Reviewer's report

**Title:** Prevention of exacerbations in patients with COPD and vitamin D deficiency through vitamin D supplementation (PRECOVID): a study protocol

**Version:** 5  
**Date:** 4 August 2015

**Reviewer:** Adrian Martineau

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This manuscript describes the protocol for a RCT of vitamin D supplementation to reduce risk of moderate / severe exacerbation of COPD. Strengths include a multicentre design, and recruitment of a patient population with proven vitamin D deficiency at baseline and a recent exacerbation. Vitamin D will be given weekly – more frequently than in the two existing trials in this field.

**Comments:**

1. Although weekly dosing may have some PK benefits over monthly / 2-monthly dosing, adherence is likely to be less good. What provision will be made to optimise adherence and to monitor it?

2. The trial by Lehouck et al showed a benefit only in those with profound D deficiency – i.e. with baseline 25(OH)D <25 nmol/L. Are there any plans to conduct a sub-group analysis in this group?

3. Adherence to completion of a study diary may be much less than 100% - is there a run-in period, and is proven ability to complete the diary an eligibility criterion? It should be.

4. Do the authors see any ethical issue in randomising patients with known vitamin D deficiency to placebo?

5. Multiplicity of secondary outcomes: there is a very large no. of secondary outcomes – this could lead to type 1 error. Is any adjustment for multiple analyses being made for this multiplicity? If no correction is to be applied, then the investigators may wish to add a comment to the effect that analysis of 2y outcomes is exploratory in nature. Participants are being asked to complete a large amount of paperwork, including at least 5 questionnaires - SGRQ, SF-12, CCQ, HADS, CESD. Will this heavy requirement adversely affect retention / follow-up?

6. Abstract, Background: The authors write: ‘Previous studies have not demonstrated a beneficial effect of vitamin D on exacerbation rate in COPD patients. However, posthoc subgroup analyses suggested protective effects in vitamin D deficient patients’. This is not completely accurate – the ViDiCO trial (Lancet Res Med 2015) pre-specified sub-group analysis among participants with baseline D deficiency, and found a protective effect – these analyses were not post hoc.

outcomes are not provided. For example, ‘Pro- and anti-inflammatory cytokines will be analysed’ – which? Lines 294-5 – both the previous trials explored immunological mechanisms – this feature of the Precovid trial, while worthwhile, is not novel.

8. Other RCTs of vitamin D supplementation have reported that genetic variation in the vitamin D pathway can modify the effects of supplementation (e.g. Martineau et al, Lancet 2011). Will participants be genotyped to detect such effects?

9. It is recognised that a proportion of exacerbations do not precipitate consultation with a doctor, and so remain untreated with antibiotics / steroids. Is any attempt being made to capture such ‘unreported exacerbations’?

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests