Author's response to reviews

Title: Management of osteoporosis and associated quality of life in post menopausal women

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Author's response to reviews: see over
1. **Reviewer's report:**

Reviewer: Stuart Silverman

**major revisions**

1. Please explain Table 1. Why were the 849 patients not eligible. Over half had a fracture. The patient flow and selection are confusing: The study design required that investigators included all women who had undergone a fracture or experienced a fracture in the previous six months into a patient registry. Investigators were then expected to include the first three women who fulfilled the eligibility criteria (postmenopausal, OP diagnosis, OP treatment) into the study itself. The remaining women in the patient registry who fulfilled the eligibility criteria were supernumerary to requirements (three patients for each investigator) and not included in the study analysis population. We can thus compare the 1306 women entered into the study with the 849 other eligible women who consulted the investigator during the study period and thus detect any selection bias and ensure the representativity of the sample. In fact, a difference was observed, with more women diagnosed by BMD being entered into the study than expected (see Reply to Point 2 below). We have made several changes to the manuscript to clarify this issue. The ‘Subjects’ sections of the Methods and Results have been rewritten to clarify. We have changed the name of the main population of 1306 women analysed to ‘Study Analysis Population’ in both the text and the Flow Diagram (Fig 1), so that this is more explicit. We have also added a paragraph to the Discussion on study design, in which the rationale for comparing the registry and study analysis populations is clearly explained.

2. In the questionnaire population, please divide into patients eligible based on BMD vs fracture. Were there any differences: This Table has been added to replace the original Table 1 which the Referee found confusing. The results in the previous Table are now in the text. The new Table suggested by the referee is all the more useful since a modest selection bias was detected in favour of patients diagnosed by densitometry being entered into the study. It is thus important to evaluate how women with OP diagnosed by densitometry differ from those diagnosed due to occurrence of a fracture. The principal difference was that the former group was younger. They were also more likely to be prescribed SERMs, which is probably associated with their younger age, since we know from the multivariate regression analysis (Table 5) that SERMS tend to be prescribed to younger women.

3. It would have been of interest to study patients with OP by BMD or fracture who did not receive medications and understand if this was associated with treating MD type. We agree that this is an interesting question. However, the entry criteria for the study specified that the patient should have an osteoporosis treatment prescribed, so we cannot address this question with the data collected.

4. When was this study conducted? Physician recruitment took place between November 2007 and April 2008. Physicians could recruit patients over a three month period, so the last patient was entered into the database in July 2008. This is now specified at the beginning of the Methods section.

5. Why was FRAX not used as a variable? The FRAX risk assessment tool was only published in April 2008, when the study was nearing completion. Although the risk factors assessed in our study cover the different items in FRAX, the definitions are not always identical and the
FRAX risk cannot thus be calculated retrospectively. We have added a statement to the Methods that the factors evaluated include those considered in FRAX. Furthermore, the patients in our study were all treated, and how treatment influences the FRAX assessment has not been evaluated for French patients.

6. How were patients recruited in practices? Were they consecutive?: Yes, the patients were included consecutively into the registry. The first three patients in the registry who fulfilled the eligibility criteria (postmenopausal, osteoporosis diagnosis, osteoporosis treatment). This is now specified in the Methods.

7. The conclusion as stated is circular. Since patients were dx as OP by BMD they had a BMD. Do the authors mean that most patients with fx had a BMD? We mean that more women are getting BMD and being diagnosed due to low bone mass than before. This is true for all physician specialties. We have rewritten the paragraph for clarity.
2. **Reviewer's report:**

Reviewer: Deborah T Gold

- **Discretionary Revisions** (which are recommendations for improvement but which the author can choose to ignore)

- **Minor Essential Revisions** (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. Grammatical, spelling and usage errors abound. Incorrect use of commas: The manuscript has been checked and revised by an English scientist with experience in the field and validated by an American medical communications professional. Comma use reflects contemporary standard British English usage.

2. When you discuss bone mineral density scores (introduction and later), you refer to “a bone mineral density (BMD) more than 2.5 standard deviations below the average value in young women.” Are those French norms? If so, say so. If not, tell us what 30 year olds you are using as normative. **Yes, for the study, these are French normative values. This is now specified in the text of the Methods. In the Introduction, this is a general statement about the definition of osteoporosis.**

3. In the 2nd paragraph of the Introduction, you refer to the NOF guidelines, then to the new French guidelines. All postmenopausal women have three major risk factors: age, gender, and postmenopausal status. What other risk factors are relevant here? **These are specified in the French guidelines (Reference 8) and include comorbidities predisposing to OP, low BMI, corticosteroid treatments, etc. We have added a sentence listing the principal risk factors in the text.**

4. Methods, Participating Physicians: You use the term CEGEDIM database. Please define for those who don’t know what that means. **This has been defined and explained more fully.**

5. Methods, Subjects: Clarify why up to 10 women were recruited from each physician, but only 3 were used: **This is an attempt to optimise the representativity of the study and ascertain any selection bias. See reply to Point 1 of Referee 1. A paragraph has been added to the Discussion to explain and clarify this point.**

6. Methods, Data collection: You say that the physician collected data including “the age at menopause (if this had occurred)…” It is my understanding that this sample was constructed of postmenopausal women. If so, wouldn’t it have been impossible for the menopause NOT to have occurred. Clarify. The criteria for the Registry population were women with previous BMD or previous fracture. The criteria for the Study Analysis Population were postmenopausal status, OP diagnosis and OP treatment. Thus, “the age at menopause (if this had occurred)…” is a relevant question for the Registry Population. Of course, women in whom it had not occurred would have been excluded from the Study Analysis Population. **See Reply to Point 1 of Referee 1 for the relationship between the Registry and Study Analysis Populations, and how we have attempted to clarify this.**

7. Same: Where is the list of risk factors from? Why not just use FRAX risk factors? **They come from the French guidelines for OP or OP fracture risk factors. In addition, risk factors for falls (eg poor visual acuity, hypnotic use) are also included. This is now specified in the Methods. As regards FRAX, see reply to point 5 of Referee 1.**

8. Results, Participating Physicians: Did you consider a table containing demographic or other info on physicians? **We have provided information in the text for the cases where these variables differed from the national average.**

9. Results: Osteoporosis treatments: Can you provide data on calcium and vitamin D supplementation? At minimum, please give the numbers rather than “large majority”. **The requested data are provided in Table 3.**
10. Results, Variables associated with treatment choice: You say, “difference between SERMs on the one hand and the specific osteoporosis treatments (bisphosphonates and strontium ranelate) on the other.” I would argue that SERMs ARE specific osteoporosis treatments. If you want to differentiate between them and other treatments, do so in a way that is meaningful. We agree and have reworded the phrase accordingly in a more neutral way.

11. Second to last paragraph of paper: You mention the sponsors of the research and how that might have influenced treatment choices. I would agree that it did. That is why we pointed it out as a possible source of bias in the Discussion, and suggested that the observed association between ongoing vs planned treatment and treatment class may be artefactual. However >60% of patients were already treated at the index consultation and only 15% of all patients were prescribed a treatment in the medication class in which the sponsor is active. The description of the treatments prescribed provided in Table 3 refers only to treatments already prescribed before the study, so these data should accurately reflect current treatment practice. This is now explicitly stated both in the Results and in the ‘limitations’ paragraph of the Discussion.

12. Also, you make your own argument why the quality of life data should be discarded. Without a healthy control group, your data aren’t very useful. We should perhaps have stated that we do not have a healthy control group within the study (this has now been specified in the Discussion). However, the SF-12 is a generic QoL profile whose normative values are known. A score of 50 on the Physical and Mental Component Summaries reflects ‘normal’ values in the general population. The difference of measured scores from 50 provides a useful index of impairment of quality of life that can be compared with other populations, both in other diseases and in other osteoporotic populations. We believe that our QoL data are informative for two reasons. Firstly, there is a paucity of published information on QoL of women with osteoporosis in real-world conditions (outside the context of clinical trials). Secondly, the large number of subjects included in the study allowed us to perform subgroup analyses that revealed unexpected associations which may be important for physicians to be aware of. For example, QoL was almost as poor in women with ancient fractures as in those with recent fractures, and vertebral fractures were associated with lower MCS and PCS scores than hip fractures.

• Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

13. IMPORTANT: You discuss the new national guidelines for France, but you do it much too late and without explaining what those guidelines are. Is this truly an investigation of whether physicians are following those guidelines? Please bring the guidelines up early, explain briefly what they entail, and explain why they are important. The introduction has been rewritten to put more emphasis on these guidelines and to explain what they recommend.

14. Clarification of purpose of study and justification of quality of life assessment. The latter is not well justified. The last part of the introduction has been revised to clarify the objectives of the study and the issues addressed in this article. See reply to point 12 for a justification of the QoL data.

15. Table format: Titles are way too long and contain information that should be included in footnotes. We have separated the titles from the footnotes in the revised version of the manuscript.

16. In the second paragraph of the Intro, you say, “Public health policies for osteoporosis in France need to take into account the fact that diagnosis and management of women with osteoporosis is spread across three medical specialities, namely general practice, rheumatology and gynaecology.” This makes no sense whatsoever. In the US, those specialities plus endocrinology, geriatrics, internal medicine, and so on are also part of the mix. We know that no single group of physicians treats this disease. But public health policies should have nothing to do with WHO is treating but more with WHAT is being done (or in many cases, not done). Clarify. The sentence has been removed and the breakdown of specialties moved to the Methods in order to justify the choice of physicians included in the study. The reason for choosing to investigate these three
specialities in the study is that, according to published data, they diagnose virtually all OP in France. If we seek to be representative of OP management in France, these are the specialties to study. In other countries, the situation may be different, and we have added a sentence to the ‘limitations’ paragraph of the Discussion to indicate that the findings may not necessarily be generalised to other healthcare systems or cultures. The focus of our results nonetheless remains on what is being done for the patients in terms of treatment after they have been diagnosed and, with the multivariate analysis, an attempt to shed light on what influences how they are treated. We consider such information to be valuable in terms of public health policies.

17. At the end of the Intro, you begin to refer to adherence issues. Terminology here is at issue. Please read the guidelines from ISPOR (http://www.ispor.org/sigs/MCP_accomplishments.asp#definition) as well as the following paper (Cramer JA, Roy A, Burrull A, et al. Medication Compliance and Persistence: Terminology and Definitions. Value Health 2008;11: 44-7.). These will inform you that you should use the term compliance and perhaps persistence in describing this problem. **We have replaced ‘adherence’ by ‘persistence’ throughout.**

18. Results, Subjects: Table 1, the usual place in which scientists characterize their samples, is way too sparse. Other demographic and disease-related data belong here. We have replaced it by a new Table 1, characterising demographic and clinical features of women diagnosed by densitometry or fracture or both. Additional clinical data specifically relevant for osteoporosis are provided in Table 2 (these data are only available for the patients in the study analysis population for whom a medical questionnaire was completed). See also reply to Point 2 of Referee 1. Also, what do you make of the statement: “Women in the questionnaire population were younger, had been more frequently evaluated by densitometry, reported less fractures and were more frequently treated.” I am very concerned by the fact that there are three critical variables on which these two groups have significant differences. You must address this. **We have added a paragraph to the Discussion on the study design which explains how this selection bias towards women with OP diagnosed by densitometry might have arisen and how it may have an impact on the results. The over-representation of women with OP diagnosed in this way is however modest (86% in the study analysis population compared to 81% of all eligible women in the registry). Although this difference corresponds to a small but measurable discrepancy in the % of women with OP being diagnosed by densitometry, it should have no effect on the multivariate analysis of factors related to prescription choice, since reason for diagnosis was entered into the analysis as a covariable. The description of the study analysis population provided in the new Table 1 allows readers to appreciate any differences between women diagnosed by OP or by fracture occurrence.** And in the final paragraph under Subjects, this phrase has two problems: “consistent with a diagnosis of osteoporosis (< 2.5). Women consulting a specialist were more likely to have been prescribed a densitometry…” Please add SD after <2.5; also we do not prescribe densitometry. Find a more appropriate word. **SD has been added as suggested and ‘been prescribed by’ replaced by ‘undergone’.**

19. Results, Quality of Life: I would delete the section on quality of life in its entirety. This does not add substantially to the paper and seems to be added as almost an afterthought. See reply to Point 12 above. In the last sentence of this section, you use “localisations”, a word that doesn’t appear in any American or British dictionaries. **In its American spelling, ‘localization’ can be found in Webster’s US dictionary, and also features in Chambers and the OED for British English. However, we have replaced this term by ‘site’._**

20. Discussion, paragraph 3: Do you cover all approved medications for osteoporosis? Does the term bisphosphonates include zoledronic acid? What about teriparatide? Clarity: **Zoledronic acid was not available in France when the study was conducted and teriparatide is not prescribed by GPs and only used vary rarely by rheumatologists. The number of patients using this treatment was extremely low (n = 11) and teriparatide is thus included in the ‘other treatments group’. Otherwise, all osteoporosis treatments approved in France are covered. This is now specified in the Results.**
Note: The writing is not terribly clear nor does it always reflect acceptable grammatical or usage guidelines. This manuscript desperately needs an editor whose first language is English. The manuscript has been checked and revised by an English scientist with experience in the field and validated by an American medical communications professional.

Level of interest: An article of limited interest

Quality of written English: Not suitable for publication unless extensively edited. See above.

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.