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: 1 Date: 22 November 2013

Reviewer: Barbara J J Boucher

Reviewer's report:

Comments on a study protocol for BMC Endocrine Disorders entitled ‘A randomized placebo-controlled clinical trial to study the effects of vitamin D supplementation on glycaemic control in type2 diabetes mellitus.

In particular, to consider the following queries, with responses to these queries in blue after each query.

1. Will the study design adequately test the hypothesis? Compared with most other similar studies now out, many of which are not covered in either the introduction or discussion but should be included one would think so! However, there are some points of information that suggest certain modifications would improve the chances of the study producing answers that will stand up to the test of time, as mentioned in the specific comments listed below.

2. Are sufficient details provided to allow replication of the work or comparison with related analyses: if not, what is missing? I believe so; however, there are some aspects of the proposed RCT where additional data inclusion should be considered, as detailed in the specific comments below. Especially important matters to include are (1). Season of study needs more specific information since if the RCT is done winter to summer the change in season, and increased sunlight, may have effects independent of vitamin D status, whilst if done from summer to winter, similar factors might obscure what would otherwise be a positive result. (2. Safety checks are not specifically mentioned. Many RCTs using large interval doses do point of care serum calcium checks early on. The minimum one must offer is the provision of written advice on when to seek advice and about how to get it [contact details etc.] which should be included in this type of RCT and should be stated in the plans to satisfy ethics committees and also to help anyone planning to carry out similar studies, especially where older people and women are included as undiagnosed primary hyperparathyroidism is increasingly common with age and in women more than men (3). There is no mention of an external monitoring committee though this is implied on page 9, where premature termination of the trial is mentioned. Also, who checks data to see when individuals develop abnormal responses requiring their withdrawal from the RCT. This should be stated. (4). How will checks be made that subjects can measure the doses of liquid oral doses correctly and what will they use for self-dosing? This is a safety matter and should be specified though it is also
important information for others planning any similar RCT. (5), additional details
on how measurements are made of BP, etc should specify the period of sitting or
non-smoking beforehand, and what time weight and height are taken [both
change over 24 hr] to help anyone planning to emulate this RCT. (6). How far the
25(OH)D assays can detect both the D2 and D3 metabolites, i.e. total 25(OH)D,
should be stated, together with the CV for these assays and what QC scheme
will be in use. The CVs for all non auto-analyzer data should be stated.

3. Is the planned statistical analysis appropriate? I believe that it is but I am not a
statistician and further opinion is required.

4. Is the writing acceptable? On the whole it is but there are remarks that are
unclear and need clarification as listed below in the specific comments.

5. ALSO, the consort Table should show that numbers in all groups will be given
at each stage.

Specific comments.

Dosing with vitamin D:- monthly has been pretty standard but recent evidence
suggests intact vitamin D3 is 25-hydroxylated in many target tissues increasing
availability for activation locally, thus, with its short half life in the circulation it is
likely to be more effective given daily, matching how early man got his vitamin D
from sunlight. Since there is evidence that daily dosing is being more effective on
end points than interval dosing future RCTs may use this dosing schedule
increasingly and maybe this could be done in this RCT.

RE recent literature, RCTs of vitamin D for quality of life in T2DM is novel but
there are several RCTs out in 2013 of vitamin D in T2DM for metabolic benefits,
these should be quoted [in addition to refs 16-21], and since some were effective
on T2DM related end points those end points could usefully be more prominent
in the planning.

AGEs once formed are irreversible so how is an RCT going to see improvements
in the skin – only if skin is replaced significantly within the span of the RCT, so
data on this would be helpful.

The benefits of vitamin D repletion have mainly been shown in deficiency [<25
nmol/l], so that stratification should include this cut-off. Also it is likely that the
earlier that vitamin D deficiency is corrected in the disorders leading to T2DM the
more effective it is. Therefore, I am doubtful that any RCT of vitamin D will make
large improvements in beta cell function, though IR may be reduced which will be
useful. Despite this, a definitive answer on the value of vitamin D in T2DM is
needed so that this type of RCT is going to have to be done.

Inflammatory changes reduced by corrected D deficiency include reductions to
normal in plasma MMP9, first shown in 2002 [Timms et al] and confirmed in
several RCTs since then. Since MMP9 is especially important in atherosclerosis,
known to be increased in T2DM, it would add value to this RCT if plasma
samples could be taken for MMP9 assays.

Most measures of T2DM and associated metabolic abnormalities vary with
season and improvements coincide with when vitamin D status increases, thus,
adjusting for season is a real problem since it could obscure changes associated
with changes in vitamin D status. It would be useful, therefore, for seasonal
differences in all the end points to be examined in the control group to see what
adjustments for season may be appropriate in the treated group.

3-6/12 is most unlikely to show any changes in AGEs, as above, so mention of
earlier evidence on this would be useful in the background.

There was ‘no funding’ for this RCT but this RCT must be costing money, where
is this coming from?