Reviewer’s report

Title: Cost-effectiveness of different treat-to-target strategies in rheumatoid arthritis: results from the DREAM registry

Version: 0 Date: 21 Dec 2018

Reviewer: Katie Druce

Reviewer’s report:

General comments

This is an interesting paper which could have clinical impact. However, I have a number of concerns and I think this paper would benefit from revisions to make the methods section more succinct from the point of the Markov model, but also making sure that all methods are covered:

In general I find it hard to follow how the real patient data has been used and which sections refer to real data and which do not. This is particularly hard due to phrases like "patients are imagined to", "However, in real life," and then "All patients initially enter the model on the first medication of their treatment protocol". See also the below comment for Page 7 line 44 - Page 11 line 2.

There is also some methodology missing including how EQ-5D was used and QALYs calculated - these may not be familiar to all readers. Finally, the results section includes lots of content more suited to the discussion (e.g. interpretation of findings, rather than just statement of findings

Specific comments

Page 5 line 5-7 - I am unconvinced that the statement "higher disease activity, characterized by inflammation of the synovial fluid." Is correct, would higher disease activity not actually be characterized by one of the disease activity measures such as DAS-28? Are higher disease activity scores ALWAYS caused by inflammation?

Page 5 line 15 - I am not sure treating fatigue is currently a target for treatment.

Page 5 line 30 - this sentence would read better as "The approach currently recommended for RA treatment….."

Page 5 line 39 - If the target is "either remission or low disease activity" (line 32) is it true to say "The focus on rapid suppression of inflammation results in high initial costs"? I think you need to be clear whether you are referring to strategies which use inflammation only, or composite measures. Given that the analysis is latterly about DAS28, I think it is incorrect to suggest that the focus is only on suppression of inflammation.
Page 7 line 44 - Page 11 line 22 - this section is quite heavy for a clinical journal. I find it hard to follow which sections refer to real people's data and which don't. E.G. page 8 lines 49-59, do you refer here to people who were actually observed or are these hypothetical scenarios you have created in the data.

I wonder if you might be able to provide a more high level summary and give specific details as an appendix.

Page 12 line 2 - "A negative ICER can be hard to interpret." Should be discussed in the methods.

Page 12 line 7-12 - "The negative ICER thus shows that initial combination therapy is a cost-saving, and thus dominant strategy. This indicates that initial combination therapy is cost-effective and preferable over step-up therapy" feels more suited to the discussion.

Page 13 line 32 - The sentence "That strategy yields more QALYs at a lower cost." Feels redundant because you've already mentioned it was cost effective.

Page 13 line 35 - "The difference in cost between the two strategies is considerable" this feels more like a discussion sentence as "considerable" suggests you are evaluating the difference.

Page 13 lines 40-57 - The whole paragraph from "As mentioned above, the (negative) ICER" to "tapered lowering medication costs." Does not read like a result section and is more suited to a discussion.

Page 14 lines 13-15 - when you mention "more effective (in terms of EQ-5D utility)" I am left wondering how you used the EQ-5D in order to make this assertion and I realised it is not clear from the methods section how you used this.

Page 14 line 18 - you say "will accrue" do you mean that hypothetical patients DID accrue? Or at least you should soften this statement by indicating that this is what your data suggest as we cannot know if this is generally true.

Page 15 lines 12-17 - it is not completely clear how the Schipper et al. paper supports this conclusion when they had different comparators.

Page 15 lines 25-42; Page 16 lines 5-15 - I find myself wondering again the extent to which these data are based on real life and observed transitions. If these patterns are entirely fictional, how do we know this cost analysis has any validity in clinic? But if they aren't fictional (as suggested on page 16), I am confused how they were created.

Page 16 line 15 - "Adherence in RIC I and II was good." Is a standalone sentence and it is not clear what the meaning/impact of it is.

Page 16 line 25-32 - I am unclear what you mean by the paragraph "However, for comparison of the two strategies, this cost calculation method was adequate because the comparisons are made within this study. Obviously, comparison of this study with other publications should be
conducted most carefully." Also, you have made a comparison to the Schipper et al., so I am wondering how appropriate this is.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Unable to assess

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I recommend additional statistical review

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