Author’s response to reviews

Title: An economic analysis of human milk supplementation for very low birth weight babies in the USA

Authors:

Grace Hampson (ghampson@ohe.org)

Sarah Richards (sarah.l.roberts@kcl.ac.uk)

Alan Lucas (a.lucas@ucl.ac.uk)

David Parkin (dparkin@ohe.org)

Version: 2 Date: 02 May 2019

Author’s response to reviews:

Thank you for a really useful set of comments. We believe these have improved the manuscript. Our responses are as follows:

Editor

We note that reviewer 2 feels that you didn't fully reply to them in the first round of revision. We would offer you the opportunity to reply to their comments, and also would ask you to more directly address one of their original points: "Moreover, the paper does not include any validation exercise of the model, which is necessary for conducting further simulations." We do feel that this is a valid comment, and either needs to be addressed with information about validation, or an outline of the limitations the lack of validation of the model introduces to the study.

Thank you. We have now added the following text to the discussion section:

In terms of model validation, we considered the Assessment of the Validation Status of Health-Economic decision models (AdViSHE) tool [26]. The tool does not give a validation score, but invites model developers to think through various elements of validation of the conceptual model, data inputs, the computerized model, and operational aspects. The model has undergone cross validity testing with other conceptual models; extreme values testing and tracking of patients through the model; and validation in comparison to alternative analyses and using alternative input data. Validation could be further built upon by seeking additional validation on the choice of input variables and results with a panel of clinical experts. This was not within scope of the current analysis.
Reviewer 1

1) Page 4, line 21 "supplemented by" is repeated twice

Thank you. This has now been deleted.

2) Reference 14 is now a published manuscript: https://protect-eu.mimecast.com/s/4-i-CREMumBXkcOFquo?domain=ncbi.nlm.nih.gov - this trial has also had an economic evaluation published alongside it (https://protect-eu.mimecast.com/s/aKY0CVL5iw98LIQ87aa?domain=ncbi.nlm.nih.gov)

Thank you for pointing this out. Unfortunately these papers do not report the data we require (only severe RoP which has substantially different incidence and resource implications) so we have kept the original reference, but have removed the text which states that no full paper is available.

Reviewer 2

The authors made some revisions on the framework in Figure 1, which is still preliminary.

The figure shows the complete clinical structure that is reflected in the model – there is no more that we can add at this stage.

Moreover, the authors did not provide convincing evidence, such as other published studies, to demonstrate the validity of the results on the benefits, i.e. the results on mortality reduction are still beyond reasonable estimation.

Apologies, we had previously mis-read your comment as applying to NEC rather than mortality, and thus did not review the correct content or respond adequately. You raise a really important point. We had previously (in line with best practice) used the mortality rate from the cohort data (Hair et al.) to reflect mortality with usual practice of care and applied the treatment effect from the trial data (Abrams et al.) to calculate mortality with EHMD. However, as you have pointed out, this results in an unreasonable estimate of lives saved. For this reason, we have now changed this to use only the retrospective cohort study data (Hair et al.) to reflect mortality. This data is chosen because it is less favourable to EHMD (and is therefore a conservative assumption) than the trial data. This results in a smaller number of lives saved (36 in a hypothetical cohort of 1,000) which is in line with the published data. The results (Table 3, 4, main text (including sensitivity analyses) and abstract) have been updated accordingly. The EHMD now results in greater cost savings than previously, as fewer lives are saved, and therefore fewer babies incur healthcare costs. The previous results are retained as a sensitivity analysis.
The text in the methods has also been edited to reflect this change in inputs. The explanatory text now reads as follows:

“There is one exception to this, where for mortality we use estimates from the retrospective cohort study [13] to estimate mortality in the usual practice of care and EHMD groups in the base case. This is because, for this outcome, combining the data sources resulted in what appeared to be an unrealistically high number of lives saved by the EHMD. These results are presented separately as a sensitivity analysis.”

We have also revisited your original comment on validation, and have added the following text to the discussion section:

In terms of model validation, we considered the Assessment of the Validation Status of Health-Economic decision models (AdViSHE) tool [26]. The tool does not give a validation score, but invites model developers to think through various elements of validation of the conceptual model, data inputs, the computerized model, and operational aspects. The model has undergone cross validity testing with other conceptual models; extreme values testing and tracking of patients through the model; and validation in comparison to alternative analyses and using alternative input data. Validation could be further built upon by seeking additional validation on the choice of input variables and results with a panel of clinical experts. This was not within scope of the current analysis.