Author’s response to reviews

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

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Author’s response to reviews:

Rebuttal Letter

Dear dr. Paul Studenic,

Thank you for providing us with the opportunity to revise our manuscript “Cost-effectiveness of different treat-to-target strategies in rheumatoid arthritis: results from the DREAM registry”.

Please find enclosed the revised version of our manuscript. This letter includes a detailed response to each point raised by the two reviewers. They had interesting suggestions and we agreed with the feedback that was given. We modified the manuscript accordingly. Additionally, the entire manuscript was checked carefully for other possible errors. Changes in the manuscript were highlighted using ‘Track Changes’. These can be found in the supplemental material.

We would like to greatly thank the reviewers for their constructive criticism and for their thorough efforts in helping to improve our manuscript.

We hope the revised version to be acceptable for publication and look forward to hearing from you.

On behalf of all authors,

Sincerely,

Celine Johanna van de Laar

Reviewer 1
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

1. 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?

Response: Thank you for pointing this out. We have deleted the latter part of the sentence. Page 5, line 3

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

Response: we have deleted the examples pain and fatigue from the sentence. Page 5, line 6.

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

Response: Thanks for this suggestion. We agree and have adjusted accordingly. Page 5, line 12

4. 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.
Response: We agree, with the target being remission or low disease activity, there is more than just a focus on suppressing inflammation. We have adjusted the text to make this more clear. Page 5, line 16

5. 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.

Response: Thank you for pointing this out. The current study is a model based health economic evaluation in which health economic consequences of two treatment strategies are evaluated within a mathematical framework. All data input for this framework (i.e. DAS28 state transition probabilities and EQ5D and cost weights) were calculated directly from the various DREAM cohorts, as described in the “data sources’ section. This general methodology is in accordance with the ISPOR principles for good practice for decision analytic modelling in healthcare evaluation. We have now added a section at the beginning of the methods section in which this is explained. Page 6, lines 15-22, page 7 lines 6-8.

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

Response: Thank you for pointing this out. We have moved the interpretation to the discussion. Page 15, lines 11-16.

7. 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.

Response: Thank you for these valuable points. We have indeed rephrased and/or moved several sentences to the discussion section:

- Explanation about a negative ICER and its implication has been moved to the discussion. Page 15, lines 11-16
"That strategy yields more QALYs at a lower cost" was adapted to make it more clear that it is not only cost-effective, but that combination therapy is also dominant. Page 14, line 7

"The difference in cost between the two strategies is considerable". This indeed felt like an evaluation of the difference, we have deleted the word ‘considerable’. Page 14, line 8.

We have moved the sentence: “Overall, there are more patients in remission in initial combination therapy strategy than in the step-up therapy strategy at each time point. This reduces health costs, increases utility, and medication can be tapered lowering medication costs.” To the discussion. Page 15, lines 19-21.

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.

Response: Thank you for pointing this out. We have included an elaborate description of how the EQ-5D is used in our study on page 8, lines 4-12.

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.

Response: You are right, this is based on what our data suggested. We adjusted the sentence accordingly. Page 15, lines 7-11

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

Response: Thank you for pointing this out. We have removed the comparison from the manuscript. Page 16, lines 18-22

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.

Response: We have removed the comparison with Schipper et al. Furthermore, in cost effectiveness studies it would be desirable to comprehensively assess different types of
healthcare costs. However in practice it is almost never the case that sufficient information is available to do this.

We now clarify in the discussion section that readers should consider that no out-of-pocket costs were measured in our study and that insufficient information was available to evaluate productivity using the friction method (hence we evaluated productivity loss using the human capital method) when comparing our results to results obtained in other studies, for which different types of costs may have been assessed. Page 12.

12. 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.

Response: Thank you for pointing this out. In response to your comment number 7 we have added an extra section to the manuscript in which it is clarified that the current study is a model based approach in which all model input is derived from real-life data. (Page 6, lines 15-22) as in accordance with the ISPOR principles. Furthermore, as we described throughout the manuscript, the modelling framework we expanded upon for this study has previously been used in various publications. In the original publication by Welsing et al. (which was published in Pharmacoeconomics) there is evidence with respect to the predictive validity of the framework is provided. This is now mentioned in the methods section (Page 8, lines 15-18).

13. 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.

Response: Indeed, this sentence is standalone. We have deleted the sentence. Page 17, line 20.

Reviewer 2

1. In the "Material and Methods" section, the registries on which the calculation are based are mentioned, but no details on the status quo of the registries at the time of calculation are given (number of patients, therapies given etc.) for the two cohorts. This information should be added, preferably in a Table.

Response: Thank you for this suggestion. This was an omission in our manuscript. We have added a table which summarizes patient characteristics in the supplemental material.

2. The economic calculations are based on the situation in the Netherlands. To what extent are the results generalizable to an at least European general population? This should be added in the "Discussion" section.
Response: Thank you for this valuable suggestion. This is indeed an interesting element. We have added a paragraph in the discussion section discussing this. See page 18, lines 5-13.

3. Where other bDMARDs other than TNF-blockers considered in the calculations. Are there any differences between TNF-blockers?

Response: The patients in the DREAM Remission Induction Cohorts predominantly used anti-TNF-α. Even though most bDMARDs are sometimes said to have very similar effectiveness, we did not make this generalization to biologicals for RA in general.

4. The last sentence in the "Discussion" section does not make sense. The sentence should probably end like this "…. Compared with step-up therapy, but also lower costs"

Response: Thanks for pointing this out, we have adapted accordingly. (Page 18, line 17).