Author's response to reviews

Title: Oral vitamin B12 for patients suspected of subtle cobalamin deficiency: a multicentre pragmatic randomised controlled trial

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Author's response to reviews: see over
Dear Editor and Reviewers,

Please find enclosed our corrections and comments in response to your review of our article, "Oral vitamin B12 for patients suspected of subtle cobalamin deficiency: a multicentre pragmatic randomised controlled trial."

Below we provide, in bold type, a list of the reviewers’ comments, followed by our responses and description of changes made to the paper. The entire revised document was sent to San Francisco Edit to have them edit and improve our manuscript.

We thank you all for the time spent on our manuscript and for your relevant comments, which we have done our best to address. We are grateful for your important contributions in improving this manuscript.

Regards,

Paul Vaucher
Bernard Favrat
Editor

1. Abstract: the abstract should follow the form Background-Method-Results-Conclusions
The Abstract was restructured as indicated.

2. Please reformat your conflict of interest and contributions sections into: Competing Interests, Authors’ Contributions, Acknowledgements.
These sections were modified as suggested.

3. We would strongly suggest that you remove the data on clinical symptoms.
We removed the data on clinical symptoms as suggested. However, we chose to keep the hematological values (MCV and hematocrit) and MMSE score in the manuscript, as these validated measures may be useful for future meta-analysis. We did not emphasize these values, nor did we discuss the absence of effect on the MMSE, as small changes for populations with mild dementia are not expected to be detectable with such a measure.

4. Please clarify whether the measurements from blood samples were centralized or not. If they were not centralized, please acknowledge this as a limitation.
Blood samples were centralized at the GP offices before being sent to the principle centre, where all blood samples were analysed using a single method. These details were clarified in the Methods section and were added to the Abstract.

5. Finally, we suggest that you need to acknowledge relevant trials in the field.
A review of the literature was performed in Medline and Embase to update our previous review, as new publications may have appeared in the course of the previous year.

Referee 1: Eleanor Pullenayegum

1. Abstract, Results: In addition to giving the mean decrease at 95% CI in MMA levels in the intervention group, it is important to give this in the control group as well, for comparison.
In the previous version of the manuscript, the results were reported as the observed difference between the treatment and placebo groups. This detail was clarified in the current version of the manuscript.

2. Results, middle of page 10: It's not clear whether the seven patients who had co-alam levels below the threshold at 1 month were excluded from all analysis, excluded from 4-month analysis, or retained for all analyses. Intention to treat analysis would require them to be retained for all analyses.
Intention to treat analysis was respected for the seven patients who received active treatment at one-month follow-up. This detail was clarified in the current version of the text.

3. Table 3: Was the heteroscedasticity accounted for in calculating the p-values and 95% CIs in Table 3?
This calculation was corrected, and robust standard error was used to take heteroscedasticity under consideration. This detail was also added to the Statistical Methods subsection of the Methods in the current manuscript.
Referee 2: William Stone

1. Abstract. The sentence “Adherence to treatment was verified by an electronic device” is vague. Please provide a descriptive name to the “device.”

The name of the device was added.

2. A sentence cannot begin with a number like “50.” Please change “50 patients...” to something like “A total of 50 patients...” Similarly change “13 general practices...” to “Thirteen general practices...”.

We screened and corrected the entire manuscript for this suggestion.

3. The sentence “The number needed to treat to detect a metabolic response at one month was 2.6” is not clear. What is “2.6”- does this have units? Please clarify.

The units for NNT were added (patients).

4. Page 4- “a 4-month” should be replaced with a “four month.” All whole numbers less than ten should be spelled out (see http://www.dailywritingtips.com/10-rules-for-writing-numbers-and-numerals/).

This suggestion was implemented throughout the manuscript.

5. Page 6- Provide a descriptive name for the “electronic device.”

The description of the measuring methods for adherence was moved from page 4 to this section, and the name of the device manufacturer was added.

6. Page 6- Was “serum MMA” levels measured (as in the text) or “plasma MMA” (as in Table 2)?

As the samples were all centrifuged, the concentrations were measured in serum and not in plasma as incorrectly stated. We corrected this statement and used the term “serum” throughout the current version of the manuscript.

7. Page 8- “et al” should “et al.” (al.is an abbreviation for the latin alii).

This correction was included in the current version of the manuscript.

8. Results: Almost all the references to the Tables are incorrect, e.g., the reference to “Table 2” should be to “Table 1”, etc. Please check all the text.

The references to tables were checked and corrected where necessary.

Referee 3:

1. The results from the laboratory analyses on change in MMA, homocysteine and cobalamin levels are of limited interest, because well designed, larger published studies have provided more sound evidence.

There is indeed no need to plan further trials to support the benefit of vitamin B12 supplements in patients with vitamin B12 deficits. However, this trial was designed to evaluate the potential effects of vitamin B12 supplements for cases of borderline deficiency. Most existing trials have studied the effects on serum B12 concentrations, but not on other metabolic markers. As such, this study is novel.

We identified three recently published systematic reviews that highlight the lack of trials studying the effects of vitamin B12 alone on MMA [1-3]. Three [4, 5] of the four identified randomised clinical trials on the subject had smaller sample sizes than our study. The only study [6] with a larger sample size included 195 patients in three groups (B12, B12 and folic acid, placebo) and stratified the analysis by initial MMA. The final power was therefore not much better than the power achieved in our study. We have therefore been unable to identify larger
studies providing more evidence than our study, and we would be grateful if the reviewer could indicate the references she wishes us to cite.

2. The results from the clinical evaluation of possible change in symptoms and signs of cobalamin deficiency do not prove anything. First, the trial was not statistically powered to demonstrate such changes. Second, using 16 different study centres to test 50 patients aged between 18 and 91 years, made the clinical testing extremely prone to measurement errors.

As pointed out by the Editor of BMC Medicine, even if this study is underpowered, the 95% confidence interval is within clinically non-significant effects. However, we agree that the method used to measure clinical effects was neither standardised among clinicians nor validated. Furthermore, MMSE has been shown to be irrelevant for detecting small changes for patients suffering mild dementia. As requested by the editor of BMC Family Practice, we have removed results that do not use validated measures. We do wish to point out that benefit of oral vitamin B12 on cognition is still contested [3].

References