Author's response to reviews

Title: Vitamin D to prevent acute lung injury following oesophagectomy (VINDALOO): study protocol for a randomised placebo controlled trial.

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Author's response to reviews:

13th March 2013

Dear Trials Editor,

Many thanks for considering our manuscript ‘Vitamin D to prevent acute lung injury following oesophagectomy (VINDALOO): study protocol for a randomised placebo controlled trial’ for publication in Trials.

In response to the reviewers’ comments I attach a revised manuscript with a point-by-point response to the concerns below. I understand reviewer 1 has no concerns. In response to reviewer 2 comments:

Major compulsory revisions

A) Time point for assessment of the primary endpoint "extravascular lung water index" is not clearly mentioned. [Day 1 post-operative day is a very long period relative to procedure and onset of pulmonary edema. Authors have shown data
to say that ELWI is stable within a 2 hour period but not over 24 hrs. Single or multiple time points can be measured (multiple pre-defined end points are preferable but since trial has already started, it is not possible) and in case of single end point, protocol should specify the timing of assessment.

Response: the time point for assessment of the primary endpoint ‘extravascular lung water index’ is clearly mentioned as at the end of oesophagectomy – to clarify this further I have revised the manuscript to state that this is measured within one hour post-operatively. In terms of one of the secondary outcomes being EVLWi day one post-operatively, I have revised the manuscript to define when exactly this is being measured on day one (9am on day 1). In response to concerns with regard to multiple time points, we will be measuring EVLWi pre-operatively (as a baseline) immediately post-operatively (within one hour) and on day one post-operatively (9am on day 1).

B) Permutated block size of 5 cannot be used for equal distribution into two groups. The block sizes have to be even to get equally distributed two groups. [It is possible that the actual block size is ten (since the drug/placebo comes in packs of ten). If that is the case, then the protocol should be revised to reflect the same.

Response: randomisation is indeed in permuted block size of 10 and not 5 and is reflected in the revised protocol.

C) The secondary end points duration of ventilation days and hospital stay mentioned in statistical analysis are not mentioned under outcome measures.

These would be very relevant and meaningful outcome measures.

Secondary end point of ventilator free days is being adopted rather than duration of ventilation and hence not mentioned in the secondary outcomes, although this data will be collected. Hospital stay is notoriously an unreliable outcome measure and is not being used but again this data will be collected.

Discretionary revisions

A) ‘The only study looking at vitamin D in patients with sepsis suggests that patients have a lower level than ITU controls’ has been revised to healthy controls.

B) We agree the in-vivo relationship between LL37 and vitamin D is yet to be fully discerned.

C) The protocol manuscript is reflective of the Medical Research Council funded
trial however there is a translational sub-study in which we will be measuring other covariates and biomarkers. We will be measuring LL37 as part of this sub-study.

D) The trial drug (vitamin D or placebo) is being administered orally as we are aware of the delayed bioavailability of intramuscular vitamin D. Our patient group are able to take oral liquids and in any instance of difficulty the trial drug is administer via the percutaneous gastrostomy/jejunostomy.

I hope this answers the reviewers concerns and meets the required changes required for manuscript acceptance.

Looking forward in advance to you reply.

Many Thanks

Dhruv Parekh