although the MRC-ss and handgrip dynamometry are both validated tests to assess muscle strength as part of routine care their use is limited to those who are alert and able to obey instructions. Therefore, their use in RCTs is somewhat limited due to missing data.

Physical ability and quality of life

Various tools have been used in RCTs of nutritional therapy to assess physical function, mental capacity, cognition, level of disability and health related quality of life at many different time points (Table 3). In most cases these assessments are completed at 6 or 12-month after discharge and the nutrition intervention did not impact the outcome measured.

Physical function

The physical function in ICU Test (PFIT) score provides a functional assessment in the critically ill population (49, 94). It examines four components of endurance, function and strength as previously described (94). In an observational cohort cumulative calorie deficit was associated with lower PFIT scores at ICU discharge (60). The PFIT score has been used in one single-center RCT, with no differences seen in associations with the nutrition intervention; however, missing data again limited interpretation, with only 36% (22/60) of the study cohort included (32).

Other measurements of physical function that have been used include; the 6-minute walk test, the 4-metre timed walking speed test, the functional performance inventory and the Short Form-36 (SF-36) (physical component). The EDEN trial (14) evaluated the effect of initial trophic feeding versus full feeding and in a 12-month follow up study they reported that there was no strong evidence that there was a differences between groups in any physical function outcome measured (6-min walk distance, 4-metre timed walking speed test, or the functional performance inventory) (36, 37). Similarly in a trial of supplemental

parenteral nutrition there was limited evidence that there was a difference between groups for the 6-min walking test at hospital discharge (in 14% of the study population) or in the SF-36 (physical component) score at 6 month follow up (40).

Disability

Functional limitations may lead to disability, which is defined by the restriction in participation though a given social role (48). Common measures of disability include discharge destination, assessment of the ability to return to work, and independence in performing activities of daily living. Employment status and the degree of disability have been assessed in three nutrition RCTs (13, 36). In a pre-specified 180 day follow up of almost 4000 participants who were randomized to receive 100% or 70% of estimated energy requirements in the TARGET trial (12), a similar numbers of participants returned to work, with no differences in hours of work (13); additionally, there were similar amounts of participants who had no to mild disability according to the World Health Organization Disability Assessment Schedule (WHODAS) (relative risk = 0.99 (95% CI 0.88 to 1.11)) (13). Similarly, trophic feeding versus full feeding (14) in the ICU did not appear to effect employment status at 6 or 12 moths (36).

Quality of life

Health-related quality of life (HRQOL) is a multi-dimensional concept which attempts to score participants perception of physical and mental health. The most frequently used tools to assess quality of life in critical care nutrition studies are the 36-Item Short Form Health Survey (SF-36) and the EuroQol (EQ-5D, EQ-5D-3L and EQ-5D-5L). The EuroQol assesses domains of health related quality of life and the SF-36 provides a score for physical function

and mental health separately (43). Observational studies of critically ill patients have consistently reported that health related quality of life following ICU is substantially lower than population norms (36, 38, 59).

Health related quality of life scores have been included in eight critical care nutrition RCTs. In the 180 day follow up study of patients in TARGET, there was no difference in quality of life (EQ-5D-5L) in survivors (13). Likewise, in the EDEN trial, similar quality of life scores (SF-36 and EQ-5D) were reported (36). In contrast, two separate RCTs have reported small but statistically greater quality of life scores with greater nutrition provision; however, the difference observed is of uncertain importance (30, 95). None of the other studies reported any notable effects on health related quality of life and mental capacity (24, 36, 38-40).

Summary of outcome measures

The standardization of methodology and timing of assessment has merit. However the use of core-outcome sets should not stifle innovation in this field, as better tools to measure the impact of nutrition therapy are required (96). The use and development of tools which do not require significant patient participation and that are straight-forward to administer hold the most promise for larger/multi-centered trials, particularly when recruitment includes a proportion of patients admitted to the ICU with a neurological disorder who may have ongoing cognitive impairment. Some of these advancements may include technology to precisely measure body composition at the bedside and techniques or biomarkers that promptly detect muscle loss or weakness (97, 98). However, it must be noted that improvements in such outcomes may not result in overall enhancements in outcomes which are important to patients such as functional ability or quality of life. When study cohorts

are unaffected by cognitive impairment, tools which require patient participation may remain more relevant (99).

Conclusions

A variety of patient centered and surrogate outcomes have been used to evaluate the effect of nutrition therapy during critical illness. Whilst mortality remains the gold standard outcome for large RCTs, future RCTs may need to include substantially greater numbers of participants than have been used in previous trials if small but clinically relevant differences in mortality are to be detected. Current funding and logistic constraints preventing very large nutrition trials in critical illness supports the continued search for alternative patient-centered and surrogate outcomes for proof of concept and mechanistic studies.

Nutrition therapy has been shown to have varying effects on many patient centered outcomes and there is a lack of constancy in the tools used and limited data is available. Many of the outcomes used have substantial limitations and those which require volitional measurements may confound results. Of the surrogate outcomes, there is considerable interest in muscle mass, however standardized protocols for assessment need to be established. Moreover, a causal relationship needs to be proven between muscle mass and outcomes which are imported to patients before it can be considered a useful surrogate outcome. Future research should also consider the length of nutrition therapy and the likely impact on long term outcomes.

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Table 1. Tools to measure patient centered and surrogate outcomes and strength and limitations (17-19, 43, 45, 49, 72, 100)

Surrogate outcome	Tools	Strengths	Limitations
Health related quality of life	Short Form-36 and RAND-36, EuroQol-5D and EuoQol-5D-L, Eastern Cooperative Oncology Group (ECOG) performance status, Zubrod/WHO Performance Status, Charlder Fatigue Questionnaire, Employment status, Barthel Index, iADLs, WHODAS	Reproducible assessment tools	Population norms not established for all countries, the timing of assessment can affect results, limited to the population who can communicate and engage in follow up
Physical Function	Physical function in ICU test, Functional Status Score for ICU, Physical component SF-36, discharge destination, 6min walk test, 4-m timed walk speed, functional activity score for physical exercise, ICU mobility scale	Validated assessment tools, strong relationship with quality of life	Limited to those who can participate and some tools have subjective components to assessments. No validated assessment which can be utilized across the continuum of care. Assessment tools may not reflect actual daily functionality and quality of life
Muscle Strength	Handgrip strength Medical research Council Sum Score (MRC-ss)	Handgrip is an objective measurement; MRC has been validated in the critically ill population with excellent inter-rater	Limited to those who can participate, manual muscle testing has elements of subjectivity, regional muscle strength, such as handgrip strength is limited by the lack of standardization in protocols and it may not

		reliability	reflect functional ability or quality of life.
Muscle Mass	Dual –energy X-ray Absorptiometry (DXA) Computed tomography (CT) Bioimpedance techniques (SF-BIA, MF-BIA and BIS) Ultrasound	For all methods limited patient participation is required. Ultrasound is available in all intensive care units and it is minimal invasive. BIA and BIS devices are portable and minimal invasive.	For all methods further validation is required to confirm predictability of patient centered outcome and edema is likely to present challenges to accuracy. Ultrasound is user dependent and protocols require further validation. CT and DXA provide radiation and requires transfer out of the ICU. BIA and BIS are depended on device-specific algorithms, which may not be appropriate for the ICU population (none have been validated for critically ill patients)
Nutritional Status	Subjective global assessment (SGA) Global Leadership Initiative on Malnutrition (GLIM) criteria Body mass index (BMI) NUTRIC score (Nutrition risk) Nutrition Risk Screen (NRS)	Minimal patient participation and SGA is a validated assessment tool	Reliant on pre-admission history, SGA incudes subjective components, BMI is not indicative of patient centered outcomes or nutritional status. NUTRIC score and the NRS are not a nutrition assessment tool
Weight	Bed, hoist, chair and stand on scales	Objective and generally widely available	Confounded by fluid status, severity of illness and bed rest. Medical stability and equipment availability limit its use
Other	Mid upper arm	Objective	Limited data that supports

Anthropometry	circumference Mid arm muscle circumference Skin fold measurements		associations with patient centered outcomes and the impact of nutrition therapy. Intra-rater reliability and the presents of edema limits it use.
Biochemical markers	Albumin Pre-albumin Nitrogen balance Urea: Creatinine ratio	Easy to measure, widely available and objective	Lack of data to suggest that nutrition influences change or that these are predictive of patient centered outcomes

Abbreviations: BMI, Body mass index; iADLs, SF-BIA, Single frequency Bioimpedance analysis; MF-BIA, Multi-frequency Bioimpedance analysis; BIS, Bioimpedance spectroscopy; Instrumental Activities of Daily Living; SGA, Subjective Global Assessment; WHODAS, World health organization disability assessment schedule.

Table 2. Summary of tools used to measure patient centered and surrogate outcomes in nutritional therapy randomized control trials

Study	Anthropometry	Biochemical	Muscle Mass	Muscle Strength	Physical function, mental capacity and health related quality of life
Allingstrup[24] (2017) Eat-ICU	Weight and BMI (baseline only)	24-hour urine nitrogen (baseline)		Handgrip strength (failure to complete)	SF-36 (6 months)
Casaer [25](2011) EPaNIC	Weight, BMI, nutrition risk screen (NRS) (baseline)				6-min walk test (hospital discharge), Independent in all activities of daily living
Casaer[26] (2013) Sub study of EPaNIC	Weight, BMI and nutrition risk screen (baseline) Weight repeat in 11 out of 15 patients		Changes in muscle and fat volume & intramuscular lipid/water content using CT analysis (baseline & approximately day 8)		
Clifton[27] (1985) Head injuries	Weight (baseline and weekly)	Albumin Nitrogen balance			
Deane[13] (2020) TARGET D180	BMI (baseline only)				EQ-5D-5L, return to work, hours worked, effectiveness at work,

					disability (WHODAS) and Adelaide activities profile (6 months)
Doig[29] (2015) refeeding	BMI, SGA (fat and muscle wastage) (baseline only)	Albumin (baseline)			ECOG performance status and RAND-36 (90 days)
Doig[28] (2015) IV Amino acid	BMI, SGA (fat and muscle wastage) (baseline only)				Zubrod/WHO Performance Status and RAND-36 at 90 days
Doig [30] (2013) Early PN	BMI (baseline only), SGA (fat and muscle wastage) and MUAC (baseline and twice weekly in ICU)	Albumin recoded (not reported)			ECOG performance status and RAND-36 (60 days)
Ferrie[31] (2016) PN Protein	Weight, NUTRIC score and NRS-2002 (baseline only). MUAC, Triecept skinfold, leg circumference and SGA (baseline, day 3,7)	Nitrogen balance (day 3 and 7)	Ultrasound muscle thickness (biceps, forearm & quadriceps) and CSA of Rectus femoris (baseline, day 3 & day 7)	Handgrip strength (day 7 & ICU discharge)	Fatigue – Charlder Fatigue Questionnaire (day 7 in ICU)
Fetterplace[32] (2018) FEED	Weight, MUAC, SGA (baseline, day 5 and ICU discharge)	Albumin (baseline and ICU discharge)	Ultrasound thickness of quadriceps (baseline, day 5, 10, 15 or ICU discharge)	Handgrip strength and MRC-ss (ICU discharge)	Physical function in ICU test (PFIT) (ICU discharge) and discharge destination (acute hospital

					discharge)
Gonzalez-Granda[33] (2018) ONCA	Weight, BMI and NUTRIC score (baseline only)		Bioimpedance analysis* (baseline and every 3 days until ICU discharge) Resistance, Reactance, phase angle and body cell mass		
Hermans[34] (2013) Sub study EPaNIC	BMI and nutrition risk score (baseline only)		Skeletal muscle biopsies of the quadriceps (day 8 post randomization)	MRC-ss (repeated 3 x per week until ICU discharge)	
Mazaherpur[35] (2016) Traumatic brain injury	Weight and BMI (baseline, week 1,2,3)	Albumin, nitrogen balance, total protein (baseline, week 1,2,3)			
Needham[36] (2013) EDEN sub study	BMI (baseline only)	Albumin (baseline)			SF-36, EQ-5D-3L, functional performance inventory, overall functional activity score for physical exercise, requirement for rehabilitation facility, fatigue interval scale

					score, hospital anxiety and depression scale, impact of event scale-revised score post traumatic event, then mini mental state examination and employment status (6 and 12 months)
Needham[37] (2013) EDEN sub study 1 year	BMI (baseline, 6 and 12 months)		Percentage fat and muscle area based on MUAC and triceps skinfolds (6, 12 months)	MRC-ss and handgrip strength (6 and 12 months)	6-min walk test, 4-metre timed walk speed (m per sec), standardized performance tests relevant to cognitive domains of acute lung injury survivors (6 and 12 months)
Reid [38] (2016) Target feasibility					SF-36, EQ-5D and employment status (12 months)
Ridley [39] (2018) Supplemental PN	BMI, MUAC (baseline and hospital discharge)			Handgrip strength (hospital discharge)	ICU Mobility scale (hospital discharge), EQ-5D-3L (hospital discharge, 90

					days, 6 months)
Wischmeyer[40] (2017) Top-up	BMI, NUTRIC score (baseline only)			Handgrip strength (ICU and hospital discharge)	Barthel Index (admission, hospital discharge), 6-min walk test, SF-36 (90 days and 6 month)

Abbreviations: BMI, Body mass index; ECOG, Eastern Cooperative Oncology Group (ECOG) performance status; EQ-5D, EuroQol-5D; ICU, Intensive care unit; MUAC, Mid Upper Arm Circumference; MRC-ss, Medical research Council-sum score; SF-36, Short Form-36; SGA, Subjective Global Assessment; WHODAS, World health organization Disability assessment schedule.

*Bioimpedance analysis devise - Nutriguard-MS analyzer (Data Input GmbH, Darmstadt, Germany)

Table 3. Characteristics of critical care nutrition therapy RCTs which include at least 1 of the selected outcome, not including mortality

Study	Sample size (n)	Study design	Length of intervention (days)	Nutrition intervention	Mean intervention energy versus control (kcal/kg)	Mean intervention protein versus control (g/kg)	Surrogate outcomes of interest
Allingstrup [24] (2017) Eat-ICU	199	Single center RCT	11	Nutrition guided by indirect calorimetry and nitrogen balance versus standard care	24 (6.6) vs. 14 (6.8)	1.4 (0.42) vs. 0.49 (0.3)	Physical function – ND
Casaer [25](2011) EPaNIC	4640	Multicenter RCT (7 ICUs)	8	Early versus late parenteral nutrition **Calorie Goal** (kcal/kg) Male > 60y = 30 Male ≤60y = 34 Female > 60y = 24 Female ≤ 60y = 30	*Not available* *Approximately*[3]*:* *30 vs. 20*	*Not available* *Approximately*[3]*: 1.0 vs. 0.6*	Physical function – ND Activities of daily living – ND
Casaer [26](2013) Sub study of EPaNIC	15	Single center RCT	8	Early versus late parenteral nutrition	*Not available (refer to main study Casear 2011)*	*Not available (refer to main study Casear 2011)*	Muscle volume[1] – ND Muscle quality ↓ (increased intramuscu

							lar fat)
Clifton[27] (1985) Head injuries	20	Single center RCT	7	High protein versus standard protein both at 150% of measured energy expenditure	52 (11) vs. 48 (8)	2.6 (0.56) vs. 1.5 (0.25)	Nitrogen balance – ND Nitrogen loss ↑ Weight and albumin – ND
Deane[13] (2020) TARGET D180	3815	Multicenter RCT (43 sites)	6	Energy dense formula (1.5kcal) versus standard (1.0kcal) at 24ml/kg ideal body weight	30.2 (7.4) vs. 17.4 (5.5) ideal body weight	1.09 (0.23) vs. 1.09 (0.22) ideal body weight	Quality of life – ND Employment status – ND Disability – ND
Doig [29](2015) Refeeding	339	Multicenter RCT (13 sites)	7	Standard feeding versus restricted feeding in patients with low phosphate levels	Approximately 1365 vs. 850kcal per day[3]	Approximately 55g vs. 32g per day [3]	RAND-36 general health score ↑ Other quality of life and physical function – ND
Doig[28] (2015) IV Amino acid	474	Multicenter RCT (16 sites)	ICU duration (LOS 11 days)	IV amino acid supplementation (up to 2.0g/kg/day) in addition to feeding versus standard care	Approximately 1215 vs. 970 kcal per day [3]	Approximately 1.7 vs. 0.7 [3]	Quality of life and physical function - ND

Doig [30](2013) Early PN	1372	Multicenter RCT (31 sites)	ICU duration (LOS 9 days)	Early parenteral nutrition versus Standard	*Not provided: Approximately 1300kcal versus 800kcal*	*Not available*	General health status ↑ Quality of life – ND Nutritional status ↑
Ferrie[31] (2016) PN Protein	120	Single center RCT	10	Higher protein parenteral nutrition versus standard protein parenteral nutrition	23.1 (3.9) vs. 24.9 (4.2)	1.1 (0.22) vs. 0.9 (0.21)	Muscle mass (US) - day 7 ↑ Handgrip - day 7 ↑ Nitrogen balance day 3 ↑, day 7 – ND
Fetterplace[32] (2018) FEED	60	Single center RCT	15	Volume based enteral feeding with supplemental protein versus standard care	23 (5.7) vs. 21 (3.3)	1.2 (0.3) vs. 0.75 (0.11)	Muscle mass (US) ↑ Nutritional status ↑ Weight, MUAC, muscle strength, physical function - ND
Gonzalez-Granda[33] (2018) ONCA	40	Single center RCT	17 – 21	Indirect calorimetry directed nutrition provision versus standard care	20.4 (5.7) vs. 20.0 (7.5)	78 (18) g vs. 59 (21) g[1]	Bioimpedance measurements[4] – ND

Hermans[34] (2013) Sub study EPaNIC	600 122 biopsy	Multicenter RCT (5 ICUs)	8	Early versus late parenteral nutrition	*Not available (refer to main study Casear 2011*)	*Not available (refer to main study Casear 2011)*	Muscle strength on first assessment ↓ Muscle strength ICU discharge – ND Muscle myofibre density and cross sectional area – ND
Mazaherpur [35](2016) Traumatic brain injury	60	Single center RCT (3 arms)	21	Continuous enteral, intermittent enteral versus enteral with supplementary parenteral nutrition	Supplemental PN: 53.1% (18.3) EN intermittent: 32.2% (14.7) EN continuous: 38.5% (19.7)[2]	Supplemental PN: 67.7% (16.9) EN intermittent: 17.2% (10.1) EN continuous: 31.8% & (15.1)[2]	Weight ↑ (no significant change in sup PN, other decreases) Nitrogen balance ↑ Albumin – ND Total protein - ND
Needham [36](2013) EDEN sub study	525	Multicenter RCT (41 sites)	6	Full feeding versus initial tropic feeding	*Main study:* *Approximately 1300kcal/day versus 400 kcal per day*	*Not available*	Physical function – ND Mental domain SF-36 ↓ Admission

							to rehabilitation facility ↓
Needham[37] (2013) EDEN sub study 1 year	174	Multicenter RCT (5 sites)	6	Full feeding versus initial tropic feeding	*Main study:* *Approximately 1300kcal/day versus 400 kcal per day*	*Not available*	Physical function, muscle strength, cognitive impairment – ND (6 months) Walking speed ↑ Executive function ↓ (12 months)
Reid[38](2016) TARGET feasibility, sub study	79	Multicenter RCT (5 sites)	10	Energy dense enteral formula (1.5 kcal/ml) versus standard enteral formula (1.0 Kcal/ml) delivered at 24ml/kg ideal body weight	*Main study:* *27.3 (7.4) vs. 19.0 (6.0)*	*Main study[1]:* *70g (20) vs. 74g (30)*	Quality of life and physical function - ND Employment status ↑
Ridley [39](2018) Supplemental PN	99	Multicenter RCT (6 sites)	7	Supplementary parenteral nutrition with enteral nutrition versus standard care	20.6 (6.3) vs. 13.6 (6.6)	1.0 (0.3) vs. 0.6 (0.3)	Muscle strength, quality of life, mobility and MUAC – ND

Wischmeyer[40] (2017) Top-Up	125	Multicenter RCT (11 sites)	7	Supplementary parenteral nutrition with enteral nutrition versus standard care	90% (16) vs. 72% (25)[2]	82% (19) vs. 64% (26)[2]	Muscle strength, quality of life and physical function – ND

Abbreviations: CT, Computed tomography, LOS, Length of stay; MUAC, Mid Upper Arm Circumference; RCT, Randomized control trial; PN, Parenteral Nutrition; US, Ultrasound.

Legend: ND = No statistically significant different between the groups, ↓ = the outcome was worsened with the nutrition intervention, ↑ = the outcome was improved with the nutrition intervention

[1]g/kg was not available, therefore results reported as gram per day

[2]energy and protein in kcal/kg and g/kg were not provided; therefore data is presented as percentage of requirements met

[3]Analysed data was not available, therefore this was estimated for mean daily nutrition delivery graphs

[4]Bioimpedance analysis devise - Nutriguard-MS analyzer (Data Input GmbH, Darmstadt, Germany)