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 Date: 12 September 2010

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:

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’.

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.

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.

The authors must clarify what precisely constitutes the revised manuscript,
preferably by including a revised manuscript without Microsoft Word’s ‘Tracked changes’.

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

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.

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)’.

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.

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
of anti-osteoporosis medication was also an exclusion criterion. A complete list of exclusion criteria should be reported.

Material and methods

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

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.

Page 15-16

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.

Level of interest: An article of limited interest

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