

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Comparative effectiveness of bisphosphonate treatments for the prevention of re-fracture in glucocorticoid-induced osteoporosis: protocol for a systematic review and meta-analysis
<b>AUTHORS</b>	Chu, Hongmin; Jang, Bo-Hyoung; Kim, GaYoon; Bae, Seowoo; Lee, Hyeju; Nam, Seonghee; Ahn, Jeonghoon

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Win Oo Kolling Institute of Medical Research, Rheumatology
<b>REVIEW RETURNED</b>	19-Mar-2022

<b>GENERAL COMMENTS</b>	<p>The authors will evaluate the comparative treatment effect and prevention of re-fracture according to the type of bisphosphonate in glucocorticoid-induced osteoporosis. It is well-written. I have a few comments for the consideration of the authors.</p> <p>Just wondering whether the effect on the re-fracture will be a secondary outcome Page 6 Line 16 "If enough studies are available to examine the causes of heterogeneity and its criteria...". How many studies exactly do you think to be enough? Page 10 Line 16</p>
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<b>REVIEWER</b>	Ramona Dobre National Institute of Endocrinology Bucharest, Romania, Pituitary and Neuroendocrine disorders
<b>REVIEW RETURNED</b>	30-Apr-2022

<b>GENERAL COMMENTS</b>	<ol style="list-style-type: none"><li>1. The outcomes need clarification. The discrepancy between and index fracture and re-fracture needs to be underlined. In the abstract, mainly the re-fracture risk is commented.</li><li>2. "However, the analysis on the BP's effect of prevention of re-fracture is insufficient. The purpose of the present study is to evaluate the comparative treatment effect and prevention of re-fracture according to the type of bisphosphonate in GIOP as the basis for reliable clinical strategies for patients." - text from introduction and "The primary outcome will be the incidence of hip, vertebral, and other fractures." - from methods. It is not clear here and in the methods section what fracture is quantifiable, the index fracture or the refracture risk. - evaluating effectiveness of BP to the GIOP patients will be included in this study" - i believe it is important to mention the control group that can include as stated in the methods other anti-osteoporotic medications, some considered to be quite effective in GIOP (eg Denosumab).</li><li>3. First question: only osteoporotic patients are included: there are</li></ol>
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	<p>studies with anti-osteoporotic treatment in patients with high doses of GCs. Second question: only osteoporosis based on BMD and FRAX, as the guideline states that osteoporosis can be diagnosed based on major fracture alone or fracture plus osteopenia and also, is we are talking about GIOP, FRAX is known to underestimate the risk of osteoporosis and also the fracture risk for these patients. Please comment. Third: although the BPs were chosen as objective for this review, comparison with denosumab and also teriparatidum needs to be underlined as these medications are very effective and widely used in GIOP and especially teriparatidum after a fracture.</p> <p>4. Methods need to be more thoroughly explained. There has to be a detailed evaluation of the comparison groups and also the types of fracture, index or re-fracture risk.</p> <p>6. See comments above.</p> <p>9,10. As stated above, the outcomes need to be better defined. There are many comparisons to be made: between different types of BP, with placebo/non-treatment and also, the main important in my opinion, the one with other anti-osteoporotic medication (denosumab/teriparatidum).</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Win Oo, Kolling Institute of Medical Research

Comments to the Author:

The authors will evaluate the comparative treatment effect and prevention of re-fracture according to the type of bisphosphonate in glucocorticoid-induced osteoporosis. It is well-written. I have a few comments for the consideration of the authors.

Just wondering whether the effect on the re-fracture will be a secondary outcome Page 6 Line 16

"If enough studies are available to examine the causes of heterogeneity and its criteria...". How many studies exactly do you think to be enough?

Page 10 Line 16

Answer: Thanks for the kind review.

We add definition of re-fracture in the method section for clarifying meaning and 'incidence of re-fracture' as secondary outcome. We write criteria of assessing heterogeneity in the method section.

Reviewer: 2

Ramona Dobre, National Institute of Endocrinology Bucharest, Romania

Comments to the Author:

1. The outcomes need clarification. The discrepancy between index fracture and re-fracture needs to be underlined. In the abstract, mainly the re-fracture risk is commented.

Answer) For clarifying outcome, we add 'incidence of re-fracture' as secondary outcome.

2. "However, the analysis on the BP's effect of prevention of re-fracture is insufficient. The purpose of the present study is to evaluate the comparative treatment effect and prevention of re-fracture according to the type of bisphosphonate in GIOP as the basis for reliable clinical strategies for patients." - text from introduction and "The primary outcome will be the incidence of hip, vertebral, and other fractures." - from methods. It is not clear here and in the methods section what fracture is quantifiable, the index fracture or the refracture risk.

- evaluating effectiveness of BP to the GIOP patients will be included in this study" - i believe it is important to mention the control group that can include as stated in the methods other anti-osteoporotic medications, some considered to be quite effective in GIOP (eg Denosumab).

Answer) Thanks for the review. We write control group`s definition with detailed medication. For evaluating effectiveness of BP, change of Bone mineral density will observed. So, we add 'rate of adverse events' for checking safety of BP treatment.

3. First question: only osteoporotic patients are included: there are studies with anti-osteoporotic treatment in patients with high doses of GCs.

Second question: only osteoporosis based on BMD and FRAX, as the guideline states that osteoporosis can be diagnosed based on major fracture alone or fracture plus osteopenia and also, is we are talking about GIOP, FRAX is known to underestimate the risk of osteoporosis and also the fracture risk for these patients. Please comment.

Third: although the BPs where chosen as objective for this review, comparison with denosumab and also teriparatidum needs to be underlined as these medications and very effective and widely used in GIOP and especially teriparatidum after a fracture.

Answer) Response to the first and second question: Due to this study mainly focusing on the GIOP patients, this review will conducted with data on the patients diagnosed with osteoporosis. In addition, FRAX is an index that is used globally, as the reviewer said, it has the disadvantage of 'underestimate the risk of osteoporosis'. However, as FRAX is the most cited and recognized index in the existing guidelines, we will use FRAX for evaluation, and cited these limitations when writing the SR.

Third: The Comparison group mentioned that they plan to compare the effect size according to the type of the control group by adding contents such as denosumab, SERM, and romosozumab.

4. Methods needs to be more thoroughly explained. There has to be a detailed evaluations of the comparison groups and also the types of fracture, index or re-fracture risk.

9,10. As stated above, the outcomes need to be better defined. There are many comparisons to be made: between different types of BP, with placebo/non-treatment and also, the main important in my opinion, the one with other anti-osteoporotic medication (denosumab/teriparatidum).

Answer) Thanks for the kind review. We indicated types of fracture according to reviewers' opinions and supplemented the comparisons section.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Ramona Dobre National Institute of Endocrinology Bucharest, Romania, Pituitary and Neuroendocrine disorders
<b>REVIEW RETURNED</b>	31-Jul-2022
<b>GENERAL COMMENTS</b>	Needs english proofing

#### VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Dr. Ramona Dobre, National Institute of Endocrinology Bucharest, Romania, Carol Davila University of Medicine and Pharmacy

Comments to the Author:

Needs English proofing.

Thanks for the kind review. Based on the editor's opinion, we have submitted the manuscript to the English proofreading service and attached the confirmation letter.