Reviewer’s report

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

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Reviewer: Karen Freijer

Reviewer’s report:

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.

Abstract:

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.

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

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.
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).

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.

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?

Methods:

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

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?

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 (line 33-34/page 9) - so no protocol? Describe the difference for this aspect in intervention compared to control group

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)

Headings "Outcome measures, cost analysis, Analysis, Economic evaluation": please change these according to more understandable structure and headings as described in CHEERS. Results are based on the EXTRA costs related to the EXTRA Effectiveness. Describe and explain clearly which were the extra costs - e.g. extra resource use = extra time of dietician (incl extra time of contact between patient and dietitian based on patients individual needs (line 32-34/page 9) and the extra time for telephone consults in the period after discharge), extra length of hospital stay ? (line 51/page 10), extra costs for nutrition (snacks, enriched food, ONS); classify these costs into direct (medical/non medical) and indirect (medical/non medical) and reasoning for the choice: depending on perspective, available data etc). Also explain somewhat more which costs exactly were meant by Pharmaceutical costs and same for "… centralized costing" (line 46/page 10)

Same for detailed description and reasoning for the extra effectiveness that is used in this cost-effectiveness study - related to extra resources used measured as … e.g. length of stay, PG-SGA unit improvement, changes in utilities etc
Then describe and rationalize the choice for the type of economic analysis with explanation and reasoning etc etc. Again take into account that the readers are mostly not known with health economics - even not the basics.

Line 19-20/page 11: Heading Analysis.. do you mean Statistics?

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.

Results:

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

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?

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

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

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

Please add the results on ICER's

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

Line 36-42/page 14:" ..... intervention would be considered cost-effective". How can this be concluded while the costs difference is not sign and also the QALY difference is not sign. Perhaps ICERs are sign? Need the information. Only the difference in unit PG-SGA is sign.

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

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!

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… .

Discussion:

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

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.

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…

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

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**

If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

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Please indicate the quality of language in the manuscript:

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