Author’s response to reviews

Title: Economic evaluation of an extended nutritional intervention in older Australian hospitalized patients: a randomized controlled trial

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Author’s response to reviews:

Editor Comments:

I have now received your manuscript back from review and I am able to inform you that, whilst it is an interesting paper, we are unable to consider it for publication without very substantial revision. Therefore, I would like to invite you to revise and then resubmit your manuscript to the journal. Please refer to the existing guidelines for performing and reporting on health economic evaluations as much as possible. I am looking forward to receiving your revised submission.

BMC Geriatrics operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

Reviewer reports:

Karen Freijer (Reviewer 1): A very valuable manuscript for nutrition science and especially for the new field of Nutrition Economics (http://www.ispor.org/sigs/NutritionEconomics.aspx)- showing the economic value of investing in nutrition as part of the total treatment of patients. Overall, nutrition is unfortunately still a very underestimated part of the total medical management of patients. Showing comprehensive economic evidence relating to its cost
effectiveness, allows nutrition to be in less danger of falling by the wayside in the current new era of competitive health care funding (Milte et al 2014).

The quality of such economic evaluations should be of high quality to be taken seriously. So I would suggest to use the CHEERS checklist/guideline for reporting your economic evaluation. This CHEERS guideline is an up to date health economic evaluation guideline, arisen from updating all existing previous health economic evaluation guidelines efforts into one current useful reporting guidance. The outline of the manuscript will then be improved as now the outline is not yet optimal and not very structured and therefore not easy to understand for readers that are not familiar with health economic evaluations such as the nutrition world. (see comments regarding methods and results).

Also a lot of health economic terms are mentioned in the manuscript - not in a structured way -, confusing readers that again are not familiar with this new field for the nutritional world. So please be more clear and structured.

Comment: We have now reported this health economic analysis as per the CHEERS guidelines (as suggested by the reviewer) and made the manuscript clear and structured.

Abstract:

Comment (1)

Line 30-31: why mention the sentence "Cost benefit analysis…… " mention that a cost-utility analysis has been performed and explain what a cost-utility analysis is this in the methods.

Response (1): We have changed the wording in the methods section of the abstract, as suggested by the reviewer to make it clear that both cost-effectiveness and cost-utility analyses were conducted. (page 4)

“A cost-effective analysis (CEA) was conducted for the primary outcome (incremental costs per unit improvement in PG-SGA) while a cost-utility analysis (CUA) was undertaken for the secondary outcome (incremental costs per quality adjusted life year (QALY) gained).”

We also contrast these types of economic evaluations under the heading of Heath economics in Methods section on page 14:

“A CEA is a type of economic evaluation whose outcomes are expressed in terms of natural units while outcomes in CUA are reported in terms of QALYs [26].”

Comment (2)

Line 46: why using the word "participant"….please change in "included patient"

Response (2): This sentence has been modified as suggested. (page 4)
“Mean Australian Medicare costs per included patient were lower in the intervention group compared to the control arm (by $907 per patient) but these differences were not…”

Comment (3)

Conclusion: the statement that the intervention is cost-effective needs to be refined according to the primary and secondary outcomes. For the primary one the effectiveness was significant (the adjusted improvement in PG-SGA scores), but the effectiveness on the QALYs was not significant. Also the delta costs were not significant. so how to interpreter these results … Also it is mentioned in this conclusion that it is about patients discharged from acute care, whereas this has not been mentioned in the methods… please be consistent in the total story line.

Response (3): We have modified the conclusion according to the primary and secondary outcomes as suggested by the reviewer and have deleted acute care from this section.

As is the case in most economic evaluations undertaken alongside clinical trials [1, 34], this health economic analysis was based on data drawn from a clinical trial that was only powered to detect differences in clinical outcome (PG-SGA) but was not powered to detect differences in costs and QALYs between the two groups. In line with best practice guidelines [34, 35], our analysis focused on determining the likelihood of the intervention being cost-effective as opposed to hypothesis testing relating to whether the cost and QALY differences were statistically significant. To clarify this we have amended the conclusion in both the abstract and main text.

Abstract

“This health economic analysis suggests that the use of early and extended nutritional intervention in older general medical patients is likely to be cost-effective in the Australian health care setting in terms of both primary and secondary outcomes.”

Conclusion on page 22

For both primary and secondary outcomes, the results of our health economic analysis suggest that the use of early and extended nutritional intervention in older general medical patients is likely to be cost-effective in the Australian health care setting.

Comment (4)

Introduction:

Please use the right reference for the statements in the manuscript: e.g. Lit ref nr 4, 5 and 6 for the statement can better be supported by using also the cost of illness analyses for DRM (DeMan&Ljungqvist 2009, 2010 for Eu costs related to DRM and country related analysis such as Freijer et al 2013 etc).
Response 4: We thank reviewer for the suggestion and have now added two new references to the studies by Ljungqvist et al (Ref no 7) and Freijer et al (Ref no 8) in the text. (page 6)

Comment (5)

Line 29: indeed more economic evaluations alongside nutrition clinical trials are needed, but please don't ignore that already a lot has been published regarding the cost-effectiveness of nutrition interventions in health care - see also syst reviews such as Milte et al 2013, Freijer et al 2014, Elia et al 2016. Very important to state this as otherwise the nutrition world will not be optimal informed.

Response (5): We have included references to previous economic evaluations highlighted in the systematic reviews in line with this suggestion: (page 6)

“Three recent meta-analyses have [9-11] have indicated that nutrition intervention has economic benefits but have also suggested that there is a need for further high quality studies to confirm these findings in different age groups and in different health care settings, as the majority of these studies have been conducted in Europe.”

We have now also discussed these meta-analyses in relation to our health economic analysis by adding a new section in the discussion on page no 21.

Comment (6)

Describe the real objective of this economic evaluation. Now only part of the total is mentioned (secondary outcome = QALY), but not the primary endpoint. Why?

Response (6): We have now clearly spelt out the objective of this economic evaluation on page 6 & 7.

“This trial found a trend towards an improvement in nutritional status and quality of life and a significant reduction in length of hospital stay but there was no reduction in mortality or readmissions at 3 months follow up. Although the resources needed for the intervention were modest and the anticipated clinical benefit (nutrition status) was small [12], no economic evaluation was originally conducted to examine whether the intervention was worth pursuing from an economic perspective. The objective of the present analysis is to detail the methods of an economic evaluation undertaken to assess whether the individualized nutrition intervention was value for money and report upon its findings. The results of the evaluation will help determine whether allocation of resources for improvement of nutritional status of older hospitalized patients is justifiable.”

We have also made it clear that there were two outcomes: a primary outcome expressed in terms of improvement in PG-SGA scores (cost-effectiveness analysis) and a secondary outcome reported as gains in quality adjusted life years (QALYs) gained (cost-utility analysis) as suggested by the reviewer. (page 7)
“Consequently, the primary outcome of this evaluation was expressed in terms of incremental costs per unit improvement in the PG-SGA (CEA) and the secondary outcome reported in terms of incremental costs per QALYs gained (CUA).”

The decision to express the unit improvement in PG-SGA as the primary outcome was based on the need to be consistent with how outcomes were reported in the original clinical trial. We still fully report the results based on the primary and secondary outcomes so that the interested reader can use either in interpreting the results of our analysis.

Comment (7)

Methods:

Line 24: Please add again ref 7 to the first sentence add

Please update this section in a constructive way following CHEERS as a guidance to have a good overview of what has been done. Now this section is not clear- no structure despite the headings... most of the required information is somewhere in the method section but as said not obvious (e.g. perspective, discounting, timeline, costs, effectiveness etc. Better to understand when perhaps headings will change such as: intervention vs control; costs; effectiveness; economic analyses; statistics - see CHEERS) Also no not clear what the differences were between the intervention and the control group! For example: it is mentioned in line 54/page7 that all recruited patients were classified as malnourished using the PG-SGA and then randomized to intervention or control group. Whereas in the control group section on page 10 it is mentioned that the classification on malnourishment has been established by using the MUST ...?? Not clear at all. Also table 1 and table 3 are very confusing.. Please show all the characteristics at baseline compared to all the characteristics in base case analysis. Don't understand the MUST score in baseline in table 1 and the PGSGA at baseline in Table 3?? Nutritional assessment: this has been done before randomizing the patients into control and intervention group as described in line 54?

Response (7): We have added the reference in line 1 as suggested and we have reworded the Methods section as per CHEERS guidelines as suggested by the reviewer and have also changed the section headings accordingly.

Table 1 has been corrected and PG-SGA and EQ5D scores have been added and MUST removed to avoid confusion and maintain consistency with Table 3. (pages 7-13) (Table 1 & 3)

Comment (8)

Intervention:

Please describe in detail the exact intervention: define exactly what the extended intervention is vs control - now not clear. In the overall conclusion it is mentioned "... the use of an early and extended nutritional intervention". So early is within 24 hours in intervention but what was this
then in the control? About nutrition: what was extension in detail vs control? What has been used as required amount of protein for these patients (should be 1.5 g/kg body weight/day = for DRM - see international guidelines on this topic and incl e.g. fightmalnutrition.eu) and how was this in control group? What about the daily intake of vit and min in intervention group vs control group? Very important to state that also an optimal intake for these micronutrients is needed, otherwise no use to have an increased intake of protein (vit and min are needed to have the protein being active on the right places in the body!). What was the total intervention to meet these increased requirements? So, how many servings of the described ONS was given to the patients and at what time of the day? Describe also if these ONS also contain the important vitamins and minerals! Aim was to meet 100% of requirement of patients protein and energy requirement... please indicate also that it is very important to meet at least the basic amount of daily requirement for vitamins and minerals! Most important for the DRM patients is increased required amount of Protein but only together with vitamins and minerals and then energy is important! With increased protein intake, also the energy will be taken care of as with protein products also energy will be increased to meet the minimum for the body to be able to spend the increased protein intake for the right areas and not to be used as energy source. So focus is increase of protein together with adequate (RDA) vitamin and mineral intake.

Frequency of contact between patient and dietitian was depending on individual patient's needs (line33-34/page 9) - so no protocol? Describe the difference for this aspect in intervention compared to control group

Response (8): We have attempted to address these issues and have rewritten the intervention section as follows: (pages 9-10)

Intervention

Nutrition intervention was initiated within 24 hours of hospital admission and aimed to meet 100 percent of patients’ energy and protein requirements for ideal body weight, calculated using commonly adopted predictive equations[14] along with an adequate intake of essential vitamins and minerals. Intervention patients received an individualized nutrition intervention by the dietitian, depending upon their underlying medical conditions, protein, energy, vitamin and mineral requirements and food preferences. Nutritional strategies employed by the dietitian included provision of oral nutrition supplements (ONS) (1-2.2 kcal/ml and 0.05-0.12 gm of protein/ml), mid-meal snacks and food fortification with consideration given to individual patients’ food preferences and taste. The ONS utilized were Resource (475 kcal, 19.7 g protein) and Sustagen (248 kcal, 12.5g protein), which in addition to protein provided a range of nutrients. Multivitamins were not separately prescribed but were left to the discretion of the treating clinicians. In addition, dietetic counseling was provided to the patients and care-providers to augment energy intake using a range of strategies including recommendation of energy and nutrient dense food items, increasing the number of meals they ate, and consumption of energy, protein and nutrient-rich snacks. Patients who needed assistance with meals were flagged, so that a ward based staff member provided help during meals. The frequency of contact between patient and dietitian during the hospital stay varied depending upon individual patients’ needs and the length of hospital stay. If the dietitian thought that the patient was unable to achieve their daily energy and nutrient requirements then they received almost daily input.
Where patients were discharged to a nursing home then the dietitian contacted the nursing home manager and forwarded the recommended nutritional care plan to be followed. The hospital covered the cost of commercial oral nutritional supplements at the time of discharge for patients where ≥50% of the patient’s daily energy requirements were determined to be required from supplements. All intervention patients were contacted by a monthly telephone call by the research dietitian for 2 months. Each call lasted an average of 30 minutes and a structured format was used to collect information about their recent weight, compliance with dietetic plan, any side effects with supplementation. They received dietetic counseling with a focus to reinforce compliance with the intervention. Compliance with the dietetic plan was assessed by using a 24 hour self reported dietary recall. In this trial, patients were assessed to be compliant by the dietitian if they were able to meet at least 75% of their energy and protein requirements.

Comment (9)

Control group:

Please describe in the same manner as in the intervention group how the daily nutrition looked like, meaning describe how usual care was looking like from admission up to 3 months post-discharge. How can the control group been screened by MUST when in lines 54-57/page 7 it is mentioned that all recruited patients were assessed using the PG-SGA and then randomized into intervention or control group. What is the protocol about requirement for protein?, vit min taken into account etc in usual care? So which nutrition was given in usual care by the dietitian. And what was the nutritional management for patients not at high risk of DRM (so the ones who were not referred to a dietitian etc)

Response (9): The usual policy in our hospital is that all patients are screened by a nurse with MUST and only high risk patients are referred to the dietitian for intervention. The reality is that MUST screening rate is low around 50% [2] and very few patients are seen by the dietitian and are discharged without any intervention and there is no dedicated outpatient dietetic follow-up. In this study, all patients underwent PG-SGA assessment for confirmation of nutrition status and patients allocated to the control group followed usual care and in case they were referred to a dietitian by their clinicians, then they received same intervention but only up to the period of hospital discharge with no outpatient follow-up telephone calls. We have now clarified this in the control group section of the manuscript. (page 10)

Control group:

“Patients randomized to the control group followed usual care currently operative in Flinders Medical Centre. It is an expectation that all patients are screened for malnutrition by using MUST tool by the admitting nurse and patients identified as high risk are referred to the dietitian. Dietetic input occurs only if patients are flagged as high risk and referred by a health care professional with no dedicated outpatient follow-up after discharge. In this study, the control patients were flagged as malnourished and this was documented in the case notes for clinicians to make decisions regarding nutritional care. Where the ward dietitian received referral for these patients, the patients followed same nutritional care as the intervention group until hospital discharge but did not receive any additional post-discharge telephone follow-up.”
Response (10): We have reworded the methodology according to the CHEERS guidelines as suggested by the reviewer.

We have specified that the cost-effectiveness analysis has used an incremental approach where incremental (extra) costs and incremental (extra) effectiveness between the two study arms have been compared.

On page 14 we say the following:

“An incremental approach was used in order to determine, where appropriate, the incremental cost effectiveness ratios (ICERs) expressed as the incremental cost per unit improvement in the PG-SGA (primary outcome) and incremental costs per quality adjusted life year QALY gained (secondary outcome). The ICERs were calculated as incremental costs divided by incremental changes in outcomes.”

In terms of identifying sources of the extra effectiveness or extra costs a priori, we need to point out that we evaluated cost differences due to not just the disparities in intervention costs between the two arms but also due to differences in the whole suite of resultant Medicare costs. The explanation for the differences in costs identified in this study are presented in the results section on page 17.

Comment (11)

Line 19-20/page 11: Heading Analysis. do you mean Statistics?
Response (11): We have clarified that this refers to Descriptive statistics by adding a sub-heading under the Analytical methods. (page 14)

Comment (12)

Economic Evaluation:

Please describe here the type of analysis chosen and reasoning. Can you please add the ICER’s for primary and secondary outcome measured… incl CI's and describe

Please describe the bootstrapping method etc in a heading about statistics to improve structure - now included in lines 22-58/page 12 and lines 1-27/page 13…. Not clear as such.

Response (12): We have clarified this in the methods section under economic evaluation as suggested by the reviewer. As indicated in this section, the choice of type of economic evaluation (cost-effectiveness and cost-utility analysis) were guided by the type of outcomes of effectiveness evaluated in the study. In line with best practice guidelines [3, 4], see also Briggs A, Starkie H and Wu O. “Chapter 62 – Health Economics in Asthma and COPD”. In: P. J. Barnes, J. M. Drazen, S. I. Rennard and N. C. Thompson, eds. Asthma and COPD (Second Edition) Oxford: Academic Press; 2009: 751-760.), we do not present estimates of the ICERs and their CI’s because the intervention dominates usual care. In such an instance where an intervention is both cheaper and more effective than usual care, it is not necessary to present estimates of ICERs. However, we do present all the differences in costs and outcomes between the two study arms, together with bootstrapped 95% CIs, for the interested reader wanting to conduct any threshold and other analyses.

The details on bootstrapping are now presented in the revamped structure that follows CHEERS guidelines as suggested. (pages 14-15)

“Economic Evaluation

Two types of economic evaluation (CEA and CUA) were used in this study. Their choice was informed by the types of outcomes measured in the main trial [12]. A CEA is a type of economic evaluation whose outcomes are expressed in terms of natural units while outcomes in CUA are reported in terms of QALYs [26]. Consequently, the primary outcome of this evaluation was expressed in terms of incremental costs per unit improvement in PG-SGA and the secondary outcome reported in terms of incremental costs per QALYs gained (CUA).

Within-trial economic evaluation with respect to the primary and secondary outcomes was undertaken allowing for bivariate uncertainty with bootstrapping of participant costs and outcomes to maintain the covariance structure. We used non-parametric bootstrapping [27] to derive 5,000 paired estimates of mean differences in costs and outcomes from participant level data in order to account for uncertainty due to sampling variation in cost–effectiveness/cost-utility. The bootstrapped pairs are presented in the form of a cost effectiveness planes (CEP) [28]. Cost effectiveness acceptability curves (CEACs) which depicts the probability of the
intervention being more cost effective compared to the usual care arm at different willingness-to-pay thresholds were also constructed.”

Comment (13)

Results:

Please improve structure.. see earlier comments.. (e.g. make subsections about base case and sensitivity analysis)

Response (13): This has been corrected and reworded as advised and according to CHEERS guidelines

Comment (14)

Line 41-42: it is described that 776 did not meet inclusion criteria… please change into how many patients did not meet the exclusion criteria to be consistent with the methods - in the methods it has been described that all patients were considered for participating this study unless they met the exclusion criteria… so we don't know the inclusion criteria… please be consistent

Line 42/page 13: suddenly it is mentioned that 148 patients were recruited… not clear when you only mention the total of 1668 and 776 were excluded… then this will leave a total of 892 patients… so what happened with the other patients when only 148 patients were included?

Response (14): This has been reworded as advised. (page 16)

“A total of 1668 patients (Figure1) admitted to the Department of General Medicine were assessed for participation in this study, whereof 892 met the inclusion criteria. Of the 892, 744 patients refused to participate due to various reasons (Figure 1). One hundred and forty eight patients were therefore recruited and randomized to control (n=70) and intervention (n=78) groups.”

Comment (15)

Table 1 and Table 3 used for this section are very confusing - see earlier comments.

Response (15): We have corrected Table 1 by adding PG-SGA and EQ5D scores, so that it is now consistent with Table 3.

Comment (16)

Line 58-59: please change kilojoules into kcal…! KJ is not being used anymore for years.

Response (16): This has been changed to kcal as advised. (page 16)

“655 (95% CI 587.3 to 772.1) kcal of energy”
Comment (17)

Line 1-2/page 14: ".... Compliant with intervention... ".. how was this in month 3 as the timeline was 3 months post-discharge. Please add to be complete

Response (17): The compliance was checked at 1 month and 2 month phone call and we have made this clearer in the text. (page 16)

“73% and 77.2% patients were compliant with the intervention at 1 month and 2 months post-discharge, respectively.”

Comment (18)

Please add the results on ICER’s

Base case: Why is difference between adjusted and unadjusted that big? Please explain.

Response (18): Please refer to our response to comment no 12 in methodology section above.

Comment (19)

Line 43-50/page 14: please add the % of mean results in each quadrants of CEPs.

Response (19): We have modified graphs as suggested by the reviewer and now include the % of mean results in the CEPs.

Comment (20)

Line 51-59/page 14: the text is not matching what is shown in fig 3 - adjust the scale of fig 3!! This is not a curve and cannot be used as such... adjust the scale so the curve can be seen!

Response (20): The scale has now been adjusted and figures for the PG-SGA revised so that they can be read off the curve easily. Therefore, the willingness to pay (WTP) figures illustrated are now $1000 per unit improvement in PG-SGA scores and $50,000 per QALY gained.

Comment (21)

Sensitivity:
All results in sensitivity analysis were not significant besides the total costs... please explain conclusion in this section ... confusing as in base case, only sign difference in PG-SGA unit and in sensitivity analysis only difference in total costs is sign and nothing on effectiveness...

Response (21): Please refer to our response to comment 12 from this reviewer.

Discussion:

Comment (22)

Please be more careful with conclusions based on Non Sign results!

Response (22): We now emphasize that these results suggest the likelihood of the intervention being cost-effective, as per responses to comment no 3 from this reviewer.

Comment (23)

Line 3-5/page 16: "... be related to the overall sign longer length of hospital stay...."... in the total manuscript nothing has been shown/described about the difference in this resource use in both arms.. Please add in methods and results.

Response (23): We have added this resource use in both methods and results section of the manuscript as advised by the reviewer. (pages 14 & 16)

“Length of hospital stay (LOS) was adjusted for in hospital mortality.”

“Length of hospital stay (LOS) was however, significantly shorter in the intervention patients (9.9 (SD:7.2)) vs. 6.9 (SD:5.3), P<0.005), in control and intervention groups, respectively (Table 3).”

Comment (24)

Please add a discussion on the probable reasons why no sign results were measured on utilities. As in other nutrition studies also no sign results were measured using the EQ-5D-3L or 5L.. this can be because these tools are validated in pharma trials, whereas nutrition effects are more difficult to be measured, especially in such a short time frame for nutrition intervention... this has been described in these other CEA for nutrition interventions in patients e.g. Neelemaat et al 2012 and also more recent studies... First effects of nutrition that are measurable is nutritional status, than due to this the effect on functional and clinical outcomes (after a minimum intervention of 6-12 weeks) and due to that, then only an effect on utilities can be measured... probably needing measurement during a longer time of period... to be investigated...

Response (24): we have included discussion on the probable reason for non-significant results and have included the comments suggested by reviewer along with a new supporting reference. (page 19)
“The differences in costs and HRQoL outcomes were however not statistically significant… At least two reasons may explain the statistically insignificant cost and HRQoL differences between the two trial arms. The first may be because the original trial [12] from which the data for this study were obtained was not powered to detect differences in costs and HRQoL, a result seen elsewhere [34, 35]. Another reason specific to HRQoL could be a short duration of nutrition intervention in our study. The impact of nutrition intervention on utilities is complex and may not be evident after a short period of intervention. After initiating nutrition intervention the temporal pattern that usually follows is - first improvement in nutrition parameters like weight then functional outcomes and lastly improvement in HRQoL [36]. Future nutrition intervention trials of sufficiently long duration may help verify this hypothesis.”

Comment (25)

Limitations:

Line 27-32: these sentences are suddenly discussing a cost-of-illness study and the details of such a study, whereas this has nothing to do with this cost-effectiveness study!! Totally different types of studies… so why suddenly mentioning this??

Line 32-43/page 18: please be consistent in using the right terminology. In these lines you mean that outcomes are depending on perspective, included costs type

Response (25): We have reworded this paragraph and removed the reference as suggested. (page 22)

“Due to differences in design and organization of health-care systems, our study results cannot be generalized to other settings and countries and further studies are needed to contribute to the evidence of cost utility of nutritional therapy”

Reviewer 2

Comment (1)

Nele Van Damme (Reviewer 2): Thank you for studying the cost-effectiveness of a nutritional intervention. This is really important in times of scarcity. Although, I found no clear information on your primary and secondary outcomes concerning cost-effectiveness in the result section and none in the discussion section.

Response (1): We have now clearly indicated the primary and secondary outcomes in methods section of the abstract and later on in the text as suggested including in the introduction, methods, results and discussion sections on pages 7, 11, 14, 17 and 18.

Comment (2)

Abstract
'Cost-benefit analysis was measured in terms OF quality-adjusted life years …'

Response (2): This has been corrected to cost-utility analysis

“A cost-effective analysis was conducted for the primary outcome (incremental costs per unit improvement in PG-SGA) while a cost-utility analysis (CUA) was undertaken for the secondary outcome (incremental costs per quality adjusted life year (QALY) gained).”

Comment (3)

Introduction

Can you add the aim of your study clear and specific (e.g. according to PICO).

Response (3): The aims of the study has now been mentioned clearly as advised by the reviewer. (page 7)

“The objective of the present analysis is to detail the methods and report upon the findings of an economic evaluation undertaken to assess whether the individualized nutrition intervention was value for money. The results of the evaluation will help determine whether allocation of resources for improvement of nutritional status of older hospitalized patients is justifiable.”

Comment (4)

Methods: Study design and location

The title doesn't cover the content. Besides design and location, also datacollection, ethical considerations, setting, and participants are described. This paragraphs reads difficult because of a lack of coherence, structure, and logical sequence of the content.

Response (4)

We have changed the title to “Economic evaluation of an extended nutritional intervention in older Australian hospitalized patients: a randomized controlled trial” to better reflect the contents in the manuscript.

Comment (5)

Methods: Nutritional assessment

In accordance with 'health-related quality of life': can you add information on the validity of the PG-SGA in this paragraph?

Response (5): The information about the validity of PG-SGA has now been added as advised with a reference. (page 12)
“PG-SGA has been validated in various settings including older hospitalized patients and has a high sensitivity and specificity to diagnose malnutrition [18].”

Comment (6)

Methods: Health-related quality of life

Is it possible to summarise the results of the validation of this instrument?

Response (6): The validity results have been summarized as advised by the reviewer. (page 12)

“The EQ-5D-5L has been validated in different clinical populations including patients with multiple chronic illnesses, rehabilitation and orthopedic patients awaiting joint replacement surgery [22-24]”

Comment (7)

Methods: Intervention

Try to avoid long sentences. These are difficult to read. E.g. 'A combination of strategies …'

Response (7): This has been reworded as advised by the reviewer and we have now made sentences shorter in various places.

Comment (8)

Methods: Cost analysis

Try to avoid long sentences. E.g. 'Pharmaceutical costs …'

Data on ethical consideration should be better combined in one separate paragraph. Your paragraph 'Design and location' also contains data on ethical considerations.

Response (8): This section has been reworded using CHEERS guidelines as advised by the other reviewer and we have now made sentences short.

Comment (9)

Methods: Analysis

How did you decide on your sample size?

Response (9): The sample size was calculated based upon the change in the PG-SGA score from the baseline in the clinical trial [12], which provided data for this economic evaluation. A previous study has suggested that a shift of 3 (SD 4.1) [5] in PG-SGA is clinically meaningful,
so, assuming an effect size of 0.35, alpha=0.05 and power of 80%, a sample size of 86 (43 in each group) was calculated to be sufficient.

Comment (10)

Can you describe more specifically what you mean with 'Basic descriptive statistics were used…'

First sentence is not grammatically correct:. Better: 'Continuous variables were expressed as mean or median [interquartile (IQR)] ranges.

Try to avoid long sentences.

Response (10): This has been corrected as advised by the reviewer. (page 14)

“Continuous variables were expressed as mean (standard deviation (SD)) values or median (interquartile (IQR)) ranges.”

Comment (11)

Methods: Economical evaluation

Can you integrate the correct concepts concerning heath economic evaluations: e.g. cost-utility.

Response (11): This has now been corrected to describe correct concepts of cost-effectiveness analysis and cost-utility analysis as suggested by the reviewer. (page 14)

“Two types of economic evaluation (CEA) and CUA) were used in this study. Their choice was informed by the types of outcomes measured in the main trial [12]. A CEA is a type of economic evaluation whose outcomes are expressed in terms of natural units while outcomes in CUA are reported in terms of QALYs [26]. Consequently, the primary outcome of this evaluation was expressed in terms of incremental costs per unit improvement in PG-SGA and the secondary outcome reported in terms of incremental costs per QALYs gained (CUA).”

Comment (12)

Results

In general: This paragraph should be less difficult to read if more conform/more comparable to the method section (e.g. sequence, titles, paragraphs and content).

Response (12): The methods section has been reworded with reference to CHEERS guidelines as suggested by the other reviewer and now conforms with the results section.

Comment (13)

Results: Base case analysis results
Please, can you add or describe clearly the results on your primary (cost per unit improvement in the PG-SGA) and secondary outcome (costs per qaly gained).

Avoid interpretations in your results section: 'This entails that the intervention dominated the control group as it was both cheaper and more effective that the former implying that the intervention would be considered cost-effective'

Response (13):

As the intervention dominates usual care, we do not report ICERs in line with best practice guidelines [3, 4], see also Briggs A, Starkie H and Wu O. “Chapter 62 – Health Economics in Asthma and COPD”. In: P. J. Barnes, J. M. Drazen, S. I. Rennard and N. C. Thompson, eds. Asthma and COPD (Second Edition) Oxford: Academic Press; 2009: 751-760.). We do however-present all the differences in costs and outcomes between the two study arms, together with bootstrapped 95% CIs, for the interested reader wanting to conduct any threshold or other analyses.

Comment (14)

Discussion

Can you formulate an answer on your specific study aim and describe the results on your primary and secondary outcome at the beginning of this section?

Response (14): We have summarized the answers at the beginning of this section. (page 19)

“The findings of this study indicate that, in older general medical malnourished patients, the health care costs were lower while nutrition status and HRQoL was better among those in the individualized nutrition screening and intervention arm compared to those in the group that received usual care with no post discharge dietetic follow-up. This result suggests the intervention was likely to be a cost-effective alternative to usual care…”

Comment (15)

Can you add a reference concerning the validity of the PG-SGA.

Response (15): A new reference regarding validity of PG-SGA has been added in the as advised by the reviewer. (page 19)

Comment (16)

I would suggest an additional topic for the discussion: In the introduction you described a 'trend towards an improvement in nutritional status' determined in the RCT. In your health economics study, you identified that the units improvement in the PG-SGA were significant higher in the
intervention group. It would be interesting if you discuss these findings in relation to each other. How can you explain this 'difference'?

Response (16): The results in our original trial were based upon complete case analysis of unadjusted differences with 46 patients in the control group and 57 patients in the intervention group. As shown in Table 3, the complete-case-analysis differences in the PG-SGA scores between the two trial groups (both adjusted and unadjusted) was statistically insignificant. In this economic evaluation, and based on subsequent statistical and health economics advice, our base case analysis was based on imputed cases (imputed using multiple imputation) with the differences also adjusted for baseline differences. As can be seen in Table 3, the adjusted differences based on imputed cases are statistically significant (1.3238 (95% CI: 0.0240, 2.3858)). The differences between the results of the clinical paper and those in the current paper are therefore purely due to the method of analysis.

Comment (17)

Your discussion topics concern costs, but no reference was made to cost-effectiveness which was the main outcome of your study.

Response (17): We have included a reference of a cost-effectiveness study by Norman et al in the discussion. We have also added three new references of meta-analyses comparing cost-effectiveness of enteral nutrition and discussed these in relation to our health economic analysis. (page 20 & 21)

“Norman et al [46] in their study in malnourished patients aged 50.6 ±16.1 years, with benign gastrointestinal disease found that 3-month nutritional supplementation with ONS increased HRQoL and was cost-effective from a German statutory health insurance perspective. Unlike our study which included older patients with multiple comorbidities, however, this study was restricted to a relatively younger population of patients with benign gastrointestinal disease and nutrition intervention commenced only at the time of discharge.”

Our study results are also in line with the findings of three recent meta-analyses [9-11] conducted in different patient groups which suggest that the use of enteral medical nutrition in the management of disease related malnutrition (DRM) can be an efficient intervention from a health economic perspective and may lead to cost-savings.”

Comment (18)

Table 1

This table also contains outcomes of the study, not only 'baseline characteristics'. Please, can you make this more clear?

Response (18): We have corrected Table 1 which now only shows baseline characteristics.

Comment (19)
Table 2

'Intervention costs' were not completed for the base case analysis.

Are the 'intervention costs' of 22 AU $ correct? You described in the method section already 37.16 AU $ per hour for an accredited dietician, and there are also other costs (e.g. nutritional supplements). Can you explain this?

Response (19): The actual cost of the intervention was $286 per patient (made up of two 30-minute phone calls at $37.16/hour = $37.16 and packages of supplements for 90 days for 36/73 patients at $6/package = $19,440 which when averaged over all 73 patients in the intervention group = $286). We re-did the entire analysis, and have reduced the cost difference from $1,172 to $907, still in favor of the intervention). We have amended the text to reflect how the cost was calculated. (page 13)

“Costs associated with the intervention itself (primarily dietitian staff costs for making follow-up telephone calls (30 minutes per month for two months i.e. two phone calls per patient for all patients) and costs of supplements for the entire study period for nearly half (36) of the patients) were estimated by combining staff time spent/number of supplements provided and published information on wage rates obtained from published resources ($37.16 per hour for an accredited dietician) and unit costs for supplements sourced from hospital accounts records ($6 per package per day).”

Comment (20)

This table is not consequently organised (e.g. use of italics, use of blanc rows).

References to footnotes not correct? Only 'a' and 'b'?

Footnotes not correct: 2 times 'b'

Response (20): Table 2 has now been corrected.

Comment (21)

Table 3

Footnotes: no 'c'?

Response (21): Table 3 has been corrected

Comment (22)

Figure 3a
For me, it's not clear how to compare this figure with the results in the text. In the text you describe 'willingness to pay values as low as $50 per unit'. On the X-as, I cannot identify the probability of intervention being cost effective at a willingness to pay values as low as $50, because the scale at the X-as ranges till 500,000. Can you make this more clear?

Response (22): We have changed the scale of figure 3a to make this clearer.

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