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SCHOUTEDEN, Eline; Bels, Julia L. M.; van de Poll, Marcel C. G. & Presneill, Jeffrey (2025) Missing data and long-term outcomes from nutrition research in the critically ill. In: Current opinion in clinical nutrition and metabolic care, 28 (2) , p. 160 -166.

DOI: 10.1097/MCO.0000000000001098
Handle: http://hdl.handle.net/1942/45390

Current Opinion in Clinical Nutrition and Metabolic Care

Missing data and long term outcomes from nutrition research in the critically ill

--Manuscript Draft--

Manuscript Number:	MCO280215R1
Full Title:	Missing data and long term outcomes from nutrition research in the critically ill
Article Type:	Review Article
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We thank our three reviewers for their supportive comments.

In response to the questions or comments from our three reviewers, the updated manuscript has a few sentences added, with added sentences indicated as coloured font with underline (tracked changes). All changes are also listed individually below.

Reviewer #1
References: please respect journal style
References are now first three authors, then et al.

Reviewer #2
1. Abbreviations that are non-standard, such as PRO and HUS, do you mind writing these out in full each time rather than using the abbreviation?
"Patient reported outcomes" has been substituted for PRO
"Health utility score" has been substituted for HUS

2. Physical performance tests (L100-118): Is there any evidence that patients actually care about these post ICU? While patients care about health-related quality of life, whether they can walk 200 or 250 metres in 6 min after surviving ICU, intuitively, is unlikely to be a priority – but if I am wrong, I'd love to be informed.
Line 117 new sentence inserted, with new supporting PLOS One 2024 [24].
"Of interest, some patients may respond to an awareness of lowered physical activity and functional capabilities with increased motivation to do more physical activity [24]."

3. Line 156-Line 161: Would it be worth mentioning that when conducting a survivor only analysis, large nutritional trials have attempted to account for missingness – for example by undertaking sensitivity analysis using the worst value for each score for patients who died before assessment and analysing for differences in baseline characteristics between survivors who didn't complete HRQOL assessment and those who did
Line 149 New sentences inserted and suggested reference to Deane et al 2021 included as new reference [33]:
"A recent report describing quality of life and functional outcomes at six-month following a randomized critical care nutrition intervention [33] was improved by also reporting differential mortality and the results of sensitivity analyses [13] of composite outcomes constructed with "worst value" scores for patients who died before assessment."

Reviewer #3
The authors might refer to the crucial SPIRIT-PRO guidelines, even if they have been published in 2021.
Line 75 New sentence inserted to mention SPIRIT-PRO, and suggested 2021 reference added as [16].
"International, consensus-based guidelines are available for the inclusion of patient reported outcomes in clinical trial protocols [16]."

Regarding the Precise RCT one might wonder if the paradoxical "beneficial impact" of higher protein intake on the secondary outcome 6-minute walking distance (in contrast to the primary endpoint) is a result of the

secondary outcomes not being corrected/penalized for non-random missing in patients who died before the time point of assessment. Imputation or simply attributing the lowest distance walked by a survivor (or zero meters) to the non-survivors could be a valuable sensitivity analysis. Reviewer #3 makes very reasonable suggestions on possible further sensitivity analyses for the Precise RCT. No addition on this point has been made to the manuscript as these detailed possibilities are probably covered by our overall advice on how to proceed with missing data.

A recent example of assessment of long term outcome in nearly 90% of 2 year survivors and attributing non-survivors the lowest score in a sensitivity analysis addressing non-random missing values, might be worth citing. I might be biased tough, as the paper was published by our team.
Line 204 Several new sentences added, as well as the suggested 2024 reference as [42]
"Very recently, pre-planned secondary analyses [42] became available of all-cause mortality and physical functioning scores two years after randomization in the multicenter EPaNIC parenteral nutrition randomized controlled trial. By two years the mortality approached 20%. With the advantage of access to Belgian National registry data, physical function was determined for almost 90% of two-year survivors. Statistical imputation of the remaining missing physical function data was conducted using two imputation models, with non-survivors attributed the lowest possible score.

Missing data and long term outcomes from nutrition research in the critically ill

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Structured Abstract (181 words)

Purpose of review

The use of functional outcomes in critical care nutrition research is increasingly advocated, however this inevitably gives rise to missing data. Consequently there is a need to adopt modern approaches to the foreseeable problem of missing functional and survival outcomes in research trials.

Recent findings

Analyses that ignore unobserved or missing data will often return biased effect estimates. An improved approach is to routinely anticipate the types and extent of missing data, and consider the likely mechanisms of that missingness. The researcher and their statistical advisor may then choose from a number of modern strategies to assess the sensitivity of the research conclusions to the patterns of missingness contained in these research data. Methods widely employed include multiple imputation of missing observations, mixed regression models, use of composite outcome variables with subjects who die being attributed a value reflecting the lack of ability to function, and selected Bayesian methodology.

Summary

Conclusions from clinical research in critical care nutrition will become more clinically interpretable and generalizable with the adoption of modern methods for the statistical handling of missing data.

Keywords:

Missing data

Statistical analysis

critical care nutrition

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Introduction

In the field of critical care nutrition many knowledge gaps exist despite decades of research, with the ideal nutritional regimen potentially differing according to the clinical context of individual patients [1-3].

Eight years ago in an editorial in The American Journal of Clinical Nutrition [4], research into optimal clinical nutrition was described as based on many confounded or biased observational epidemiological analyses with a few, mostly small, randomized trials, supplemented by recommendations based on expert opinion. Within three years of that call, two important statistical tutorial articles were published in the same journal, detailing methods for handling missing research data [5, 6].

Recent years have seen substantial advances, with publication of multiple relevant large randomized trials. However, these methodologically-improved critical care nutrition trials have not delivered the hoped-for general evidence of benefit on “hard clinical endpoints”, such as mortality, duration of mechanical ventilation, or length of ICU/hospital stay [2, 7, 8].

Within this challenging context, trial design for nutritional interventions in ICU has also expanded beyond assessing primarily survival to include evaluation of functional outcomes in ICU patients, such as muscle strength, physical performance, and quality of life [7, 8], where the increased subjectivity of the latter outcomes may risk greater average bias [9]. These expanded research horizons are in accordance with developments across all of critical care research, where collection of longer-term survival and functional outcomes is increasingly advocated [10, 11].

A recent consensus conference has attempted to reduce substantial heterogeneity regarding time points, outcomes and measurement instruments in trials of nutritional and metabolic interventions in critical illness. It was recommended that all clinical research on nutritional and

metabolic interventions report results at 30 and 90 days post-randomisation on survival and activities of daily living. Additional potential measurements included physical function, nutritional status, muscle/nerve function, frailty, body composition, and organ dysfunction [12].

In this paper we aim to summarize the currently understood causes, consequences and remedial strategies relevant to missing data that mitigate against bias relevant to critical care nutrition research evaluating mortality, functional outcomes or both (Figure 1).

Patient reported outcome measures

The *estimand* framework, recently described in the ICH E9(R1) Statistical Principles for Clinical Trials addendum [13], aims to align design, conduct, and statistical analysis plans with the treatment effect or effects of interest. Among these, patient-reported outcomes and/or surrogate outcomes such as symptoms, function, and other health-related quality of life (HRQoL) outcomes complement traditional clinical endpoints such as survival [14, 15]. International, consensus-based guidelines are available for the inclusion of patient reported outcomes in clinical trial protocols [16].

Common patient-reported outcome measures in critical care nutrition research include instruments to asses overall health-related quality of life such as the EuroQoL 5D-5L (or 3L) [17] and the 36-Item Short Form Health Survey (SF-36), or more specific questionnaires such as the Hospital Anxiety and Depression Scale (HADS) or the Clinical Frailty Scale (CFS) [18]. The possibility to perform follow-up taken by phone or even from a proxy without an in-person visit helps to increase retention of these measurements during follow-up. However, the volume of patient-reported outcome data requested needs to be considered, as respondent burden has been reported to lead to high rates of missing data and poor reporting of patient outcome results [19]. Another complication for analysis of patient-reported outcomes is that patients with and without missing scores may differ systematically [20]. It is clear that missing patient-reported outcome data threaten the interpretability and generalizability of findings by

introducing potential bias. Addressing these issues requires insight into missingness mechanisms, and consideration of possible methodological solutions to overcome missing patient-reported outcome data problems during data collection and statistical analyses [21]. In the setting of incomplete patient-reported outcome responses, mixed modeling and multiple imputation of patient-reported outcomes may be appropriate alternative analytic strategies that provide similar estimates of the average treatment effects in randomized controlled trials [20].

Physical performance tests

Physical performance tests such as the Medical Research Council (MRC)-sum test, handgrip strength, 6-minute walk test and the Short Physical Performance Battery pose a threshold to participation, since they require in-person attendance at a follow-up visit and a patient who is physically able to perform the test, which may further impair the collection of accurate responses from reluctant or disabled ICU survivors. This problem was exemplified in the recent PRECISe randomized controlled trial that tested the effect of high versus standard protein on functional recovery in people with critical illness using the EQ-5D-5L health utility score as the primary endpoint [22]. In that study, a substantial number of surviving patients contributed to the primary outcome assessment using telephone or e-mail without attending physical follow-up. Moreover, the proportion of surviving patients able to perform the 6-minute walking test was substantially lower than the proportion of patients able to undergo an MRC-sum assessment. Although the absolute and relative number of patients able to perform a 6-minute walking test increased during the course of the follow-up (Table 1), it is important to note that out of the 935 patients who entered in the intention-to-treat analysis, only 287 (31%) were able and willing to perform at least one 6-minute walking test at any timepoint during the follow-up. Thus, although the 6-minute walking test is considered a reliable measure for functional status [23], it may be not representative for cohorts with a high incidence or prevalence of severe disabilities.

Thus, when designing a study it is important to take into consideration the likelihood that the included patients will be able to contribute to the primary analysis for patient reported outcomes and physical performance tests, that are increasingly advocated in critical care (nutrition) research. When patients are included in the acute phase of critical illness, when the outcome is still unsure and the probability of death or disability is high, it is important to be cautious of outcomes that cannot reliably account for death or disability. Physical tests therefore seem to be particularly appropriate for research in patients with a high probability of survival, e.g. enrolled towards the end of their ICU admission, or even thereafter [10]. Of interest, some patients may respond to an awareness of lowered physical activity and functional capabilities with increased motivation to do more physical activity [24].

Missing data causes, consequences and strategies for analysis

Successful clinical research requires acknowledgement that information supposed to be collected about participants may not be available for a large variety of reasons, and the absence of this information may lead to bias. Practically all critical illness nutrition research needs to anticipate and plan for these complications, and routinely implement the now well-described steps for handling these challenges to the scientific validity of research analyses and interpretation.

Missing data may arise in many ways, from patient dropout and loss to follow-up, registry or data linkage errors or other patient-related factors such as physical or cognitive disabilities. The increasing number of studies addressing the role of nutritional interventions on longer-term functional outcomes [25, 26] is accompanied by participant retention challenges. Functional outcome studies in critical care report highly variable rates between 18% to 100% of participant retention in studies evaluating post-hospital outcomes in survivors of critical illness [27]. Some of this variable follow-up adherence may be associated with patient characteristics such as age or disease severity, both of which are relevant to critical care

outcomes [28]. As well, loss to follow-up in trials usually increases with the total duration of follow-up or the elapsed time since enrollment [28, 29].

The relatively high mortality accompanying critical illness is a further analytical challenge, which especially applies during the early stages of critical illness when intervention trials have been most commonly conducted. For example, the 60-day mortality was 32% to 35% in the EFFORT Protein RCT [30] and mortality by day 180 was 38% to 42% in the PRECISe randomized controlled trial [22].

Further to this complexity, exposure–outcome relationships in studies impacted by death and attrition due to separate causes may be distinct, the predictors of death and other causes of attrition of subjects from the trial may be different, and outcomes of interest for the deceased may be better regarded as undefined rather than missing [31]. Even though randomization generates comparable treatment and control groups, patient deaths before the measurement time point of their outcomes may result in the truncation by death problem where remaining survivors differ in background variables that are prognostic to the outcome [32].

Especially in the past, clinical nutrition research has often addressed these challenges simply by ignoring death and conducting selective "survivors-only" analyses [28]. However, it is clear that also properly addressing the mechanisms of missing data is crucial to new knowledge discovery, as improper data handling with incorrect assumptions may often create biases that undermine the validity of a study's findings and materially affect the clinical implications of the research. A recent report describing quality of life and functional outcomes at six-month following a randomized critical care nutrition intervention [33] was improved by also reporting differential mortality and the results of sensitivity analyses [13] of composite outcomes constructed with "worst value" scores for patients who died before assessment.

Methods for the statistical analysis of data with missing values depend on the underlying mechanism of the "missingness", which has been subject to decades of complex exploration

in the mathematical statistical literature. Terms that will be encountered include “missing completely at random” (MCAR), “missing at random” (MAR) or “missing not at random” (MNAR), while alternative terms include “informative missingness” and “informative censoring” [21, 34]. While researchers need to have heard of the above longstanding MCAR/MAR/MNAR classification scheme, it is more important to understand the practical implications of these technical terms [35]. When there are missing data in multiple variables, the plausibility of the MAR assumption may be difficult to assess. The best way to handle missing data depends on the assumed causal relationships between variables and their missingness, and what these relationships imply in terms of the 'recoverability' of the target estimand [35]. The most important action for the researcher is to anticipate the likely mechanisms of relevant missing data, determine in what circumstances analytical bias may occur due to the missing data mechanism(s), and obtain early on skilled biostatistical support to identify what methodological solutions exist to minimize or overcome missing data problems during data collection and statistical analyses. The ready feasibility of analyses limited to available complete cases, so common in past critical care nutrition research, is offset by the narrow circumstances where ignoring missing data in that way may yield valid results [21, 35]. Researchers should anticipate the likely need for more sophisticated alternative methods for missing data, such as multiple imputation of missing observations, or regression-adjusted association estimates using generalized linear mixed models, or Bayesian approaches dealing with missing observations [36], supported by sensitivity analyses [37] conducted under alternative plausible assumptions [35]. The results from these analyses should be presented along with those from the primary analysis [37].

Several approaches to account for patient deaths are available, depending on the chosen outcome measure. For the primary outcome of time-to-discharge-alive from hospital in the EFFORT Protein trial [30] (measured from randomisation to 60 days) death was a competing risk, and so patients who died within 60 days of ICU admission were considered to have never been discharged alive regardless of previous hospital discharge. Other approaches to

developing an estimand may be useful within a composite variable that includes mortality. Analyses assessing “alive status” in clinical outcomes (e.g. days alive and out of the hospital within a given time period) may allocate a zero (or lower) score for mortality. While these methods that consider both illness severity (length of periods with life support or in-hospital) and mortality may result in a better model fit to data, these “days alive and at home up to 90 days after ICU admission” (e.g. as applied in the forthcoming TARGET Protein trial [38]) and similar count outcomes may come with increased methodological complexity and potentially challenges to interpretability [39]. One such challenge is that the relative power of potentially applicable statistical tests may be dependent upon the magnitude of the treatment effect for the individual components of the composite score [40].

ICH / FDA advice for clinical trials [13] measuring physical functioning suggests the construction of an outcome variable on a continuous scale, with subjects who die being attributed a value reflecting the lack of ability to function. Such composite variable strategies can be viewed as implementing the Intention-To-Treat (ITT) principle when the original measurement of the variable might not exist or might not be meaningful due to the intercurrent event of a patient death [13]. If a treatment saves lives, its effect on various measures in surviving patients may be of interest, but it would be inappropriate to say that the summary measure of interest was only the average value of some numerical measure in survivors [13]. That is, the important outcome of interest is survival along with the numerical measures in survivors. To this end, the EuroQoL [17] health utility score is a useful instrument in trials with high mortality as it accounts for death as a health state within the range of all potential health utility scores. Although the EuroQoL health utility score is still frequently reported in survivors only [11], some current trials such as the PRECISe trial [21] and the REPLENISH trial [41] use this important feature of the EuroQoL health utility score [22, 41]. The PRECISe [22] trial thus including death as a health state (scored 0), and found worse health-related quality of life in the intervention group. Losses to follow-up were important and reported as comprising 7·5% in the standard protein group and 10·9% in the high protein group. Very recently, pre-planned

secondary analyses [42] became available of all-cause mortality and physical functioning scores two years after randomization in the multicenter EPaNIC parenteral nutrition randomized controlled trial. By two years the mortality approached 20%. With the advantage of access to Belgian National registry data, physical function was determined for almost 90% of two-year survivors. Statistical imputation of the remaining missing physical function data was conducted using two imputation models, with non-survivors attributed the lowest possible score.

There are numerous publications that provide useful information on both the effects of various forms of missing data and also the currently recommended approaches to handling and reporting incomplete data in both observational and randomized controlled research projects [37, 43, 44]. While informed guidance is readily available in the scientific literature, the choice of appropriate statistical methodology for an individual research question may be improved by biostatistical support. Unfortunately, potential bias around the handling of missing data, and incomplete transparency around methodological decisions in observational and randomized studies continue to threaten the validity and reproducibility of modern critical care nutrition research and the international guidelines derived in part from those research results [45, 46].

Conclusions

Research into critical care nutrition has improved in recent years with adoption of outcome studies measuring both patients' survival and functional status in the short and longer term. When designing studies, the anticipated mortality and disability of the study population should be taken into consideration when selecting physical and patient reported outcomes. The practical inevitability of missing data, combined with a likely substantial proportion of mortality in these very sick patients, requires critical care nutrition research to routinely plan to address the multiple sources of missing data and consequent potential bias in analyses. Research trials must strive to preserve the initial randomization, maximize patient follow-up, and then evaluate

the available data using recommended methods, supplemented by missing data imputation or other appropriate methods, conventional or Bayesian, that deal with the specific mechanisms of missing data under study. Demonstration of the sensitivity of research trial conclusions to the trial's analytical assumptions and the effects of missing data should now be routine in this field of research.

2629 words (not including Table 1 and 42 references)

Key points

- Missing data is common in critical care nutrition research
- Improved research strategies exist to directly address this formerly ignored problem
- At least one missing data strategy should be specified in the initial research design, according to the types of data missingness that may be anticipated
- The sensitivity of trial conclusions to the missing data should be evaluated routinely and reported with the main trial results

Acknowledgements

ES + JB + JP = none.

MvdP Research support, Consultancy, speaker and travel fees from Nutricia Research

Financial Support and Sponsorship

ES + JB + JP = none.

MvdP Research support, Consultancy, speaker and travel fees from Nutricia Research (same as above)

Conflicts of Interest

ES + JB + JP = none.

MvdP Research support, Consultancy, speaker and travel fees from Nutricia Research (same as above)

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280 Table 1 *Retention of patient reported and physical outcomes in the PRECISe trial [22]*

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Figure 1 Characteristics of outcome measures commonly assessed within critical care nutrition research projects

Figure 1 footnotes

PROMs = patient-reported outcome measures

EQ-5D-5L = 5-level EuroQol 5-dimension measure of health status

SF-36 = Short Form (36-item) health survey

MRC-SUM = Medical Research Council-sumscore of global muscle strength

Bulleted references

***ref 7 This review describes the heterogeneity in measurement of health-related quality of life in critical care trials and provides some examples of death as a competing risk.**

***Ref 11 The scoping review further highlights the importance of accounting for death as a cause of missing data in critical care research and the underappreciation of this in many ICU trials.**

****Ref 21 The PRECISe trial is the first large RCT on nutrition in critical care that uses functional outcomes as a primary endpoint. It nicely exemplifies the importance of accounting for death while doing so.**

****Ref 22 This paper proposes a Core Outcome Set that can be used to standardize assessment of functional outcome in nutritional interventional trials in critical illness both in timing and manner.**

****Ref 28 The Effort Protein trial was the first RCT on protein targets in critical illness, powered for a clinically relevant primary endpoint and used a time-to-event-alive approach to assess survival and recovery simultaneously.**

**** Ref 34 Very recent discussion of biostatistical aspects of sensitivity analyses, clearly written in a form accessible to clinical researchers.**

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Figure

	Proposed application	Example	Advantage	Disavantage
PROMS	**Application:** large scale studies with individual follow-up + can be assessed remotely - subjective	EQ-5D-5L	Includes death within range of possible scores	Is a global measure
		SF-36	Includes physical component score	Does not account for death
Physical tests	**Application:** individual follow-up in cohorts with low incidence of death & disability after enrollment + more objective - requires in-person assesment of able & willing patient	MRC-SUM	Easy execution	Maximum score rapidly achieved
		Handgrip strength	Continuous outcome without ceiling	Tests only upper extremity strength
		6-minute walking test	Tests total physical performance	Requires basal fitness
Clinical outcomes	**Application:** registry-based studies + often readily available - may ignore functional recovery	Time-to-event alive	Large statistical power	Necessitates censoring for death
		Days-alive-and-free-from-event	Incorporates death into continuous variable	Sometimes difficult to interpret for clinicians

Table

Table 1 *Retention of patient reported and physical outcomes in the PRECISe trial [21]*

Follow-up (days)	patients known to be alive	EQ-5D-5L	MRC-sum	6-MWT	6-MWT:MRC-sum
30	597	529 (89%)	308 (52%)	65 (11%)	65:308 (21%)
90	508	443 (87%)	295(58%)	207 (41%)	207:295 (70%)
180	483	436 (90%)	261(54%)	213 (44%)	213:261 (82%)

Table footnote

This table provides the percentage of patients being assessed for the given outcome as a function of the number of patients known to be alive at the time of the respective follow-up visit. The final column provides the fraction and percentage of patients who were able to perform both an MRC-sum assessment and a 6-minute walking test