Author’s response to reviews

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)

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Author’s response to reviews:

Thank-you for the reviewer comments, and for the opportunity to revise our manuscript. We have highlighted the comments from your journal in bold followed by our responses.

REVIEWER #1 COMMENTS:

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 (25(OH)D level) to intervene and break blinding?

RESPONSE: This should have said that the Safety officer would review the participant’s vitamin D level from the Day 7 sample (as was stated in Table 4) to identify participants at potential risk for vitamin D toxicity in real time. We have corrected this in the text. In the event that a patient has an elevated 25(OH)D level (defined as a 25(OH)D level >200 nmol/L), the Safety Officer will refer the patient to Endocrinology. Endocrinology will manage the patient and may elect to have the blinding code broken. The following text has been added to the last paragraph under Allocation Concealment and Blinding:

“In the event that a participant’s Day 7 25(OH)D level is >200 nmol/L, the Safety Officer will refer the patient to Endocrinology. The patient will be managed clinically as determined by Endocrinology, who may elect to unblind the participant.”

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.

RESPONSE: In the event that a patient presents with clinical symptoms of severe vitamin D deficiency (e.g. hypocalcemic seizures), and the treating physician plans to administer a high dose of vitamin D, the patient would not be enrolled in the study (excluded due to physician refusal). In addition, burn patients at participating sites are often administered a large dose of vitamin D as part of standard treatment. Again, if the treating physician planned to administer high dose vitamin D, the patient would not be enrolled. This was been added to the manuscript (see Interventions section).

3. Methods: P14 L36 - how have you accounted for the variability in pre-intervention 25(OH)D 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.

RESPONSE: The assumption that 75% of patients will achieve goal levels is based on our systematic review and meta-regression which analyzed the 25(OH)D response to high-dose vitamin D in children with varying initial 25(OH)D levels. To account for within group
heterogeneity, we assumed that ~16% of intervention group will not achieve target levels and arrived at the assumption of 75% achieving target as follows (text added to Sample Size section on p14): “Based on our systematic review and meta-regression we anticipate that 10,000 IU/kg will raise the vitamin D level by 70 nmol/l. Assuming a group average value of 40 nmol/L in the intervention arm, this will result in a post-load group 25(OH)D level of approximately ~110 nmol/L. Given a standard deviation of no more than 35 nmol/L we would anticipate that 16% of the group will not achieve a post-load value of 75 nmol/L (z-score of -1). However, given that some of the older children (weight above 40 kg) will receive less than 10,000 IU/kg, we have reduced our estimate of proportion achieving target to 25%.”

The placebo arm is essential for several reasons. First, we would not be able to determine the feasibility of recruiting patients into a placebo-controlled RCT within the control group. Secondly, we would not be able to evaluate our ability to maintain blinding without a control group. We have defined thresholds that must be met to establish feasibility of recruitment and maintaining blinding before proceeding to a phase III trial. These objectives are not compared between groups, but the control group is still required to determine whether feasibility can be established. Based on reviewer comments, we have modified the statistical analysis section to reflect that secondary outcomes (e.g. hypercalcemia, hypercalciuria) will be presented descriptively and that any comparisons between groups will be considered exploratory. This study will allow us to generate group means and confidence intervals for patients exposed and not exposed to the rapid restoration dose of vitamin D, which will support the design and power calculations for the subsequent trial.

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.

RESPONSE: Thank you for the suggestion. We feel that a 5% dropout rate is adequate when planning the sample size, as we have also specified a window of 48 hours for the Day 7 sample (primary outcome). Further, we have stated a priori that if bloodwork cannot be obtained on day 7 ± 48 hours (e.g. no access to bloodwork, patient discharged), the patient’s 25(OH)D level from Day 3 will be used for the primary outcome. We anticipate that the number of patients for whom we cannot obtain a Day 7 or a Day 3 sample will be <5%. As part of this pilot trial however, we will evaluate our ability to accurately predict ICU length of stay >48 hours and access to bloodwork at Day 7. Based on this evaluation, the expected dropout rate may be adjusted upwards when planning the subsequent phase III trial.

5. Methods: Table 2 - the prediction of expected ICU stay 48 hours and hospital > 7days by the medical team will be interesting to analyze in and of itself and include in results for future planning of PICU trials.
RESPONSE: Thank you for the suggestion. We agree that this data will be interesting to analyze and valuable when planning future stages of this research program or for other PICU trials.

REVIEWER #2 COMMENTS:

1. Page 0: Abstract: Could authors provide date rather than continue until fall Page 4: Abstract: Line 11: Could authors provide date rather than fall.

RESPONSE: The date has been provided in the abstract on pages 0 and 4. We anticipate that recruitment will end by November 30, 2017.

2. Randomization Page 9: Line 58: Why was 30 days of age chosen for stratification?

RESPONSE: The following explanation has been added to the manuscript to explain why we have chosen to stratify by age: “We have decided to stratify by age as neonates can respond uniquely to medications due to different water/fat content, hepatic and renal functioning. Further, calcium homeostasis and the definition of abnormal for both hypercalcemia and hypercalciuria are different for neonates. Stratification by neonatal status (age <30 days/admitted to NICU) will ensure that these differences are equally distributed between the two groups.”

3. Statistical Analysis Page 16: There appears to be a lot of hypothesis tests being undertaken. However, as this is feasibility/Pilot study the study isn't powered to detect differences between groups. Could authors provide more justification for undertaking the tests?

RESPONSE: We have modified the statistical analysis section based on this comment and comments from the editor. The focus of analysis for secondary outcomes will be to provide estimate for the outcome and understand potential variability (e.g. standard deviations and confidence intervals). Secondary outcomes will be presented descriptively by group, with any between group comparisons considered exploratory.

4. Protocol feasibility - How will this be decided, what are success criteria, for recruitment etc.?

RESPONSE: The success criteria for protocol feasibility were previously summarized in Table 3, however in response to this comment and comments by the editor, we have outlined the success criteria in detail within the manuscript (see Outcomes section, page 13).
EDITOR COMMENTS:

1. Randomisation: It is not usual to include the block size in the protocol - please could you remove reference to the block size?

RESPONSE: This text regarding block size has been removed.

2. Statistical analysis: The Wilcoxon sign rank test is appropriate for paired analyses - I think you mean the Mann-Whitney test (aka Wilcoxon rank sum test)? As feasibility studies are not powered to detect differences between groups, analysis should focus on confidence interval estimation, rather than hypothesis testing. Could you amend the statistical analysis section, to reflect that analysis will focus on confidence interval estimation, with any hypothesis testing considered secondary. Regression modelling in particular should be viewed with caution and presented as exploratory.

RESPONSE: Wilcoxon sign rank test has been corrected to Mann-Whitney. The Statistical Analysis section has been amended to reflect that analysis of secondary outcomes will focus on confidence interval estimation and that any planned comparisons between groups are exploratory and hypothesis generating.

3. Progression to future trial: I note that criteria for progression according to feasibility outcomes are listed in table 3; would it be possible to discuss these criteria in the main body of the text, to clarify what conditions must be met for the study to progress to phase 3?

RESPONSE: We have outlined the success criteria in detail within the manuscript (see Outcomes section, page 13).

ADDITIONAL COMMENT FROM THE AUTHORS:

Also of note, at the time of submission, this study was a single-centre study. Since that time, we have added two international sites in Austria and Chile. Both sites are actively recruiting. The manuscript has been updated throughout (using track changes) to reflect this change. In addition, to account for the 7 patients who received two doses of study drug before the dosing procedure was modified (see Discussion, second paragraph), the sample size was adjusted upwards to 67 patients. This change has also been reflected throughout the manuscript using track changes. Finally, we also recently made a change to the stopping rules during DSMB review. These changes were approved by the DSMB yesterday and have been incorporated into the manuscript using track changes. Finally, the section on Trial Status and Supplementary Material 3 have been updated to reflect the current state of the trial.
Thank you for considering this submission.

Sincerely,

Dr. Dayre McNally, Corresponding author VITdAL-PICU Study