Reviewer's report

Title: Enteral vitamin A for reducing severity of bronchopulmonary dysplasia in extremely preterm infants: a randomised controlled trial

Version: 2 Date: 01 Jul 2017

Reviewer: Erik Jensen

Reviewer's report:

This manuscript describes the protocol for an RCT evaluating oral vitamin A. This is an important medication to evaluate using a robust experimental design. I have a few questions/comments for the authors to consider.

1. Regarding the title. The primary outcome of the study is a reduced severity of BPD, not prevention. Would a title that states this more clearly be appropriate?

2. The background sections state that the use of vitamin A is not widely accepted because of discomfort and the risk for trauma. I would suggest a slightly more detailed discussion here may be warranted. The Tyson trial did not find major issues with trauma, although I agree some clinicians and families may have concerns regarding this. Other issues with IM vitamin A that limit use have been significant drug shortages, high cost, as and questions of efficacy. The 95% CI about the NNT in the Tyson trial is large and during the US shortage, there was no evidence of a change in BPD rates from pre/post availability -leading some to question the true efficacy of the drug.

3. The authors may want to use the term enteral throughout rather than non-invasive to describe the administration route for the medication. Some may consider naso/oral-gastric tube administration to be "invasive." While not a needle stick, it does require placing a catheter into the body.

4. Re background. Antenatal steroids have not been shown to reduce BPD, however postnatal steroids have. I agree good nutrition is important, but also not sure that has been proven to prevent BPD as well.

5. The criticism of the existing oral vitamin A trials for lacking sufficient power to detect differences in BPD rates is sound. However, will this trial have sufficient power to detect a difference in BPD rates? I understand that isn't the primary outcome, but this trial may potentially suffer the same criticism if underpowered for BPD?
6. Regarding the RDR assessment - will this be done in the placebo patients as well - or at least blood draw in both. The text says that the blood sample will be collected after administration of 5000 IU vitamin A. Presumably this would be after placebo as well unless unblinding will take place?

7. Re sample size - if the primary outcome is assessed in an in-hospital assessment and that is used to determine the sample size, what is the 20% "loss to follow-up" expected to result from?Trial exit by family/physician request? early deaths? May help to mention this as follow-up (I imagine this is post-discharge?) isn't stated as a study outcome.

8. My greatest concern with the protocol is the primary outcome. My understanding of the Quine et al. paper is that this maneuver was only conducted in infants with BPD who were receiving nasal cannula support. Infants breathing in room air and those on higher support (CPAP, mechanical ventilation) were not evaluated. How will the proposed assessment of V/Q matching in this trial be conducted in infants on room air and receiving higher level support? Is the comparison between infants receiving low and high level respiratory support valid? Will for instance the R shift of a baby on high mean airway pressure while weaning FiO2 be corrected for the level of support when compared to infants receiving only low flow NC? The protocol also states that the lowest permissible FiO2 is 14%. Is the plan to trial some infants to less than standard oxygen in room air? Is this necessary - if infants are stable on room air do they require assessment with FiO2 < 21%? This is unlikely to be performed clinically by providers outside of this trial.

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?  
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