Author's response to reviews

Title: Bone Mineral Density (BMD) Changes in a Bone Health Plan Using Two Versions of a Bone Health Supplement: A Comparative Effectiveness Research (CER) Study

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Author's response to reviews: see over
Title: Bone Mineral Density (BMD) Changes in a Bone Health Plan Using Two Versions of a Bone Health Supplement: A Comparative Effectiveness Research (CER) Study

Version: 3 Reviewer: Bo Rud

Reviewer's report:

Major Compulsory revisions

General comments

The revised manuscript is difficult to read. The authors have used the Microsoft Word ‘Tracked changes, and the revised manuscript contains text in red that is underlined, which appears to be added. In addition, the revised manuscript contains text in red that is striked out, which appears to be deleted. However, in some places the expected revisions in the manuscript are in red, striked out text. Hence, it is unclear if the striked out text in red represents deletions or additions.

For instances:

We used this format to comply with the requirement to highlight suggested changes in the manuscript. As you point out, the result is very difficult to read. As an alternative, we have forwarded a suggested finished copy with corrections and suggested changes made in the copy. We’ll pass on our response to all of each reviewers’ s comments integrated along with responses to the two reviewers’ latest suggestions.

Page 8

The size of the paid incentive for providing daily reports of side effects is in red striked-out text, hence supposedly deleted. Nevertheless, the authors state in their response to this reviewer that ‘The size of the incentive has been added to the proposed revision’.

We have corrected this replacing the use of “incentives” with “reporting fees” as now explained in the proposed revised manuscript.

Page 9

In response to this reviewers comment, the following section appears to be added on page 9: “using dual-energy X-ray absorptiometry (DXA) total body scans (GE Lunar Prodigy, LUNAR Corporation, Madison, WI, USA). Total body BMD has been found to correlate over 90% with spine and femur measurements. Longitudinal precision was monitored using repeated measures of total bone density phantoms provided by the manufacturer.’

However, the added section is in red striked-out text, hence supposedly deleted.

This has been corrected in the proposed revised manuscript

Page 10
On this page it states ‘To evaluate the safety of the Plan, the 43-item blood chemistry blood testpanel and a 50-item Quality of Life inventory [14] shown in Tables 2 and 3 were administered to all study participants at baseline and at the end of six months.’ Table 2 and 3 are added to the revised manuscript to report safety results, but ‘shown in Tables 2 and 3 ’ is in red striked-out text, hence supposedly deleted.

**Corrected in proposed revision.**

The authors must clarify what precisely constitutes the revised manuscript, Language editing is generally needed. An example of inconcise language is given below:

On page 9 it is stated that ‘The primary outcome of this study was to assess efficacy of the two plans by comparing within group baseline/ending changes in BMD and, since it was a CER, the same changes between the two different bone-health plans.’

First, the concept of study purpose appears to be confused with the concept of primary outcome measure.

**We agree that this discussion is unclear and can be more clearly entitling the subsection “Measurements” and describing what measurements were used to assess efficacy and safety and when these measurements were taken. The section has been re-written accordingly.**

Second, the meaning of the words ‘..and, since it was a CER, the same changes between the two different bone-health plans’ is unclear -is there more than one primary outcome?

**We agree. We think the proposed changes clarify this.**

Third, ‘baseline/ending’ is inconcise. The authors should state the length of the observation period: ‘..changes in whole body BMD over six months’.

**We agree. We think the proposed changes clarify this.**

Finally, the study design is unsuited for assessing the effects of the entire bone health plan, because the interventions in the two groups are identical except for the bone-health supplements. A more concise description of the study purpose and the primary outcome measure is needed.
The only difference between the two plans is the composition of the bone-health supplement which suggests the increases in BMD in AlgaeCal-2 are a function of supplement effects only. Thus, the comparison is actually between two bone-health supplements, not two plans. However, in view of the potential interactive effects of the plan with the supplements, we avoided the suggestion that the differences were limited to the supplements without data from additional study arms in which subjects took only the two supplements without the accompanying plan.

Specific comments

Background section, p. 4-5.

The arguments presented by the authors in favour of the sequential design are vague. It remains unclear how the physical activity and health literacy components could pose placebo and blinding challenges in a RCT. These components were identical between the two groups, hence no blinding issue. In addition, the issue of placebo is irrelevant in the present context, because there is no placebo group. Finally, RCT’s do not necessarily preclude a real world situation. If a RCT was considered unfeasible for practical or economical reasons, then it should simply be stated so.

We have clarified the basis of the concern about the effects of placebos and provided a more straightforward statement as to the economic issues underlying the decision.

P. 6

To reduce the length of the manuscript and to keep the material and methods section focused the following section should be omitted ‘Cultured human osteoblast cells (hFOB 1.19) were treated…… to calcium carbonate or calcium citrate (1.5,1.4 fold, respectively)’.

While we think these sentences are worth retaining, we agree that is should be removed from the Material and Methods section and put in the Discussion section.

In addition, reference 7 should be referred to after the following sentence:

A recent in vitro study with AC Page demonstrated that it can serve as a superior calcium supplement compared to the two most commonly used calcium salts, calcium carbonate and calcium citrate.

Done.

Subjects, p. 7-9

The only explicitly stated exclusion criteria are pregnancy and lactation. However, in the response to this reviewer’s comments the authors state that use Material and methods

As stated in the “Subjects” section, subjects “….certified that they had reviewed the Informed Consent with their personal healthcare provider or physician and that they had no medical conditions that would preclude their participation”. Since there are no
studies bearing on the safety of the bone-health supplement, we thought it presumptuous to suggest to the subjects that we knew the conditions that would preclude their participation and deferred this decision (or passed the buck) to their healthcare provider.

It should be reported in the manuscript that participants were asked to discontinue use of other bone active supplements during the study.

Added.

Page 10
The notion of ‘compliant over expected’ used in Figure 2 as well as the notion of ‘over-expected changes’ (p. 12) remains undefined in the methods section.

Page 12
In the revised manuscript, the unexpected decline in the MAPC in BMD in partially compliant participants in AlgaeCal 1 remains underexposed in the results section and ignored in the discussion section.

In the authors reply, it is argued that the average BMD loss in the partially compliant participants in AlgaeCal 1 was reduced by dropping 5 subjects as outliers. From this argument it appears that the unexpected BMD loss persisted even after exclusion of the 5 outliers.

The authors also argue that the difference between the partially compliant subgroup and the expected change did not reach a statistically significant difference. In other words, there is no statistical evidence that the partially compliant participants in AlgaeCal 1 had a more pronounced BMD loss than expected with no supplementation. But, this is a non-inferiority line of thought, where it is hypothesized that AlgaeCal 1 may not be superior to no supplementation, but certainly not statistically inferior. Such a hypothesis is inconsistent with the arguments presented by the authors in the discussion section (p. 15-16) favouring a superiority hypothesis regarding the effect of AlgaeCal on BMD as compared to no supplementation.

The authors should present more data on the unexpected BMD decline in partially compliant participants in AlgaeCal 1 in the results section. Furthermore, this unexpected finding affects the primary outcome, and therefore it should be discussed in the discussion section.

The most parsimonious explanation for the absence of any change in BMD for the partially compliant sub-group taking AlgaeCal-1, is what the evidence suggests, that this bone-health plan had no effect on BMD when subjects only partially adhered to the plan, but did promote change among more compliant subjects. Conversely, when following the plan with AlgaeCal-2, even the partially compliant subjects increased their BMD and subjects classified as had greater increases than partially compliant subjects taking AlgaeCal-2. Thus, the data suggest that there may be a threshold below which no changes in BMD occurs and above which changes do occur. The threshold appears to be between partially compliant and compliant subjects taking
In the revised manuscript, the authors have retained a lengthy discussion about placebo effects in the discussion section. As stated in the primary review this is speculative because there is neither a placebo group nor an untreated group. To reduce the length of the manuscript and to maintain focus the section on placebo effects should be omitted.

We have shortened this discussion retaining only a few sentences since, rightfully or wrongfully, this was a consideration that the grantor expressed in making his decision in favor of an open-label protocol. It seemed like a logical question most readers would raise. The grantor wanted to create more “real world” conditions similar to those in which consumers would follow the plan, reduce enrollment difficulties, avoid a potential volunteer biases from subjects who didn’t want to spend 6 months with a 50-50 chance of receiving an inactive placebo, and have more treatment subjects available for sub-group analyses.

**Level of interest:** An article of limited interest

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

**Declaration of competing interests:**

I declare that I have no competing interests
Reviewer’s report

Title: Bone Mineral Density (BMD) Changes in a Bone Health Plan Using Two Versions of a Bone Health Supplement: A Comparative Effectiveness Research (CER) Study

Version: 3

Reviewer: Jeannette Beasley

Reviewer’s report:

1. The authors acknowledge that comparing actual to expected change in BMD are based on assumptions, and elaborate that the expected change will always be negative. This assures that the supplement will look more favorable than the appropriate comparison, which is change from baseline. If the authors consider this information a valuable addition to the manuscript, it should be limited to the discussion rather than the results (much less the primary finding discussed in the abstract).

   We think the comparison with expected changes provides the reader with useful, not necessarily “valuable”, information about what one could expect if the supplement had no effect at all, particularly since it reflects an age- and gender-adjusted norm. Since comparisons with expected changes and change from baseline are both reported, it allows the reader to decide which comparison is more useful. We think both comparisons should be retained.

2. The rationale provided in the methods for choosing not to conduct a randomized, controlled trial is problematic. The desire to evaluate the plan under real world conditions is listed as the reason for not conducting a placebo-controlled trial, however participants were paid incentives for providing daily reports of side effects and supplement usage (p8). This would not happen under natural conditions.

   We agree that it is virtually impossible to conduct any intervention study under the natural conditions that consumers are likely to follow the plan, particularly when incentives for adherence are paid. However, it is our view that instead of paying incentives for adherence, paying subjects a “reporting fee” would attenuate some of the incentive bias and provide us with useful compliance data to examine dose-related changes. We have written the incentive section (pg 7) to further clarify this procedure. With regard to placebos, we have found in previous studies telling potential subjects they have a 50-50 chance they will receive a placebo for a 6-month study can lead to volunteer bias selecting out those subjects who may have a compelling need to improve their bone health.

3. Though presenting results as annualized change with only six months of data does not affect the statistical significance of the finding, it does multiply the effect size by two. The authors state the purpose of using annualized change is to allow
for comparisons with other studies; however, the manuscript provides no such comparisons with other studies. The results section should present the actual observed changes over six months, and if the authors wish to compare annualized changes to other studies, this could be added to the discussion.

We agree that, although it has no effect on the statistics, it does “double” the effect and makes the bone-health plan look more favorable. However, we provided annual change data since we thought readers were more likely to make comparisons with annual changes that are almost universally reported in the literature and six-month changes are virtually non-existent in the literature.

4 The authors state that the information regarding the site of BMD measurement (femoral neck, proximal femur, lumbar spine) was added to the paper – page 9 has a deleted sentence indicating it was “total body”. As typically reported in the literature, this information should be clearly stated in the tables and figures.

To avoid confusion, we have added “Total Body” to the title and added it to the abbreviations listed for BMD and DXA.

5 Recommend removing the listing of Blood Chemistries and changes (if not, correct P value for calcium) and QOL measures from the manuscript. This information could be summarized in the text.

The blood chemistries and QOL measures were not provided in the original manuscript, but were added at the suggestion of another reviewer and will be left to the decision of the editor.

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

Quality of written English: Acceptable Statistical review: Yes, and I have assessed the statistics in my report. Declaration of competing interests:

I declare that I have no competing interests.