

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

TITLE (PROVISIONAL)	Using serum urate as a validated surrogate endpoint for flares in patients with gout: protocol for a systematic review and meta-regression analysis
AUTHORS	Morillon, Melanie; Stamp, Lisa; Taylor, William; Fransen, Jaap; Dalbeth, Nicola; Singh, Jasvinder; Christensen, Robin; Lassere, Marissa

VERSION 1 - REVIEW

REVIEWER	Dirk F Moore Rutgers University, USA
REVIEW RETURNED	25-Apr-2016

GENERAL COMMENTS	<p>The meta-analysis plan outlined here is quite well thought-out. My main question concerns the plan to use SAS proc mixed to fit a random-effects model to the data. If the authors are able to obtain the original data from the selected studies, this would be fine, but this doesn't appear to be part of the plan. Thus, the authors will have one summary measure for SU for each paper and one summary outcome (for each objective). There would thus be no measurements at the individual level to define the random effects.</p> <p>The meta-analysis is still possible. Lacking individual-level data, however, will weaken the conclusions.</p>
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REVIEWER	Dr A Abhishek The university of Nottingham UK
REVIEW RETURNED	02-May-2016

GENERAL COMMENTS	This is a well thought through and well written systematic review protocol.
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REVIEWER	Lihua Duan Department of Rheumatology and Clinical Immunology, The First Affiliated Hospital of Xiamen University, Xiamen, Fujian, China
REVIEW RETURNED	12-Jul-2016

GENERAL COMMENTS	In this manuscript, the authors addressed the serum urate as a validated surrogate endpoint for flares in gout patients. This is a meanful review, which will be helpful for the patients treatment. As the statistical methods is out of my knowlege, a additional statistical review will be better.
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Question 1: The meta-analysis plan outlined here is quite well thought-out. My main question concerns the plan to use SAS proc mixed to fit a random-effects model to the data. If the authors are able to obtain the original data from the selected studies, this would be fine, but this doesn't appear to be part of the plan. Thus, the authors will have one summary measure for SU for each paper and one summary outcome (for each objective). There would thus be no measurements at the individual level to define the random effects. The meta-analysis is still possible. Lacking individual-level data, however, will weaken the conclusions.

Answer: We thank the reviewer for thoughtful input to the strengths and limitations associated with our suggested approach. We agree that the inference from these analyses will be strongest if it comes from IPD meta-analysis (i.e. a simple pooled analysis). However, there are also potential limitations associated with only asking for the original data – for instance whether the data sets that are available to us have been collected systematically.

Action: (we have now inserted on page 14, and added the reference page 23. Changes is highlighted) Although our meta-regression analysis is undertaken correctly from a technical point of view, relations with averages of patients' characteristics can be potentially misleading. Thus, following our systematic review, we will attempt to get access to individual participant datasets investigating patients' characteristics, this will to some extent move us away from looking at relations across trials, to inspection of relations within trials (REF: Thompson S and Higgins J, Lancet 2005; 365: 341–46)

Reviewer 2

Question 1 This is a well thought through and well written systematic review protocol.

Answer We thank the reviewer for the kind comment.

Action None

Reviewer 3

Question: The authors addressed the serum urate as a validated surrogate endpoint for flares in gout patients. This is a meaningful review, which will be helpful for the patients treatment. As the statistical methods is out of my knowledge, an additional statistical reviewer will be better.

Answer: We thank the reviewer for the positive comments regarding the proposed article and we acknowledge the positive comment regarding the purpose of the review in regard to the expected benefit for patients.

Some statistical aspects is addressed by reviewer one and answered in that section. Lots of the potential limitations are addressed in the paper by Thompson S and Higgins J (Lancet 2005; 365: 341–46)

Action None