PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Economic Evaluation alongside the Probiotics to Prevent Severe Pneumonia and Endotracheal Colonization Trial (E-PROSPECT): Study Protocol
AUTHORS	Lau, Vincent; Cook, Deborah; Fowler, Robert; Rochwerg, Bram; Johnstone, J; Lauzier, François; Marshall, John; Basmaji, John; Heels-Ansdell, Diane; Thabane, Lehana; Xie, Feng

VERSION 1 – REVIEW

REVIEWER	Gunilla Björling The Swedish Red Cross University College, Sweden Karolinska institutet, Sweden Kilimanjaro Christian Medical University College, Tanzania
REVIEW RETURNED	04-Mar-2020

GENERAL COMMENTS	Thank you for this interesting study protocol. PROSPECT (Probiotics to Prevent Severe Pneumonia and Endotracheal Colonization Trial) is a very well planned and interesting study and the results of the study can lead to new treatment guidelines in the field. Concerning this health economic evaluation, my impression is that it is well planned, the outcomes are relevant and important. It is as well good that QALY is taken in to consideration in the results. I have no comments on the study protocol and look forward to read the results of the project.

REVIEWER	Felix Achana University of Oxford
REVIEW RETURNED	10-May-2020

GENERAL COMMENTS	This is well-designed cost-effectiveness analysis alongside a multinational/multicentre randomised controlled trials with study centres in Canada and the USA, and possibly Saudi Arabia? The primary outcome is the incremental cost per VAP avoided over the study follow-up. The main strengths of the study are the study design (utilising RCT as vehicle to collect costs and effects) and description of detailed costing exercise to capture relevant resource use and costs. The primary weakness seems to be a lack of cost-utility analysis and shorter-time horizon over which cost-effectiveness will be evaluated. It would have been nice to see plans for modelling to extrapolate outcomes over longer-time/lifetime horizons and evaluate feasibility of estimating the cost/utility value of the probiotic. the only other comment I have relates to the planned statistical analysis of the data. The authors have described the statistical methods for summarising the data but cannot see description statistical analysis for generating incremental estimates of costs and effects. Although this is

	economic evaluation alongside randomised controlled trial, it may be necessary to perform a regression analysis to adjust for residual confounding after randomisation. Also, the study is multicentre and possibly multinational, which generates its own issues when it comes to analysis of costs and effects.

VERSION 1 – AUTHOR RESPONSE

Revision #1

Comments from the Editor:

Comment #1: Please remove the article focus and key messages sections. These are not requirements for BMJ Open.
Response #1: This has been removed as per request from BMJ Open.

Comment #2: Please revise the 'Strengths and limitations' section of your manuscript (after the abstract). This section should contain five short bullet points, no longer than one sentence each, that relate specifically to the methods. The results of the study should not be summarised here.
Response #2: This has been revised as per your request.

Comment #3: Please remove the article summary section on page 9. This is also not a requirement for BMJ Open.
Response #3: This has been removed as per your request.

Comment #4: Can you please move the first two paragraphs of the 'acknowledgements' section to a separate 'funding' section?
Response #4: This has been changed as per request from BMJ Open. We now have separate funding and acknowledgement sections.

COMMENTS FROM REVIEWER #1:

Reviewer #1:
Comment #5: Thank you for this interesting study protocol. PROSPECT (Probiotics to Prevent Severe Pneumonia and Endotracheal Colonization Trial) is a very well planned and interesting study and the results of the study can lead to new treatment guidelines in the field. Concerning this health economic evaluation, my impression is that it is well planned, the outcomes are relevant and important. It is as well good that QALY is taken in to consideration in the results. I have no comments on the study protocol and look forward to read the results of the project.
Response #5: Thank you.

COMMENTS FROM REVIEWER #2:
Comment #6: This is well-designed cost-effectiveness analysis alongside multinational/multicentre randomised controlled trials with study centres in Canada and the USA, and possibly Saudi Arabia. The primary outcome is the incremental cost per VAP avoided over the study follow-up. The main strengths of the study are the study design (utilising RCT as vehicle to collect costs and effects) and description of detailed costing exercise to capture relevant resource use and costs.
Response #6: Thank you for these favourable comments. Yes, the trial will include data from Canada, the United States and Saudi Arabia.

Comment #7: The primary weakness seems to be a lack of cost-utility analysis and shorter-time horizon over which cost-effectiveness will be evaluated. It would have been nice to see plans for modelling to extrapolate outcomes over longer-time/lifetime horizons and evaluate feasibility of estimating the cost/utility value of the probiotic.
Response #7: Unfortunately, the original design of the trial did not incorporate tools using health-related quality-of-life metrics like Euro-Qol-5D (this was not collected prospectively or part of the a priori design). As a result, there is no cost-utility analysis component of the E-PROSPECT economic evaluation; thus, we will be primarily focusing on the cost-effectiveness and cost per event prevented (i.e. ventilator-associated pneumonia, etc.). However, in future studies, we hope to include both cost-effectiveness analysis (CEA) and cost-utility analysis (CUA) methodologies which requires planning at the time of the design of the foundational randomized trial. For the PROSPECT economic evaluation, we will focus on CEA.

Comment #8: The only other comment I have relates to the planned statistical analysis of the data. The authors have described the statistical methods for summarising the data but cannot see description statistical analysis for generating incremental estimates of costs and effects.
Response #8: The description for statistical analysis plan (SAP) for generating incremental estimates of costs and effects are located in the “Base-Case Cost Effectiveness Analyses” sections:
Base-Case CEA: “The base case incremental cost-effectiveness ratio (ICER) is the ratio of incremental costs per VAP prevented of probiotics versus usual care during the period of hospitalization (from ICU admission to hospital discharge or death)”.
• This is in addition to the statistical analysis plan for generating confidence intervals around these point estimates using non-parametric bootstrapping to utilize the entire study population’s costs and effects to plot a CEA plane (see Uncertainty Analysis)
o “We will perform a probabilistic sensitivity analysis of pairs of known costs and effects, using non-parametric bootstrapping techniques to generate 95% confidence intervals. We will perform 1000 bootstrap simulations in the following manner: each simulation will draw the same number of patients per group (as per intention-to-treat), with replacement (for both events and cost) in pairs. For each sample, the difference in event rate and cost was calculated, obtaining 1000 pairs of differences in cost and event rate.”
In response to the reviewer’s comment, we have added a statement regarding generation of incremental estimates of costs and effects: (written in manuscript)
• “Clinical events such as VAP (primary outcome), CDAD, AAD and hospital mortality (secondary outcomes) will be gleaned from PROSPECT, with a statistical analysis methodology previously described. For the dichotomous outcomes, we will use time-to-event analyses. Hazard ratios and associated 95% confidential intervals will be estimated using a stratified Cox proportional hazards model. For continuous outcomes, we will report estimates of the difference between intervention and control groups, 95% confidence intervals (CIs) and associated p-values. (Page 5, Line 28).
• With these clinical outcomes above, we will then calculate incremental effects: “These dichotomous outcomes with proportions and continuous outcomes with point-estimates (e.g. length of stay, which will be used for calculation of resource utilization) will be used to calculate both incremental costs (resource utilization) and effects. Incremental effects will be defined as the difference in per-patient event rates or the difference in proportion of a clinical event (e.g. VAP) between groups. (Page 5, Line 32).
• We further go on to state (Page 7, line 32): “The incremental mean costs will be estimated from all patients in both groups based on multiplying the resource unit cost by resource utilization as described above. The incremental mean effects will be derived from PROSPECT, where incremental effects were defined as the difference in per-patient event rates or the difference in proportion of a clinical event (e.g. VAP) between groups.”

Comment #9: Although this is economic evaluation alongside randomised controlled trial, it may be necessary to perform a regression analysis to adjust for residual confounding after randomisation.
Response #9: We agree that adjustment for residual confounding may be required after randomization. Primary Cox regression modeling has been proposed in the SAP for E-PROSPECT previously, however, in response to the reviewer's comment, we have now added a more explicit statement to this effect in our protocol as well: "Regression analyses may be performed if there is residual confounding, based on previously described methodology [20]" (Page 7, Line 16).

Comment #10: Also, the study is multicentre and possibly multinational, which generates its own issues when it comes to analysis of costs and effects.
Response #10: We agree with issues of multi-center/multi-national costs and effects (costs especially). We have a multi-level approach to either acquire jurisdictional unit costs through pilot testing, impute or use a mean unit cost approach (as described in our Methods under "Unit Costs"). We are also in the process of pilot testing our unit cost data extraction based on previously described methods to obtain as many jurisdictional unit costs as possible. If there are only a few jurisdictional unit costs missing, a cost ratio imputation may be utilized in that setting (see previously described methods). For jurisdictions which likely will have very few unit costs to provide, a mean unit cost approach across all jurisdictions will be applied. Overall, we included jurisdiction-specific unit costs as many as we can to capture variability in costs among centers while also enhancing the external validity and generalizability of unit cost acquisition.
In regards to differences in effects, the PROSPECT protocol has previously described independent and blinded adjudication by the PROSPECT researchers centrally. Therefore, variability in the measurement of effects across centers and jurisdictions should hopefully be minimal given the centralized adjudication schema.

We have also re-submitted all supplemental files as PDFs, and have removed citations 46-55 (as they are not in the main document). A marked and clean copy of the main documents are also uploaded.

VERSION 2 – REVIEW

REVIEWER	Felix Achana University of Oxford UK
REVIEW RETURNED	20-May-2020

GENERAL COMMENTS	The authors have addressed all queries satisfactorily.