ANSWERING REVIEWERS

June 20, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format.

Title: Monitoring Osteoporosis Therapy: Can FRAX help assessing success or failure in achieving treatment goals?

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Name of Journal: *World Journal of Rheumatology*

ESPS Manuscript NO: 10603

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer:

Reviewer 1:
1- Please do not use slang terms in scientific writing" hot issue" or "drug holiday".
Action: We removed the terms like "hot issue", but drug holiday is a common term raised now for discussion in the management of osteorporosis, so we have kept this phrase only.
2- The authors need to define clearly FRAX and the criteria for using FRAX, how to calculate FRAX or provide a figure.
Action: The FRAX is available online and we have added its website link which allow the online calculation of the fracture risk.
3- The introduction section is vague and does not include the current findings in the field or previous studies that have conducted with similar research questions. The authors need to stress out the novelty of the work.
Action: As suggested, we have omitted some paragraphs to make it shorter.
Methods
1- Local ethical committee approved the study. you need to mention the name of the medical or academic entity that approved the study.
Action: the name of Ain Shams Ethical Committee has been included as suggested.
2- In the study design, you referred that all patients were treaded according to the guidelines either your reference or state the guidelines.
Action: treatment guidelines has been included as suggested.
3- Subjects demographics (weight, height, BMI, ages) and ethnic backgrounds (white or black, Asian, etc) are not clear.
Action: We added the data regarding the mean age of the studied osteoporosis female patients was 75.0±9.7. They were ranging between 51 and 92 years old. Weight, height are already included in the FRAX.
4- You need to state exactly the size of the sample subgroup of patients who did not show improvement.
Action: this has been added to the results: "16.9% individuals sustained new incident major osteoporotic fractures whereas in the following 3 years of observation period, 4.7% of the patients

sustained a new low trauma fracture."

5- It is unclear that all participants were scanned at 2 and 5 years or there a range of time when scans were conducted for each patient. Along the same point, please state how many scans were conducted for each patient? What is the least squared difference for repeated scans.

Action: Yes, all the patients included in this work had DEXA scan performed, for every patient, at baseline as well at 2 and 5 years of treatment. This has been added to the methods section.

6- I did not clearly understand what do you mean by diagnosis or RA or smoking were crosschecked, what do you mean by this?

Action: Smoking and rheumatoid arthritis are among the risk factors included in the FRAX calculation. Crosschecking means validation of these risk factors presence by checking the patient's notes.

7- In the measurement section " T-score= mean value of osteoporotic post-menopausal women?

Action: the equation was corrected.

Results

1. Out of the 579 participants, how many drop out and how many continued the study till the end?

The 579 continued till the end coming from a total of 1026

2. The authors stated 48% of the total low trauma was hip fractures what about the other 52%?

The data regarding the 52% of the patients has been added as suggested.

3. What is the y-axis in Figures 1, Figure 2 and Figure 3. In figure 3, it is unclear what the numbers on the top of each column are? Is this a FRAX score or percentage you need to clearly state how did you drive this number?

The Y-axis represents FRAX probability. The number in figure 3 are the mean fracture probability score (this has been added to the captions).

4. Figure legends descriptions need to change for 1, 2 and 3, please any reference to correlation from the description.

Action: that is right, the titles have been amended as suggested.

Discussion

1- The discussion section is too long and needs to be trimmed significantly

Action: amended as suggested.

2- What is the scientific basis of FRAX

Comment:

The FRAX tool has been developed by WHO to evaluate fracture risk in patients. It is based on individual patient models that integrate the risks associated with clinical risk factors as well as bone mineral density at the femoral neck.

http://www.shef.ac.uk/FRAX/

3- Why authors think that there are subgroup that FRAX assessment did not able to predict their risk of developing osteoporosis. This should be considered as a limitation of the study

This has been mentioned by other studies, one is a systematic review. In standard clinical practice there will be always resistant cases to be explained by this FRAX formula. Usually scores could not fit all cases upon which the model was designed.

4- A clear limitation section needs to be highlighted in the discussion

Action: added as suggested.

5- There are many sentences in the discussion are incomplete or does not make any sense a. – increase risk probability of what? b. - Both analyses have been challenged by what? c. Although, regression to the mean…. What do you mean by this? d. Osteoporosis therapy does not annul fracture predictions..what is that mean.

Comment/Reply:

- Increase fracture risk probability (has been corrected)

- Regression to the mean: Statistical tendency of a data series to gravitate towards the center of a distribution, provided it starts on the either end of the distribution and is free to fluctuate.

- Osteoporosis therapy does not annul fracture prediction: On introducing the FRAX, it was highlighted that it can not be use for assessment of fracture risk in patient taking osteoporosis therapy. Therefore, taking osteoporosis therapy would abolish re-using FRAX for any more fracture prediction.

6-   Conclusion section should practical implications and future recommendations.

Action: Amended as suggested.

Reviewer 2:

1.   Please provide the reference number of ethical approval in Methods, if available.

Action: the paragraph was amended.

2.   One of the key outcomes in this study was new low trauma fracture incidence. However, the manuscript does not mention how to record this data. Please provide. ???

Action: data provided as suggested.

3.   In Methods under "Patients", there is a sentence "The age range was from 50 to 79 years (mean 64.3±9.4 years)". I think this should be put in Results. Instead, the authors should tell the planned age range of the original proposal in Methods.

Action: amended as suggested.

4.   In Methods under "Measurements", the authors mentioned blood check and FRAS score of fall risk. However, I do not see any report or analysis on these parameters and I am confused their relevance to this study. Why to mention them? Please clarify.

Action: Falls risk is an independent risk factor for fractures which is not included in the FRAX, therefore, it was important to assess for it. Patient with high falls risk were referred to the falls clinic. Patients with vitamin D deficiency were treated.

5.   The statistical description is not clear enough. I cannot follow well which test for which data, esp. paired t-test. Please specify clearly.

Action: amended as suggested.

6.   Also, I am very confused on Fig. 1-3. Based on legend, they are supposed to be correlation data. What are HS and NS? What are the numbers above the bars? I think correlation data should be presented in table?

Action: The captions were amended as suggested to address these notes.

7.   Results, first sentence: please provide the number apart from the percentages. This will be clearer.

Action: amended as suggested

8.   Results, 3rd paragraph, first sentence: what is the meaning of (>0%)

Action: meaning increases in BMD in comparison to baseline

9.   Results, 3rd paragraph, second sentence: "After controlling for covariates, ..." – what are the covariates? I cannot follow what it is. Other co-factors like age, Methods did not mention at all on controlling covariates.

Action: these are the covariates are included in the assessment for the 10-year fracture probability (FRAX).

10.   In Table 3, among all the correlation coefficients, the one between BMD total proximal femur at baseline and FRAX 10-year hip fracture risk probability was up to -0.741 that was the highest one, while the others are around 0.5. Any reason or explanation why this correlation is much better than others. Please discuss.

Comment: FRAX use the BMD at the hip for the 10-year probability both for the major osteoporosis fracture or hip fracture. That is why it is expected that the BMD total proximal femur would show the strongest relation.

3 References and typesetting were updated

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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