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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Version: 2 Date: 19 Jan 2018

Author’s response to reviews:

Reviewer reports:

Karen Freijer (Reviewer 1): Thanks for improving the manuscript. It looks very nice and clear now.

Just a few minor comments:

Abstract:

Line 29: Methods section: change cost effective analysis into cost-effectiveness analysis

Response: This has been changed as suggested by the reviewer. (Methods section, page 4)

“A cost-effectiveness analysis was conducted…”

Line 50: Results: please change the word participant into patient

Response: This has been changed as suggested. (Results section, page 4)

“with patients in this arm reporting QALYs gained ….”
Introduction:

Line 31/page 6: What do you mean with this sentence? .."This is especially so as the majority of these studies have been conducted in Europe."?

Response: This indicates that only few similar studies have been conducted in Australia and we have clarified this in the text. (Introduction section, 1st paragraph, page 6)

“and very few studies are available in the Australian health care settings.”

Line 9/page 7: "…. and the anticipated clinical benefit (nutrition status) was small [12],….." A nutrition status is not a clinical benefit but a nutritional benefit!! An optimal nutrition status (nutritional benefit) can result in a clinical benefit - but is not the same. Please adapt

Response: This has been now modified as suggested by the reviewer. (Introduction section, paragraph 1, page 7)

“Although the resources needed for the intervention were modest and the anticipated improvement in the nutrition status was small....”

Methods:

Line 20/page 9: The reference [14] used to estimate the protein and energy requirement for the studied patient population in this manuscript (malnourished general medical patients ≥60 years) is very strange as this ref 14 is about critical ill patients - not comparable at all with the patient population in this manuscript. Please adapt using the literature for malnourished older patients as suggested before.

Response: This reference has now been changed to represent older malnourished patients as suggested by the reviewer. (Reference no. 15, page 26)


Nele Van Damme (Reviewer 2): Thank you for elaborating your research in more detail, and providing more structure. This really makes your report more understandable for readers not known with health economics.

Comment 1

In general
Language: Please check your text on everyday speech and non-scientific English (e.g. page 11 'Where the ward dietician received referral'; 'and for the sake of maintaining consistency'), as well as sentences which are not grammatically correct [e.g. singular versus plural ('the patient' versus 'their') in the same sentence; conjugated verb and adjective ('… is a simple questionnaire and comprising of …') in the same sentence.

Response 1: We have now corrected the document according to the suggestions. (Methods section-subheading control group, paragraph 1, page 11 and Methods section-subheading HRQoL and QALY, paragraph 1, page 13)

“If control patients got referred for a dietetic advice, then they were offered the same nutritional care plan as the intervention group only for the period of their hospitalization but received no post discharge follow up care.”

“The EQ5D 5L is a self-reported questionnaire and measures a patient’s health across five different domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.”

Comment 2

Introduction

* I still find your objective too vague. E.g. what do you exactly mean with 'value for money'? Can you describe 'value for money' in more detail (in terms of what?) + from which perspective + what about willingness to pay (cfr your discussion)?

Response 2: The value for money has now been clarified and detailed as suggested by the reviewer. (paragraph 1, page 7)

“The objective of the present analysis was to conduct an economic evaluation that assessed whether the individualized nutrition intervention was value for money when considered from a healthcare sector (Australian Medicare) perspective.”

Comment 3

As it is written now, it seems like your primary objective is to detail the method of your economic evaluation. I guess this is not? Can you reformulate this part of your text?

Response 3: (as above) This part of the text has now been reformulated as suggested by the reviewer. (paragraph 1, page 7)

“The objective of the present analysis was to conduct an economic evaluation that assessed whether the individualized nutrition intervention was value for money when considered from a healthcare sector (Australian Medicare) perspective.”

Comment 4
I have difficulties with mentioning your primary and secondary outcomes when describing your study objective, as you don't mention the results on these outcomes in your report. If I read about this outcomes in your introduction, I expect to find the specific results (e.g. ICERS) on these outcomes in your report.

Response 4: We have reported both the outcomes in the paper:

Base case analysis in the Results section on page 17 and 18.

“When the adjusted outcomes in the base case were considered (Table 3), the intervention was more effective than the control with participants in this arm reporting unit improvements in the PG-SGA that were higher by 1.3238 units (95% CI: 0.0240 to 2.3858) and QALYs that were higher by 0.0050 QALYs gained per patient (95% CI: -0.0079 to 0.0199).”

“The CEACs (Figure 3) show that the probability of the intervention being cost-effective at willingness to pay values as low as $1000 per unit improvement in PG-SGA scores was above 98% while it was 78% at a willingness to pay of $50,000 per QALY gained, the implicit cost-effectiveness threshold used in Australia [34].”

As also indicated in the first quote above, we also report both outcomes in Table 3

Sensitivity Analysis results on page 18

“In the sensitivity analysis, ignoring the missing data and using complete case analysis (Tables 2 and 3) did not have an effect on the incremental effectiveness. This is because the intervention was still more effective by 0.9849 units of improvement in the PG-SGA score (95% CI: -0.5601 to 2.5912) and by 0.0060 QALYs gained per patient (95% CI: -0.0086 to 0.0216), but was even more cheaper per patient (by $4,947, 95% CI: $1,451 to $9,030).”

Discussion on page 19

“The differences in costs and HRQoL outcomes were however not statistically significant. In line with best practice guidelines [35, 36], therefore, 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. Our results show that probability of the intervention being cost-effective at willingness to pay values as low as $1000 per unit improvement in PG-SGA was >98% while it was 78% at a willingness to pay $50,000 per QALY gained.”

Following the recommendations of reviewer 1, best practice guidelines based on the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement (Husereau et al. 2013) were followed in this evaluation. In consonance with these guidelines, and as we explained in our previous responses to this reviewer’s comments on ICERS and in the revised manuscript, ICERS are not reported in our study as these are not meaningful since the intervention was both cheaper and more effective than the comparator.
In line with the recommendations in the CHEERs statement, it is our considered view that reporting negative ICERs (i.e. negative cost difference divided by positive changes in effectiveness), is not necessary but also not meaningful as the intervention dominates the comparator. We however still report mean incremental costs, PG-SGA and QALY gains in Table 1 for the interested reader to calculate these ICERs should they wish to do so.

We further refer the reviewer to the two references that we included in our previous response (i.e.[32] Husereau et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)-explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task

“Incremental cost-effectiveness ratios are generally the most useful summary measure for comparing different regulatory interventions. Such ratios are not meaningful, however, for interventions that reduce both cost and risks…”

Comment 5

Methods

* Page 7: Can you add a paragraph 'design of the study’?

Response 5: We have now added a new paragraph as suggested by the reviewer. Study design (Methods section, page 7)

“The data for this health economic analysis were obtained from a recently conducted nutrition intervention study [12], which was designed as a randomized controlled trial.”

Comment 6

Page 7, paragraph 2: Can you change 'target population' to 'participants’?

Response 6: This nomenclature is exactly as suggested in the CHEERs statement. No change has been made.

Target population

“The participants for this study included hospitalized patients aged ≥60 years, who were confirmed as malnourished by a qualified dietitian using PG-SGA tool [13].”

Comment 7
Can you add the information on the sample size calculation to your method section?

Response 7: Information on sample size calculation has now been added in the methods section by adding a new paragraph (page 8)

Sample size

“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) [14] in PG-SGA is clinically meaningful, assuming an affect size of 0.35, alpha=0.05 and power of 80% the estimated sample size was 86 (43 in each group) was calculated to be sufficient.”

Comment 8

Page 9, paragraph 2, line 10-11: Can you add the manufacturer of the ONS?

Response 8: The manufacturer of the ONS has now been included as advised. (page 9)

“The ONS utilized were Resource (Nestle Heath Science) (475 kcal, 19.7 g protein) and Sustagen (Nestle Heath Science) (248 kcal, 12.5g protein)”

Comment 9

Page 9, paragraph 2, line 20: This sentence is not grammatically correct: 'the patient' versus 'their'.

Response 9: This has now been corrected. (page 10)

“In addition, the patients and their care-providers received dietetic counseling, to augment their energy intake by using a range of strategies including….”

Comment 10

Page 9-10 'Intervention': I have some linguistic suggestions: 'increasing the number of meals they ate'; 'collect information about their recent weight'; 'They The participants received dietetic counseling'; 'In this trial, the dietician assessed the patients as compliant to the nutritional care plan if they …

Response 10: This has been changed as suggested by the reviewer. (page 10)

“In this trial, the dietitian assessed the patients as compliant to the nutritional care plan if they were able to meet at least 75% of their energy and protein requirements.”

Comment 11
Page 10 'Control group': 'Dietetic input occurs only if patients are flagged as high risk of malnutrition and referred by a health care professional with no dedicated outpatient follow-up after discharge.' This sentence reads difficult. Can you reformulate this sentence?

Response 11: This has been reformulated as advised. (page 11)

“However, dietetic input occurs only if clinicians refer the patients and even if a dietitian sees them during hospital admission, they may not be followed after discharge.”

Comment 12

Page 11: suggestion: 'Patients referred to the ward dietician were offered the same nutritional care plan …'

Response 12: This has been modified as suggested. (page 11)

“If control patients got referred for a dietetic advice, then they were offered the same nutritional care plan as the intervention group but only for the period of hospitalization but with no post discharge follow up care.”

Comment 13

Can you summarise the results of the validity and reliability of the EQ-5D-5L?

Response 13: The validity and reliability of EQ-5D-5L has been summarised as advised. (page 13)

“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 and has been found to have a stronger convergent validity coefficient (Spearman’s coefficient 0.51-0.75) and a higher absolute informativity (Shannon’s index) as compared to the EuroQol 5 Dimensions 3 Levels EQ5D 3L [23-25].”

Comment 14

Page 14, paragraph 2, line 4: Can you specify what you mean with 'natural units’?

Response 14: This has been now clarified by adding PG-SGA. (page 15)

“CEA is a type of economic evaluation whose outcomes are expressed in terms of natural units such as life expectancy or change in PG-SGA scores…”

Comment 15

Results
* Page 16, paragraph 2, line 14: can you at the unit of measurement (days) to the numbers?

Response 15: This has now been specified in days as suggested. (page 17)

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

Comment 16

Discussion

* Page 18, paragraph 2, line 6: 'In line with best practice guidelines, therefore, our analysis focused on determining the likelihood of the intervention being cost-effective …' Do these guidelines provide reasons why to focus on the likelihood of an intervention being cost-effective rather than on clear numbers (ICER's)?

Response 16: We do not understand this comment because we never make this assertion in our paper that the focus should be on the likelihood of an intervention being cost-effective rather than on clear numbers (ICER's)? Rather, our only reference in the paper to this issue is on page 19 and it is in relation to hypothesis testing:

“In line with best practice guidelines [35, 36], therefore, 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.”

This is because, in part, hypothesis testing would ideally require appropriate sample size calculation powered on the joint distribution of the difference in costs and benefits between treatment arms [Petrou 2011]. However, this is challenging because “… large sample sizes may be needed to detect statistically significant differences because of the large variability in use of healthcare resources and cost measures, and this may be neither financially nor ethically acceptable” [Page 2, Petrou S. “Economic evaluation alongside randomised controlled trials: design, conduct, analysis, and reporting” BMJ 2011; 342 doi: https://doi.org/10.1136/bmj.d1548]

Comment 17

It seems like very little qaly's were gained: 0.005 per patient. Can you explain, that, although this little gaining, you can conclude that the intervention offers value for money based on your secondary outcome?

Response 17: Our conclusion was based on the following:

a. the intervention was both cheaper and also more effective than the comparator

b. the results shown in the cost-effectiveness acceptability curve (CEAC) indicated that the intervention had a 78% probability of being cost-effective when compared to the
comparator at a willingness to pay of $50,000 per QALY gained, the implicit cost-effectiveness threshold used in Australia.

In terms of the 0.005 QALY gain value, we are not aware of any thresholds, akin to the ‘minimum clinically important differences (MCIDs)’ used for health-related quality of life instruments such as the EQ-5D, which apply to QALY gains. Therefore, while 0.005 QALY gains can be considered to be insignificant by some, we do not believe that this is universal. For instance, Bergomo (2014) reports that QALY gains as low as 0.001 were shown to lead to conclusions that interventions were cost-effective [Bergmo TS “Using QALYs in telehealth evaluations: a systematic review of methodology and transparency” BMC Health Services Research 2014, 14:332]. Further, Drummond (2001) also argues that as long as the ultimate objective is to aid resource allocation decisions, it is the difference in incremental cost per QALY and not the improvement in utility (and ultimately QALY) that is important [Drummond M. “Introducing economic and quality of life measurements into clinical studies”. Ann Med 2001, 33(5): 344–34959].

To highlight the possibility of 0.005 QALY gains being considered insignificant, however, we have included the following caveat within the limitations: (page 22)

“The difference in QALY gains in this study can be considered to be small and therefore our result on the effectiveness should be interpreted with caution. The overall economic evaluation results nevertheless considered these QALY gains jointly with cost differences as is appropriate.”

Comment 18

Conclusion

* Can you specify your primary and secondary outcome, so your conclusion can be read independently from your report.

Response 18: The primary and secondary outcomes has now been specified in the conclusion section as advised. (page 23)

“For both primary (change in PG-SGA scores) and secondary outcomes (QALY gains), 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 as the intervention was both cheaper and more effective than the comparator. This conclusion was supported further by results of the CEACs that showed that the intervention had a high likelihood of being the cost-effective option over a range of willingness to pay values.”

Comment 19

* Is this conclusion really valid for your secondary outcome 'incremental cost per qaly gained'? It also seems like very little qaly's were gained (0.005 per patient).
* Can you add on which base you can draw these conclusions?

Response 19: Please see our responses to comment 17 from this reviewer above.

We have amended the conclusion as follows: (page 23)

“For both primary (change in PG-SGA scores) and secondary outcomes (QALY gains), 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 as the intervention was both cheaper and more effective than the comparator. This conclusion was supported further by results of the CEACs that showed that the intervention had a high likelihood of being the cost-effective option over a range of willingness to pay values.”

Comment 20

Table 2

The total DRG costs are the same for the base case analysis as for the sensitivity analysis. Is this correct?

Response 20: Yes this is correct. There were no missing DRG cost data and since pairwise deletion was used in the complete case analysis as shown by the sample sizes in Table 2, the same mean DRG costs applied for both the base case and sensitivity analyses.

Comment 21

The total intervention costs are the same for the base case analysis as for the sensitivity analysis. Is this correct?

Response 21: Yes. This again is because of the same reason as that for the DRG costs

Comment 22

Figure 3

* I don’t understand why there is no difference in the probability of the intervention being cost-effective for the different willingness to pay values.

Response 22: This is because the probability does not change appreciably at (lower) willingness to pay values shown in the graphs. The probability only begins to change significantly at much higher WTP values. We attempted to show this in our initial submission but these figures were edited at the suggestion of both reviewers so that the WTP values cited in the text could be read off much easier in the CEACs. Please note that our curves are not unique to us, as others representing the uncertainty around economic evaluation results where one intervention
dominates the other have also shown similar results. See for instance the highly referenced article by Fenwick et al [Fenwick et al. “Using and interpreting cost-effectiveness acceptability curves: an example using data from a trial of management strategies for atrial fibrillation” BMC Health Services Research 2006, 6:52 doi:10.1186/1472-6963-6-52]