Author's response to reviews

Title: Prioritising neonatal medicines research: UK Medicines for Children Research Network scoping survey

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Author's response to reviews: see over
Responses to comments from BMC reviewers MT 290609

We are very grateful to the reviewers for their perceptive suggestions about how to clarify the presentation of this work.

We have redrafted the MS considerably. This has led to a large number of changes. In this letter we have respond to the issues raised by the reviewers.

**Reviewer 1**

1. Is the question posed by the authors well defined?
   Yes, the questions posed by the authors are well defined.

2. Are the methods appropriate and well described?

   The methods used to analyse question 1 “Which medicines do you use on your Neonatal Unit?” are not adequate. Although the paper Choonara, I. and S. Conroy, “Unlicensed and off-label drug use in children” provides definitions for the terms “unlicensed” and “off-label” the authors seem to use and analyse only the “not licensed drugs”. “off-label” is not described and defined although it should have a much higher percentage than the “unlicensed” drug use.

   We agree with the importance of distinguishing between “unlicensed” and “off-label”. Unfortunately, we were not able to make this distinction on the basis of the information available to us. We wished to examine the information available to prescribers. We used the BNFC as the source document for information about medicines since it is the primary source of information for UK prescribers. The BNFC does not distinguish between off-label and off-license. It indicates which medicines are not covered by a marketing authorization with the phrase “off-license”. In almost every case for neonates, the medicines will be off-label. However, we have reported what our primary source says. We could have used other sources to dissect out the distinction between “unlicensed” and “off-label” but this would have detracted from our aim of examining an information source in everyday use.

   We have revised the methods section to clarify this point.

   Question 2 of the survey “What are the most important therapeutic gaps?” poses an open question to the neonatologists. So the wording of the answers concerning the “therapeutic gap” should be very versatile. In the methods section it is therefore important to describe how these different wording was grouped together to form the final ranking list provided in figure 1.

   The classification was done independently by two authors. We have amended the methods section accordingly.
It might have been better to offer an array of therapeutic areas to the neonatologists to have a more standardized answer.

One aim of this survey was to give a voice to the concerns of all units. For example, it is possible that the perspectives of large units may not be the same as the perspectives of small units. We deliberately chose an open question so that each unit could express their concerns.

The response rate of 36% is not representative. Surveys should have response rates above 50% minimum, especially when the network has dedicated itself to solve this kind of problem. Maybe it had been worth to send a third or fourth reminder.

Each unit was sent an initial deadline and two further reminders. Thus, each unit was given 3 prompts to return the survey.

We believe that the rate of return was sufficient to describe the pattern of medicines use for the purpose of examining information available for prescribers in the national formulary. It is unlikely that we missed a medicine in common use on UK neonatal units. The response rate limits the interpretation of the absolute numbers of neonates receiving each medicine, which is why we have not emphasized that issue.

We have amended the methods, results and discussion sections of the paper in the light of this comment.

This network is voluntary and unfunded. Although the response rate is less than we had hoped for it does indicate that at least one third of UK neonatal units were committed enough to complete a time-consuming survey. We believe that it is important to be transparent about the strengths and weaknesses of our network by reporting our response rates.

The definition of the child classes should be done according to international classification systems (EMEA or FDA): Please clarify the term “term infant” and “preterm infant”. It might be “preterm neonate” and “neonate” i.e. “newborn”.

Done

3. Are the data sound?

No, the data are not sound. The definitions of the terms “licensed”, “prescription for medicines” and “medications” are not appropriately done. The authors write: “6.2% of prescriptions were for medicines that had neither licenses nor doses specified for term and preterm infants. 63.5% of medications were missing a license or dose for either term or preterm infants.” What is the difference between the “prescriptions for medicines” and the “medications”. The numbers seems to
be very different and it is not clear whether there is a difference concerning the drug treatment.

We are grateful to the reviewer for pointing out the poor choice of words here. We have amended the MS at several points in the light of this comment and reconstructed what was Table 1 and is now Table 2.

In the revised MS we have rationalized the terminology. We have used the phrase “medicine-patient pairs” throughout the MS and defined this term in the Methods section. The Abstract, Results and Discussion have been redrafted.

We have taken the opportunity to correct a typographical error in the data presentation.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?

No, see answer to question 2 and 3.

5. Are the discussion and conclusions well balanced and adequately supported by the data?

6. Are limitations of the work clearly stated?

The most relevant limitation of the word, the low response rate, is clearly stated.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
   Yes

8. Do the title and abstract accurately convey what has been found?
   Yes

9. Is the writing acceptable?
   No, the writing is not acceptable. It is necessary the use and / or define standardized terms for describing the population investigated and the classification systems referring to.

   We are grateful for this comment which has prompted us to revise the MS extensively.
Reviewer 2

This is a very useful and interesting paper for paediatric professionals and researchers. The methodology is simple but effective. I have given some suggestions to improve the paper.

Discretionary Revisions:
The authors should consider adding the following information to the background to strengthen the rational of the study:

1) Prioritisation of research needs in medicines for children should take two important assessments into consideration: public health assessment comprising the severity and prevalence of disease and the availability of treatment alternatives (EMEA 2006); and assessment of use. This may comprise the frequency or volume of use and the licensing/labeling status of medicines for children (Ackers et al 2007, Sturkenboom et al 2008). The present study is providing much important information in medicines for neonates.


We have amended the MS to take account of these helpful suggestions.

Results:
Discretionary Revisions:
2) The authors should provide more detail and compare the characteristics of responding and non-responding neonatal units as to whether there are any significant differences.

We have done this by reporting the level of care provided by each unit and the nation of each unit. We have compared the responders to the non-responders according to level of care provided and according to nation (new Table 1).

Minor Essential Revisions:
3) Figure 1 has unexplained aberrations.

We presume this comment should read “abbreviations”. The abbreviations are explained in the Figure legend which is included in text of the MS (page 9).