Reviewer’s report

Title: STUDY PROTOCOL FOR A PHASE II DOSE EVALUATION RANDOMIZED CONTROLLED TRIAL OF CHOLECALCIFEROL IN CRITICALLY ILL CHILDREN WITH VITAMIN D DEFICIENCY (VITDAL-PICU STUDY)

Version: 0 Date: 18 May 2017

Reviewer: K Madden

Reviewer's report:

The manuscript "Study Protocol for a Phase II Dose Evaluation Randomized Controlled Trial of Cholecalciferol in Critically Ill Children with Vitamin D Deficiency (VITDAL-PICU STUDY)" by McNally and Colleagues, is a placebo-controlled pilot study to determine efficacy of a loading dose in PICU patients. The authors aim "to determine whether the dosing protocol normalizes vitamin D status, defined as a blood total 25(OH)D concentration above 75 nmol/L. Secondary objectives include: an examination of the safety of the dosing regimen (hypercalcemia, hypercalciuria, nephrocalcinosis); measures of vitamin D axis function (calcitriol levels, immune function); and protocol feasibility (eligibility criteria, protocol deviations, blinding)."

The strengths of the manuscript is that it addresses an important question in pediatric critical illness, where vitamin D deficiency has been associated with severity and clinical outcomes, but feasibility of reversing that deficiency has not been established. Another strength is that it includes a much more rapid determination of 25OHD level, allowing only those patients with level <50 nmol/L to be enrolled, limiting chance of toxicity.

I have several questions about the methods section in its current format:

1) Methods: On P10, L 53, "The Safety Officer… will review each study participant's vitamin D level from the discharge blood sample to identify participants at potential risk for vitamin D toxicity in real time" is a bit vague. Will the Safety Officer review levels at a specified time period after receiving the intervention? With a great variation in the time of ICU stay, what about the long-stay patient who remains in the ICU for many weeks - will the safety officer review their levels at any point? What will their criteria (25OHD level) to intervene and break blinding?

2) Methods: P12 L22 - what about a case of severe vitamin D deficiency noted by the care team, where a recommendation from endocrine might be a large dose approaching the intervention dose? Is this possible based on clinical practice in these institutions? It seems that the potential exists for a "double dose" in these scenarios, increasing risk of toxicity.
3) Methods: P14 L36 - how have you accounted for the variability in pre-intervention 25OHD levels, variable GI absorption, etc in the assumption that 75% will achieve goal levels? Have you performed power calculations on the placebo arm sample size for the secondary outcomes? As the placebo arm is included only for the secondary outcomes, power calculations to justify exposures are warranted.

4) Methods: P14 L38 - you may want to account for more than 5% dropout, depending on how good the medical team is at predicting length of stay.

5) Methods: Table 2 - the prediction of expected ICU stay 48 hours and hospital > 7 days by the medical team will be interesting to analyze in and of itself and include in results for future planning of PICU trials.

**Level of interest**
Please indicate how interesting you found the manuscript:

An article of importance in its field

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

**Declaration of competing interests**
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.
I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal