**Reviewer’s report**

**Title:** Radiographic progression in early rheumatoid arthritis patients following initial combination versus step-up treat-to-target therapy in daily clinical practice: results from the DREAM registry

**Version:** 0  **Date:** 21 Oct 2017

**Reviewer:** Daniel F McWilliams

**Reviewer’s report:**

This study shows that people with RA starting treatment in 2006 experienced worse radiographic progression than those that started in 2012. As the periods of recruitment in 2006 and 2012 coincided with different treatment regimens, the authors have concluded that these are the cause of the different rates of radiographic progression.

In order to try and control for the lack of randomisation, the cases were matched into pairs at baseline for the purposes of analysis. Almost all cases were matched in this manner, which either suggests that the early RA cases were very similar in 2006 and 2012, or that the matching criteria were slack. From what I can see, the matching appears to be satisfactory. The authors have also tried to control for early treatment started by GPs, by excluding people who had started DMARDs or more than 10mg of prednisolone per day. Despite the matching process, differences were observed at baseline between the 2 study groups. The 2012 group had slightly worse DAS28, but better HAQ at baseline. Other medications were also different at baseline. So one group was not more severe or active at baseline for all criteria. It is possible that this reflects differences in the treatment pathways between 2006 and 2012.

My main opinion about this study is that is supports the findings of previous clinical trials, but does not add much extra knowledge. Instead there is greater potential for unknown confounders and channelling bias to influence findings, as the study was observational. Can the authors discuss how this manuscript might add to the clinical trial data? For example, were the study populations more representative of the RA general population?

The recruitment start times of 2006 and 2012 need to be mentioned in the abstract. As many readers will only read the abstract, this major limitation needs to be clear.

The recruitment time periods from start to finish should be listed in the Methods.

The authors acknowledge the weaknesses of the study in the Discussion. I think that they could improve the manuscript (and also show their study's limitation) by adding a graph of baseline and follow up radiographic scores for each Strategy. The authors could show their main outcome variable in an attractive way, and also show the years/time periods of Strategy I and Strategy II.

If the cases from Strategies I and II were paired, why are there no paired analyses in the Results?
If the cases were matched more stringently in post hoc sensitivity analyses, would the general findings be replicated? Although the n= numbers might become much lower, perhaps the univariate findings could be replicated in this way?

Can the authors add the VAS-General Health question wording into the manuscript please? Page 6, line 29.

The radiographic scoring process needs to be described in more detail. Were all of the radiographs scored by the same 2 people? Were the scorings performed separately in 2006 and 2012? Can we have details of reliability assessments of the observers?

Can we see details of how missing variables were handled? I think that "complete case" analysis was performed. So can we know the final n= for the multivariable regression models please.

Minor suggestions:

This reviewer has a strong preference for 3 decimal places in p values…

…and also for percentages to have no decimal places.

Baseline SHS score and HAQ in Table 1 have different numbers of decimal places in the different groups.

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

Yes

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

Yes

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

Yes

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If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

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1. Grant support from Pfizer Ltd. 2010-2016.

2. None

3. No.

4. No.

5. No.

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