Reviewer's report

Title: Study protocol: A randomized placebo-controlled clinical trial to study the effect of vitamin D supplementation on glycaemic control in type 2 Diabetes Mellitus SUNNY trial

Version: 2 Date: 6 June 2014

Reviewer: Barbara J J Boucher

Reviewer's report:

Re Review of MS: 1165143891038234. By Krul-Poel et al.

The authors have answered many of the points raised satisfactorily and the alterations made in the text are helpful. However, there are a few points that have not been fully addressed in the text and these are listed below. In addition the text would benefit from editing as the English reads oddly in several places. No attempt has been made to identify the language problems in this review but this reviewer would be willing to edit the text so as to deal with these problems if this would be helpful, but would need an accessible file to do this.

Major matters

1. This may be an oversight but there is still no mention of any provision for dealing with unexpected hypersensitivity to vitamin D. Since hypercalcaemia can develop early with vitamin D supplementation, with severe renal failure, or even death, if untreated, this provision should be mentioned, as previously suggested. Normally subjects are advised as to when they should seek urgent advice and how they can access such advice, 24/7, and given a note of this as well.

2. Line 50+ assumes activation occurs only in the kidney whereas it also occurs in target tissues including islets and liver and this should be mentioned.

3. Line 229. Subjects will enter the trial over a calendar year but this may not deal with the effects of season and analysis of outcomes could still be found to be affected by season of examination since glycaemia, BP, and lipid profiles for example vary with season in many studies, as does vitamin D status. If adjustment for season is not made informed readers will be concerned about confounding, whether these are present or not.

4. You mention action to be taken over reporting adverse events but not how to avoid avoidable events such as serious hypercalcemia and its sequelae see (1); thus, the need to mention safety advice is made more obvious. Also, anyone reading the paper and planning similar work should be made aware of these risks.

5. Line 293 again, as in (4) above, references should be given here.

Discretionary [to editors and authors]

1. Line 62, ‘direct and indirect’ is an unusual description of vitamin D effects; do the authors mean rapid non-genomic effects and slower genomic effects, which they refer to in lines 69-70?
2. Line 87/8 talk of ‘most of … reviews’ but references really should be given here so that readers can see what is in the literature and be able to access it!

3. Line 96 mentions ‘serum vitamin D’, but this has not been assayed. Of course if you have those assays that would be most interesting as many target tissues can 25-hydroxylate vitamin D3 locally and cholecalciferol has a short half life – information that shows that our long standing belief that vitamin D availability to target tissues [where it is activated] depends on serum 25(OH)D is not the whole story.

4. You state in your responses that further inflammatory factors will be assessed but this isn’t mentioned in the text. Why not state that aliquots of serum and plasma will be stored at -70/80°C for further examination, whether or not you mention which factors you have in mind, such as vitamin D dependent inflammatory and anti-inflammatory factors [e.g. IL-10 and Il-6 as well as the MMPs].

5. Line 310, the term ‘interpretation’ reads oddly here, do you mean ‘to make clear recommendations for optimal serum 25(OH)D concentrations in those with T2DM’?

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests