PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	A Randomized Efficacy and Discontinuation Study of Etanercept versus Adalimumab (RED SEA) for Rheumatoid Arthritis A pragmatic, unblinded, non-inferiority study of first TNF inhibitor use: Outcomes over 2 years
AUTHORS	Jobanputra, Paresh; Maggs, Fiona; Deeming, Alison; Carruthers, David; Rankin, Elizabeth; Jordan, Alison; Faizal, Abdul; Goddard, Carolyn; Pugh, Mark; Bowman, Simon; Brailsford, Sue; Nightingale, Peter

VERSION 1 - REVIEW

REVIEWER	Michael T. Nurmohamed, MD, PhD, rheumatologist VU University Medical Center & Jan van Breemen Research Institute | Reade, Amsterdam, The Netherlands M. Nurmohamed has done (ad hoc) consultancies for. and received speaking fees from: Abbott, Pfizer, UCB, BMS, Roche & MSD
REVIEW RETURNED	22-Jun-2012

THE STUDY	The small sample size, in combination with the number of patients that did receive a biologic, but did not enter the trial, limits the external validity Too many patients went not in the trial, it becomes not clear whether or not they differ from the trial patients The supplemental documents are adequate
REPORTING & ETHICS	The research ethics have not been clearly addressed in the article. In view of the potential impact an explicit statement about relationships with the relevant pharmaceutical companies is warranted.
GENERAL COMMENTS	This paper describes a pragmatic trial indicating a similar retention rate of etanercept and adalimumab after one year treatment. This kind of investigations are essential in view of the enormous costs of biologic treatment. What is lacking in the present paper is a clear recommendation for clinicians (perhaps due to the limitations??) Major comments - Presently, no firm recommendations following this trial can be given. Please state this clearly. - It is worrisome that at least 362 patients did not enter the trial. This might indicate an allocation bias and limits the external validity of the findings. Please indicate which biologic the 362 patients received and to what extent their baseline characteristics differ from the trial patients. - A concern is the choice of the primary outcome measure as achievement of (at least) low disease activity is also important. Hence, please add the number of patients in remission and low disease activity for the two groups (is there a statistical difference?) - There is accumulating evidence that MTX prolongs the retention

	rate (and efficacy) of adalimumab. Please address. Minor comments - p6, line 34: what is meant by "have failed" is a DAS criterion used? - p 11, line 46 - 48: please add the confidence intervals. - p 13, line 10 - 12: please explain the relationship between cessation of etanercept and heart failure. It might have been that the cessation induced the heart failure... - p13, line 17 - 22: Please add whether or not the two malignancies were thought to be related with the TNF blocking agent. - Discussion: there is a lot of redundancy with the Introduction. Please adapt. - As the adverse events do not differ from what is already known, please consider to delete (or shorten) Table 3

REVIEWER	Dr Andrew J K Östör Consultant Rheumatologist & Associate Lecturer School of Clinical Medicine University of Cambridge Director, Rheumatology Clinical Research Unit Andrew Ostor has received support from (including attendance at conferences), undertakes clinical trials and acts as a consultant to Roche, Chugai, Schering-Plough/MSD, Abbott, Wyeth/Pfizer, BMS, GSK, MerckSorono and UCB.
REVIEW RETURNED	01-Jul-2012

GENERAL COMMENTS	This is a very nice piece of work comparing attrition rates of the two most widely used s/c anti-TNF agents: etanercept and adalimumab. This is a real-life study and hence subject to limitations however the authors have addressed this in the discussion. My only suggestion is regarding the first line of the discussion. I would state that this is an open-label 'real life' study as the way it is currently written is somewhat misleading. These types of studies are extrememly important and the author are commended for producing this manuscript.

REVIEWER	Christensen, Robin Copenhagen University Hospital, Frederiksberg, The Parker Institute: MSU
REVIEW RETURNED	24-Jul-2012

GENERAL COMMENTS	This is a very interesting paper; a very important subject for decision-making in rheumatology. Overall the paper is well-written; seems rigorously reported – consistent with the uploaded protocol. My peer review focus on the statistical outline:

	As the primary outcome is ”Survival on therapy”, I would strongly suggest that the authors present survival statistics fit for purpose (i.e., a KM-plot, and Hazard Ratios). The authors claim (?) that they used an Intention-To-Treat approach for the secondary outcomes, but they don't mention what approach that applied? I think it would be worthwhile if the authors refer to the 2x60 patients as being the modified ITT population. - Meaning that, for all the binary outcomes, the denominator would be 60. For continuous data I would (also) recommend using a non-responder analysis; I would replace missing data d/t dropout with the value from baseline for that individual patient (ie, meaning no change from baseline). With that said: I like the manuscript in terms of the primary outcome. For all the secondary outcomes the paper will benefit from a more rigorous ITT approach. Following the CONSORT statement for non-inferiority trials. - Otherwise it is difficult to infer from the secondary RCT outcomes; this is important from the readers perspective!

VERSION 1 – AUTHOR RESPONSE

Responses to reviewers:

Reviewer & Comments	**Author responses (with manuscript changes)**
Reviewer: Michael T. Nurmohamed	
- The small sample size, in combination with the number of patients that did receive a biologic, but did not enter the trial, limits the external validity - Too many patients went not in the trial, it becomes not clear whether or not they differ from the trial patients	Sample size in clinical trials is determined by the hypothesis being tested. The word 'small', used here, is unhelpful. We stated, in our discussion: 'Important limitations of our study were that only a proportion of patients treated with TNF inhibitors at the trial centers took part. We are unable to say precisely what proportion of eligible patients took part. We have no reason to suspect that patients were systematically excluded for reasons of disease severity or co-morbidity or other factors that limit the generalizability of our findings. We believe that, most likely, patients were not considered for inclusion because of practical considerations such as time constraints and concerns about loss of professional autonomy and patient choice [21]. Reasons

	clinicians' gave, in discussions as the trial proceeded, included a desire for less frequent injections, a preference for a drug with a shorter half-life in the case of etanercept, and concerns about self-administration of injections and thus a preference for infliximab. ' It should be clear from this text that we recognise this limitation. To what extent this limits external validity is uncertain. Our study did not have the resources to monitor new prescriptions of TNF inhibitors for all RA patients at four hospitals. We do not, therefore, have a log of the all patients treated with a TNF inhibitor during trial recruitment. Of the 362 patients known to have started a TNF inhibitor, and who were not included in the study during recruitment, we also do not know what proportion was starting their 1st TNF inhibitor. Under these circumstances showing the clinical characteristics of patients not included in the study is of limited value. We have added to our discussion to make these points clear and have drawn some comparisons with patients recruited into the British Society for Rheumatology Biologics Register.
- The supplemental documents are adequate	No response necessary.
- The research ethics have not been clearly addressed in the article.	This omission has now been corrected and the following sentence added to the section entitled 'Design Overview': ' Study approval was given by the Nottingham Research Ethics Committee 2 (Reference 06/Q2404/171). '
- In view of the potential impact an explicit statement about relationships with the relevant pharmaceutical companies is warranted.	We have complied with this request as follows, though the editor may wish to consider whether there a special case here and whether this study needs explicit statements such as these despite completion of a conflict of interest form.

	Added (under 'Conflict of Interest'): 'All of the authors have completed a disclosure form. No commercial support from manufacturers of adalimumab and etanercept was received for this study. None of the authors have any commercial associations with these manufacturers.'
This paper describes a pragmatic trial indicating a similar retention rate of etanercept and adalimumab after one year treatment. This kind of investigations are essential in view of the enormous costs of biologic treatment. What is lacking in the present paper is a clear recommendation for clinicians (perhaps due to the limitations??)	In order to make the message clear we have altered the conclusion in the abstract and the final paragraph in the discussion. The conclusion in the abstract reads: 'Clincians deciding on which TNF inhibitor to use first in a patient with active RA, and who has not responded to at least two DMARDs including methotrexate, may choose either adalimumab or etanercept in the knowledge that these drugs are similarly effective. '
Major comments	
- Presently, no firm recommendations following this trial can be given. Please state this clearly.	We believe that a clear statement can be made (see above) and hope that our efforts in changing this manuscript show this.
- It is worrisome that at least 362 patients did not enter the trial. This might indicate an allocation bias and limits the external validity of the findings. Please indicate which biologic the 362 patients received and to what extent their baseline characteristics differ from the trial patients.	Please see comments above.
- A concern is the choice of the primary outcome measure as achievement of (at least) low disease activity is also important. Hence, please add the number of patients in remission and low disease activity for the two groups (is there a statistical difference?)	We have reported DAS28 good, moderate and non-responders in our manuscript. There was no statistical difference between the two drugs. Paragraph 2 under 'Efficacy Measures' in results reads: 'The proportion of good, moderate and non-responders based on DAS28 at 52 weeks were 26.3%, 33.3%, and 40.4% for adalimumab versus

- There is accumulating evidence that MTX prolongs the retention rate (and efficacy) of adalimumab. Please address.	16.7%, 31.7%, and 51.7% for etanercept (p=0.158).' Our study was not powered to look at this specific issue and, in this case, the small numbers involved likely have insufficient power to explore this in a meaningful way in post-hoc analyses.
Minor comments	
- p6, line 34: what is meant by "have failed" is a DAS criterion used?	UK guidance requires patients have a DAS28 score of >5.1 to be eligible. The relevant sentence in the introduction has been amended.
- p 11, line 46 - 48: please add the confidence intervals.	The confidence intervals have been added.
- p 13, line 10 - 12: please explain the relationship between cessation of etanercept and heart failure. It might have been that the cessation induced the heart failure...	The following sentence has been added: 'This patient had discontinued treatment because of a skin rash prior to being diagnosed with heart failure. '
- p13, line 17 - 22: Please add whether or not the two malignancies were thought to be related with the TNF blocking agent.	The following sentence has been added: 'In both cases clinicians felt that these events were unlikely to be related to treatment.'
- Discussion: there is a lot of redundancy with the Introduction. Please adapt.	The document has been changed in many places to take into account various comments.
- As the adverse events do not differ from what is already known, please consider to delete (or shorten) Table 3	We have striven to make this shorter but cannot do this any further without making many sections meaningless. This table could easily be deleted and data summarised in text. However we believe that an electronic journal such as BMJ Open should publish such material so that researchers doing meta-analyses, for example, have ready access to detail.
Reviewer: Dr Andrew J K Oster	

This is a very nice piece of work comparing attrition rates of the two most widely used s/c anti-TNF agents: etanercept and adalimumab. This is a real-life study and hence subject to limitations however the authors have addressed this in the discussion.	No response necessary. We appreciate these comments.
My only suggestion is regarding the first line of the discussion. I would state that this is an open-label 'real life' study as the way it is currently written is somewhat misleading.	The sentence has been amended.
These types of studies are extrememly important and the author are commended for producing this manuscript.	No response necessary, thank you.
Reviewer: Robin Christensen	
This is a very interesting paper; a very important subject for decision-making in rheumatology. Overall the paper is well-written; seems rigorously reported consistent with the uploaded protocol.	
My peer review focus on the statistical outline: As the primary outcome is Survival on therapy , I would strongly suggest that the authors present survival statistics fit for purpose (i.e., a KM-plot, and Hazard Ratios).	At each visit it was recorded whether patients were continuing treatment or not. For patients who had discontinued a study withdrawal visit was undertaken. Precise dates for cessation not recorded. The data we have is the continuation status at 12 weeks, 24 weeks, 52 weeks and 104 weeks and Figure 2 has been amended to include data from all four time points. The values in Figure 2 are the same as would be obtained from a Kaplan-Meier analysis of our data if the visit times were used as the event times.
The authors claim (?) that they used an Intention-To-Treat approach for the secondary outcomes, but they don t mention what approach that applied?	It was stated in the footnote to Table 2 that the data were based on a per procotol analysis. Results of an intention to treat analysis have now been added to this table.

I think it would be worthwhile if the authors refer to the 2x60 patients as being the modified ITT population. - Meaning that, for all the binary outcomes, the denominator would be 60. For continuous data I would (also) recommend using a non-responder analysis; I would replace missing data d/t dropout with the value from baseline for that individual patient (ie, meaning no change from baseline). With that said: I like the manuscript in terms of the primary outcome. For all the secondary outcomes the paper will benefit from a more rigorous ITT approach. Following the CONSORT statement for non-inferiority trials. - Otherwise it is difficult to infer from the secondary RCT outcomes; this is important from the readers perspective!	This terminology has been used in the results section and in Table 2. Extra columns of results using this approach have been added to Table 2.

VERSION 2 – REVIEW

REVIEWER	Michael T. Nurmohamed, MD, PhD, rheumatologist VU University Medical Center and Jan van Breemen Research Institute | Reade Amsterdam, The Netherlands
REVIEW RETURNED	14-Sep-2012

GENERAL COMMENTS	Major comments - Despite the fact that it would have been very interesting – particularly in this real world setting study- to know at least the number of patients who were eligible and who were not included, and, in addition, to know the characteristics of this group, the authors have addressed this topic in the discussion section. I understand the reasons but nevertheless, extrapolation of the findings remains difficult. - As the two years data are now available, Tables 2 and 3 should be adapted accordingly. - Moreover, it is peculiar that the recommendations for clinicians (last sentences of the manuscript) are (presumably) based on the two years efficacy data, whereas these have not been provided in the present manuscript. This underscores the need for inclusion of the two year safety and efficacy data of the two therapies in the manuscript. - p 17 I do not agree with '....such that a definite recommendation favoring....' as for such a statement a double-blind RCT is necessary. Please adapt Minor comments - p 17 Please change 'bigger' into 'larger'

	My other comments have been addressed adequately

VERSION 2 – AUTHOR RESPONSE

Reviewer & Comments	**Author responses (with manuscript changes)**
Reviewer: Michael T. Nurmohamed	
Major comments	
- Despite the fact that it would have been very interesting – particularly in this real world setting study- to know at least the number of patients who were eligible and who were not included, and, in addition, to know the characteristics of this group, the authors have addressed this topic in the discussion section. I understand the reasons but nevertheless, extrapolation of the findings remains difficult.	No further comments necessary.
- As the two years data are now available, Tables 2 and 3 should be adapted accordingly.	The only data collected in year two was whether the patients were still on allocated treatment at the year 2 anniversary. This is indicated in our protocol. Data on DAS28 (and it's component features), treatment satisfaction and drug toxicity were not collected during the second year of therapy. We have added a sentence at the end of the section headed 'Design Overview' (p8) which now reads: 'This was a 52-week un-blinded, randomized, non-inferiority, multi-center, parallel group comparison of adalimumab versus etanercept in patients with active RA despite prior or current use of two DMARDs including methotrexate (unless contraindicated). Data on a key outcome, persistence with therapy, was also collected at 104 weeks.' We have also added the fact that 2 year data was a secondary outcome to the section headed 'Outcomes and follow-up'. The relevant sentence on page 9 is shown below and the added words are underlined:

	'Secondary outcomes were the proportion of patients on treatment at 6 months and 104 weeks, the 4 variable disease activity score using 28 joints based on CRP (DAS28-CRP4), the…..'
- Moreover, it is peculiar that the recommendations for clinicians (last sentences of the manuscript) are (presumably) based on the two years efficacy data, whereas these have not been provided in the present manuscript. This underscores the need for inclusion of the two year safety and efficacy data of the two therapies in the manuscript.	The recommendation in our last paragraph (shown below) could be based on either the 1 year or the 2 year data since our non-inferiority hypothesis was met at both time points. The primary end point of the study was the proportion of patients still on therapy at 52 weeks. 'In conclusion, clinicians needing to choose between adalimumab and etanercept, in a patient with active RA despite treatment with methotrexate and another DMARD, may choose either agent in the knowledge that continuation or persistence with therapy after two years is likely to be similar for these two agents. ' Key messages now include the fact that disease activity measures were comparable at one year.
- p 17 I do not agree with '....such that a definite recommendation favoring....' as for such a statement a double-blind RCT is necessary. Please adapt	We recognise that biases are more likely in an un-blinded randomised study but we do not accept that a double blind study is mandatory. The relevant sentence has been deleted.
Minor comments - p 17 Please change 'bigger' into 'larger'	Sentence now deleted.
My other comments have been addressed adequately	