PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Modeling the cost-effectiveness of combination therapy for early, rapidly progressing rheumatoid arthritis by simulating the reversible and irreversible effects of the disease
AUTHORS	Stephens, Stephanie; Botteman, Marc; Cifaldi, Mary; van Hout, Ben

VERSION 1 - REVIEW

REVIEWER	Mary Jane Bell University of Toronto, Canada
REVIEW RETURNED	14-Oct-2014

GENERAL COMMENTS	I am concerned about conflict of interest when the company funding the research is involved in protocol development and, analysis and manuscript preparation. Otherwise this is an excellent paper. I am not a statisitician and my statistical knowledge is MSc level. This paper should be reviewed by an expert in mathematical modelling. I would consult an ethicist. This is an well written manuscript addressing an import health economics topic. My major concern is whether it is ethical to have the funding company so intimately involved in the design, analysis and writing of the manuscript. Please consult an ethicist with regard to this question.

REVIEWER	An Tran-Duy Maastricht University Medical Center+ The Netherlands
REVIEW RETURNED	14-Dec-2014

GENERAL COMMENTS	This is an interesting modelling study on the cost-effectiveness of adalimumab plus methotrexate (MTX) compared with MTX monotherapy. One of the innovative aspects of this study is the simulation of the long-term effect of the treatments on the radiographic joint damage, measured by the Modified Total Sharp Score (mTSS). Clearly, the ultimate aim of this model is to capture the incremental cost and health-related quality of life of patients receiving the alternative intervention; notwithstanding, by predicting the long-term disease progression in terms of join damage and relating this to HAQ, and then relating HAQ to and health utility and costs, this study provides an insight into the pathway that a treatment strategy affects costs and quality of life, which is useful for both health economists and clinicians. Another interesting point is

	that the authors modeled the effect of the treatments on the four domains of the 28-joint Disease Activity Score (DAS28, which explain better the ACR response than the DAS28 as a composite measure. The manuscript is inevitably technical, but in my opinion the presentation is pretty clear. The model is generally well described and supported by an appendix. I have a number of comments that may help the authors to increase the transparency of the model and clarity of the manuscript, especially for the general readers who are not familiar with complex modelling techniques. TITLE I think that the disease activity is an outcome and not an intervention; therefore, there is room to improve the title so that it reflects better the nature of the study (modelling the cost-effectiveness of a treatment combination including simulation of the reversible and irreversible components of the disease). INTRODUCTION Page 4 It would be clearer if the authors could elaborate a little more about the concepts of HAQ (e.g. it consists of both reversible and irreversible components), and why modelling joint damage is an advantage. Lines 38-39: “was generally modelled implicitly… or indirectly”: please explain what the difference between “implicitly” and “indirectly” is. The authors may consider to refer to newer publications that modeled both DAS28 and HAQ (e.g. Tran-Duy et al. PharmacoEconomics 2014; 32:1015-1028). Line 44: “early aggressive RA should be treated with combination therapy”: Please clarify this, and explain how this is related to the impact of irreversible disease progression on health-related quality of life. METHODS Page 5 Line 5: “United Kingdom (UK) perspective”: Does this mean the UK healthcare setting? Probably the term “perspective” should be used to indicate that this study is carried out from a societal perspective. Line 22: “disease histories”: Please explain why these should be generated, and indicate what variables were contained in the histories and how they were sampled. Line 28: “the order of the sequence”: I think the precise expression should be “the order of the treatments in the sequence”. Lines 41-42: “latent disease activity consisting of a .. reversible … and irreversible component”: Please explain why “latent”. Also, I think joint destruction or deformity should be added to refer to the irreversible component. Line 50: “After mathematical transformations, the individual components of disease activity were captured using a multivariate normal model with shifted means:” Please clarify what transformations were made. I wonder if the expression “a multivariate normal model” means “a multivariate normal distribution”. If so, I am very much interested in knowing how the variance-covariance matrix and means were obtained at every 26-week cycle. This explanation may be added to the appendix. Page 6 I think the reasons for using logistic regression to model HAQ and utility should be provided. The meanings of the subscript values of the coefficients in the equations for mTSS, HAQ and other statistical models should be provided. I am not sure why the statistical models for mTSS and HAQ are included in the main text, while the others are put in the appendix. Is there a difference in the importance of

	these models? RESULTS Figure 3 represents consequence of the treatments by plotting HAQ against time. It is interesting to see how the mTSS changed over time in relation to HAQ change and thus the authors may think about including lines for mTSS in these graphs.

VERSION 1 – AUTHOR RESPONSE

Reviewer Name Dr. Mary Jane Bell
Institution and Country University of Toronto, Canada
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below I am concerned about conflict of interest when the company funding the research is involved in protocol development and, analysis and manuscript preparation. Otherwise this is an excellent paper.

I would consult an ethicist.

This is an well written manuscript addressing an import health economics topic. My major concern is whether it is ethical to have the funding company so intimately involved in the design, analysis and writing of the manuscript. Please consult an ethicist with regard to this question.

We appreciate the concerns of the reviewer. However, the merit of our analysis rests in its high level of scientific rigor and transparency, and the authorship by Dr Cifaldi rest in her contribution, which meets the ICJME authorship guidelines, including:
1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

It is also important to emphasize that each of the other authors have contributed to the design, analysis, interpretation and writing of the manuscript without inappropriate influence from the sponsor. We individually and collectively stand by the quality of the analysis and its findings. As such, we believe that the concerns from the reviewers are not justified in our present case.

Reviewer Name An Tran-Duy
Institution and Country Maastricht University Medical Center+
The Netherlands
Please state any competing interests or state 'None declared': None declared

This is an interesting modelling study on the cost-effectiveness of adalimumab plus methotrexate (MTX) compared with MTX monotherapy. One of the innovative aspects of this study is the simulation of the long-term effect of the treatments on the radiographic joint damage, measured by the Modified Total Sharp Score (mTSS). Clearly, the ultimate aim of this model is to capture the incremental cost and health-related quality of life of patients receiving the alternative intervention; notwithstanding, by predicting the long-term disease progression in terms of join damage and relating this to HAQ, and then relating HAQ to and health utility and costs, this study provides an insight into the pathway that a treatment strategy affects costs and quality of life, which is useful for both health economists and clinicians. Another interesting point is that the authors modeled the effect of the treatments on the four

domains of the 28-joint Disease Activity Score (DAS28, which explain better the ACR response than the DAS28 as a composite measure. The manuscript is inevitably technical, but in my opinion the presentation is pretty clear. The model is generally well described and supported by an appendix.
I have a number of comments that may help the authors to increase the transparency of the model and clarity of the manuscript, especially for the general readers who are not familiar with complex modelling techniques.

TITLE
I think that the disease activity is an outcome and not an intervention; therefore, there is room to improve the title so that it reflects better the nature of the study (modelling the cost-effectiveness of a treatment combination including simulation of the reversible and irreversible components of the disease).
The authors agree that the title could be made more explicit and have updated the title as follows:
“Modeling the cost-effectiveness of combination therapy for early, rapidly progressing rheumatoid arthritis by simulating the reversible and irreversible effects of the disease”

INTRODUCTION
Page 4
It would be clearer if the authors could elaborate a little more about the concepts of HAQ (e.g. it consists of both reversible and irreversible components), and why modelling joint damage is an advantage.
To provide further information on HAQ, the following text has been included:
“[HAQ] – a generic functional questionnaire assessing patient’s ability to carry out everyday activities that may be affected by both reversible and irreversible components of RA”

Modelling joint damage is an advantage because it allows us to capture the cumulative effects of treatment (in this particular case, early interventions). The following text has been included in the manuscript:
“Modelling joint damage captures the cumulative effects of treatment over time, yet, the irreversible radiographic damage itself has never been explicitly and directly modeled.”

Lines 38-39: “was generally modelled implicitly… or indirectly”: please explain what the difference between “implicitly” and “indirectly” is. The authors may consider to refer to newer publications that modeled both DAS28 and HAQ (e.g. Tran-Duy et al. PharmacoEconomics 2014; 32:1015-1028).
Here we use the term “implicitly” to describe the effect on radiographic function being measured via some other, observable, factor (i.e. functional outcomes). We use the term “indirectly” to describe the effects on radiographic function which are measured by assessing the impact of an element which is directly linked to radiographic function (radiographic damage) which consequently affects a different, explicitly modelled element (HAQ). No changes to the text were considered necessary.

Wes have also considered the recent Tran-Duy publication, and have referenced it accordingly when summarising the available evidence.

Line 44: “early aggressive RA should be treated with combination therapy”: Please clarify this, and explain how this is related to the impact of irreversible disease progression on health-related quality of life.
We agree that this particular sentence should be re-worded for clarity. It is not that we wish to convey that combination therapy is definitely the most appropriate option for all patients (although this is likely the case for the majority of patients). The text has been updated in the manuscript to:
“early aggressive RA should be treated as effectively as possible”

METHODS

Page 5
Line 5: “United Kingdom (UK) perspective”: Does this mean the UK healthcare setting? Probably the term “perspective” should be used to indicate that this study is carried out from a societal perspective. The model base case does not include indirect costs and is thus carried out from a UK NHS perspective. To improve clarity, text has been changed to:
“the associated direct (and, in a scenario, indirect) costs and quality-adjusted life-years (QALYs) over 30 years from a United Kingdom (UK) National Health Service (NHS) perspective.”
Also, in the discussion section, the following text is included:
“Finally, when indirect costs were included (i.e. a UK societal perspective was taken)”

Line 22: “disease histories”: Please explain why these should be generated, and indicate what variables were contained in the histories and how they were sampled.
Disease histories should be generated because of variability and heterogeneity as well as inter-dependence between the variables which affect the disease. In RA, symptoms and damage are dependent on the patient’s experience of the disease previously.

We acknowledge that the use of the term ‘ histories’ here may be confusing, and have tried to be more specific by amending the text to:

“The microsimulation model generates individual patient histories. These histories tell the story of each individual patient’s disease pathway in terms of his/her therapy and its consequences on disease activity and joint damage and the subsequent consequence of those on survival, costs and quality of life. While side effects and mortality may occur any moment, treatment decisions are made in 26-week cycles, for 1,000 patients initiated on adalimumab plus MTX therapy or MTX monotherapy (Figure 1).
The histories are generated using analyses which have been carried out on the information available in the PREMIER clinical trial.”

Line 28: “the order of the sequence”: I think the precise expression should be “the order of the treatments in the sequence”.
We fully agree and have updated the text accordingly

Lines 41-42: “latent disease activity consisting of a .. reversible … and irreversible component”: Please explain why “latent”. Also, I think joint destruction or deformity should be added to refer to the irreversible component.
We have re-worked the methods section to improve clarity. Each component of the RA disease and how these are linked in the model is described fully and clearly.

Line 50: “After mathematical transformations, the individual components of disease activity were captured using a multivariate normal model with shifted means:” Please clarify what transformations were made. I wonder if the expression “a multivariate normal model” means “a multivariate normal distribution”. If so, I am very much interested in knowing how the variance-covariance matrix and means were obtained at every 26-week cycle. This explanation may be added to the appendix.
We now realize that we have not been completely precise and yes by ‘multivariate normal model’ we do mean a multivariate normal distribution. We have changed the following text:

“Each patient’s base case score on these 4 domains was randomly taken from truncated normal distributions designed to reflect the observed base-case distribution of these variables in the PREMIER trial. The effect of therapy on each of these 4 domains at week 26 was modeled by assigning shifts in distribution means, reflecting the improvement in score observed in PREMIER. It was explicitly assumed— again on the basis of PREMIER data—that there was a positive correlation between the shifts across the 4 variables. This implied that, for, instance, a treatment that affects pain

in a patient may not necessarily improve the number of tender joints. After mathematical transformations, the individual components of disease activity were captured using a multivariate normal distribution with shifted means. The DAS28 variables were then used in an ordered logistic regression to predict ACR responses at 26 weeks."

To:

"For each patient the starting scores on the four DAS-28 domains are computer generated by drawing at random from a multivariate normal distribution which was estimated using the sample means and covariance of the logit of the four domains. The effect of therapy was modelled by shifts in the distribution means, reflecting improvements. These shifts are again generated using a multivariate normal distribution as estimated by the sample means and covariance as observed in PREMIER. Naturally, while the shifts in the means capture the improvements in the scores, the covariance matrix captures the positive correlation between the four domains. And as a consequence from the fact that this correlation is not perfect, one will find that patients improve on one, but not necessarily on another, domain of the DAS score."

In addition, we also include the following in the appendix:

"It was found that the logit of the variables followed normal distributions and the patient's base-case score on these 4 domains was randomly taken from a multivariate normal distribution which was estimated on the observed base-case distribution of these variables in the PREMIER trial. The effect of therapy on each of these 4 domains at week 26 was modelled by assigning shifts to the right in the (logit) distribution means, reflecting the improvement in score, estimated again on data observed in PREMIER (Figure S3 and Figure S4). Given the censoring at the right, we used the sample median as the estimator of the new mean. As expected, greater shifts were observed for combination therapy than for monotherapy (figure S4).The shifts follow a multivariate normal distribution and the covariance matrices in both the distribution of the baseline value as well as the shifts capture the positive correlation between the 4 variables.

The fact that the correlation is not perfect implies that, for instance, a treatment that affects pain in a patient may not necessarily improve the number of tender joints in that same patient. After mathematical transformations, the individual components of disease activity were captured using a multivariate normal distribution with shifted means."

Page 6
I think the reasons for using logistic regression to model HAQ and utility should be provided. The meanings of the subscript values of the coefficients in the equations for mTSS, HAQ and other statistical models should be provided. I am not sure why the statistical models for mTSS and HAQ are included in the main text, while the others are put in the appendix. Is there a difference in the importance of these models?
The logistic regression is better referred to as a logistic curve. This has been updated in the manuscript.

A logistic curve was chosen to account for the bounds of minimum and maximum values available on the HAQ and utility scales. Although the outcomes do not really differ, a logistic approach has the advantage over a linear model because it fits the data better.
The subscripts in the equations represent the standard errors – this is now noted in the supplementary appendix, alongside the equations, for clarity.

We agree with the reviewer's observation regarding the inclusion of the models estimating HAQ and mTSS in the main text. The model estimating mTSS has been moved to the supplementary material.

Details about the regression used to estimate HAQ were already presented in the supplementary material and have been removed from the main text for consistency.

RESULTS

Figure 3 represents consequence of the treatments by plotting HAQ against time. It is interesting to see how the mTSS changed over time in relation to HAQ change and thus the authors may think about including lines for mTSS in these graphs.

The figure that would need to be included is shown below. As we feel this figure is minimally informative, we prefer to include the following text:

The average mTSS increases almost linearly from a base line value of 19 to an average value of 106 with combination therapy and an average value of 157 with MTX.