Reviewer's report

Title: MAVIDOS Maternal Vitamin D Osteoporosis Study: Trial rationale and methodology

Version: 2 Date: 6 October 2011

Reviewer: Charlie Goldsmith

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The following lists a series of issues that could make this protocol clearer for readers.

1. P(age) 2, p(aragraph) 2. Include the date of registration as well as the date when the first patient was randomized if that has already happened.

2. P 3, p 1, l(ine) 2. The two short forms [MRC] and [NIHR] are not defined and should be in a common section such as on P 20. There are many others as well in this manuscript that should be collected together and placed there. They will not all be further identified as there are many.

3. P 3, p 3. It is not clear how many locations will be used (possibly 3), and whether there will be stratification by location. If it is a single location state the location. It is unclear from the locations of the investigators.

4. P 3, p 4, l 1. Claiming that [the first ever tests ...] without a detailed literature review with a search strategy is a little too strong. Consider saying something like [As far as we know this may be one of the first ...]. Also P 19, p 3, l 1.

5. P 5, p 1, l 4. Replace [population] by [sample].


7. P 6, p 2, l 2. Suggest rewording as [but one which has examined ...].

8. P 7, p 3, l 2. Somewhere the characteristics of the active and matched placebo should be listed. Who manufactured these products for you?


10. P 9, p 1, l 9. Include the degrees symbol with the temperature.

11. P 9, p 2, l 1. Is this study stratified? Who will prepare the randomization schedule? How is the allocation masked from those making the decision as to who should be entered in the trial? How can the allocation of the medication ensure that the designated package gets to the patient being allocated? It seems as if a nurse could be doing more than one at a time and this provides for the possibility of the nurse making a mistake with the allocation and hence violating the integrity of the randomization. Why are you publishing the block size? It does
not need to be known until the trials is analysed and published. This may make it harder to mask the next allocation from those making the decisions to enter a patient or not. Also why is the allocation starting in the middle of a block? It should be cited as a credible technique. Presumably the allocation ratio is 1:1 and should be stated.

12. P 10, p 2, l 5. The exclusion after randomization does mean that you will not be able to do an intention to treat analysis. Consider following them as well to get all the outcomes you can and then you can analyse the data with different data sets.

13. P 10, p 3. Presumably all of these things are being recorded. They could be used for hypothesis generation if recorded.

14. P 11, p 2, l 6. Is there a R(eference) for this protocol?

15. P 11, p 2, l 10 Suggest deleting [means of] as the words are redundant in English.

16. P 11, p 2, l 13. Suggest inserting [UK] after [Cornwall] as there are many more in the world. Also P 17, p 1, l 3.

17. P 12, p 1, l 2 and 3. Is there a R for these doses?

18. P 12, p 2, l 4. What plans are being made if the mother or child move to another location?

19. P 14, b(ullet) 2, l 2. Is there a R for the NHS timing?

20. P 14, Table 1. Infant urine sample is not checked.

21. P 15, p 1. What software was used to estimate the sample size? Document it.

22. P 15, p 1, l 11. Since data is a plural word, drop [s] from the end of [suggests] to read [suggest].

23. P 16, p 1. This is not the usual method of defining ITT. It is all mothers randomized. If there are no data on follow up DXA on the child, this should be handled with a credible imputation procedure, defined and Referenced.

24. P 16, p 5. This analysis should be done with ANOVA, adjusting for stratification and blocking. If the stratification and blocking have no effects, a secondary analysis can also be computed. What software is planned for doing these analyses? If you use a t test, it is called a [Student’s t test].

25. P 19, p 1. Is one of these members a trial statistician? What are the qualifications of these 4 people to be the DSMB for the trial? What powers do they have? Is there a charter for the group? It could be added as an appendix.

26. P 19, p 2, l 3. Who are the manufacturers? Did they have any role in the trial?

27. P 19, p 2, l 3 to 6. Provide Rs for these criteria.
28. P 20. This would be a good location to list all defined as well as assumed short forms in this trial.

Trials likes to publish ALL the authors to the Rs. So please take all Rs with [et al] in them and replace the words with the rest of the authors. This reviewer took a random sample of 10 Rs to check for accuracy of citation. Also, this reviewer also like to see the issue number in the R since it makes it easier for a reader to find the R when the reader wants to access it in the journal or a database.

29. P 21, R 2, l 2. Insert [(6)] after [29].

30. P 21, R 6. This R seems to be in a supplement that was not accessible to check. Try to provide the supplement number.

31. P 21, R 7, l 2. Insert [(1)] after [14].

32. P 21, R 9, l 3. Insert [(8)] after [12].

33. P 21, R 11 could not be verified.


35. P 22, R 19, l 3. Insert [(5)] after [68].

36. P 22, R 21, l 2. Insert [(6 Suppl)] after [80].

37. P 23, R 33, l 3. Insert [(3)] after [85].

38. P 23, R 34, l 3. Insert [(1)] after [127].

39. Figure 1. Explain the notation on the left. Presumably the 40 is the pregnancy term. Also, until the trial is completed, the numbers at the bottom right are hoped for. It would be better to lay out the total expectation in a CONSORT type of chart with the final publication having the actual numbers. After the first two boxes, the inequalities should have a space on either side, such as [25D < 25nmol/l 25nmol/l < 25D < 100nmol/l 25D > 100nmol/l].