Author's response to reviews

Title: Randomised placebo-controlled trial on antibiotics for bronchiectasis exacerbations in children: rationale and protocol

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Author's response to reviews: see over
27th July 2012

Dear Editors

Re: Submission of manuscript for protocol “Randomised placebo-controlled trial on antibiotics for bronchiectasis exacerbations in children: rationale and protocol”

Thank you for the review and re-considering publication of our multicentre study protocol in Trials.

We have amended the manuscript in accordance to the suggestions. We have also updated the ‘Trial status’ and corrected a few errors; all using track changes.

Thank you.

Kind regards

Anne Chang on behalf of co-authors

Reviewer’s comments

- As the trial is well designed and the paper is well written, from my opinion, it merits acceptance for Trials. My only major concern requiring compulsory revision is about multiplicity. Greater alpha consumption that the 0.05 specified can come from two ways. The first one is the interim analysis. Authors should specify the way they will take into account the previous formal look. [As they specify 0.001 for the first look, a straightforward procedure can be performing the second test at a 0.049 level.] The second one is the existence of 2 active treatment arms. If authors are willing to report as positive a result in only one active arm, they should recognize that the alpha levels from both tests 'add in some way' and the chances to declare a treatment as effective are greater than just 5%. If, for example, authors would claim that treatment A is positive unless treatment B is not, they should, for example, adjust individual alpha levels. Please note that first line in page 7 can be interpreted in the sense that the trial would only be positive if both treatment arms were statistically significant. If that is the intention, multiplicity is not a concern, but then, trial power is affected. Please clarify this sentence.

Response: Thank you for correcting our error. We have amended these by splitting the primary question, altered the alpha level and adjusted the power of our study based on the amended alpha value. We have also added a sentence to the primary outcome analysis (pg 17) to reflect the suggestion above.

Minor essential revisions

- As both active treatments are compared with the same treatment arm, maximum efficiency is achieved if more patients are allocated to the placebo arm -that is employed in both comparisons. Optimal allocation ratio is 1:1:sqrt(2). If, for ethical concerns, authors want to still in a 1:1:1 ratio, this may be highlighted.

Response: This suggestion has been added to the sample size section (pg 16).
• As the power for highlighting safety concerns would be different for the non numerable possible outcomes (any expected or unexpected adverse event), please consider deleting the requirement for statistical significance in the DSMC safety revisions.

Response: We have not done this as we are required a-priori to specify what we would consider ‘significance’. However we have added that the study is not powered for adverse events.

Discretionary revisions

• Please, consider reporting sample size and number of centres in the abstract.

Response: This has been added and other sections of the abstract truncated to maintain word count limits.

• Please, consider either deleting first words in line 8, page 6; or addressing the objectives of the second component of BEST.

Response: This objective of the component of BEST has been added to the revised manuscript (pg 6).

• In order to become fully confirmatory and to avoid ambiguities in predictors selection, please, consider fully specifying them in a prior to unmasking

Response: The predictors have been added to the revised manuscript (pg 16).

• Statistical Analysis Plan. Please consider changing in page 15 lines 11-13 as well as the last one. (Please, see baseline comparisons in the CONSORT statement).

Response: Done as suggested. We have retained the per protocol analysis component as we feel it is important.

• Please, consider clarifying methods and length of follow up for the secondary outcome "time to next exacerbation".

Response: Thank you for identifying this omission, which we have corrected in the revised manuscript (pg 10).

• Please, consider changing "hospitalised" by "previous hospitalised" in page 5, line 12.

Response: Word added as suggested.

• Please, consider changing "examine" by "explore" in page 6, point 2. (Should this exploration be performed with a subgroup analysis?)

Response: Changed as suggested.
• Please, consider reporting centres in the same order in pages 8 and 9.

Response: Changed as suggested.