Author's response to reviews

Title: The Rheumatoid Arthritis Treat-To-Target Trial: A Cluster Randomized Trial Within the Corrona Rheumatology Network

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Author's response to reviews: see over
Dear BMC Editorial Office,

On behalf of my co-authors, I would like to thank the reviewers for taking the time to provide thorough feedback on our submission. We have made substantial revisions to the manuscript in response to the reviewers’ comments and we are now submitting a revised version, taking these comments/remarks into account. Below, we have provided a point-by-point response to address each query and provide detailed descriptions of how the manuscript has been modified. Please note the page and line numbers listed below correspond to the locations of each revision in the tracked changes version of the manuscript, which we have attached as a supplementary file for the editors. Additionally, please note that the Consortium of Research Rheumatologists of North America (CORRONA, Inc) is now Corrona, LLC; the title and text have been updated accordingly to reflect this change.

We feel that we have adequately answered all of the concerns and we hope that you will consider now this revised manuscript as suitable for publication.

Thank you again, and we look forward to hearing from you.

Kind Regards,
Leslie Harrold, MD, MPH

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Reviewer 1: Raimon Sanmarti, MD, PhD

Reviewer’s Report: The design of the study is interesting and in general the methodology seems to me correct. However I have some concerns:

1.) Background: the authors comment the TICORA trial as the first trial investigating this interesting topic, however there are other studies confirming the results of the TICORA trial that are not mentioned (Schipper LG et al Ann Rheum Dis 2012 and others) whereas the Best study is not a study focusing on this objective. We thank the reviewer for highlighting these additional studies. We agree with the reviewer and have revised the text in the Background on Page 4, Lines 19-23 to include the CAMERA trial and results from the Dutch Rheumatoid Arthritis Monitoring registry as studies that supported the use of tight disease control treatment strategies. In addition, we have deleted the sentence about the BeSt study as suggested by the reviewer, as that study was designed to compare different treatments and not the impact of the T2T approach.

2.) Method/design: Why the authors decided to use CDAI rather than SDAI or DAS28? In my opinion the main outcome (CDAI < 10 at month 12) is quite punctual; perhaps the maintenance or a CDAI < 10 in several visits (from 9 to 12 months or in two consecutive visits) may be more informative. Patient recruitment: there is no mention of the disease duration or previous use of DMARDs or biologics as a selection criteria or an adjusted
analysis for these and other variables. This may be problematic in order to assure that the baseline characteristics of both populations are similar.

We acknowledge that there are several validated measures that can be used to assess disease activity, including the CDAI, SDAI and DAS28; however, we felt the CDAI was a more appropriate measure to use because it is the only disease activity index without an acute-phase reactant. In routine clinical practice settings in the United States, as opposed to research or clinical trial settings, physicians do not measure acute-phase reactants as part of standard care, so the SDAI and DAS28 cannot be calculated at every visit. The CDAI is endorsed by the American College of Rheumatology as a routine measure to follow disease activity (Singh JA, et al. Arthritis Care Res [Hoboken]. 2012;64:625-39). We have revised Page 5, Lines 16-18 in response.

While we did use the CDAI, our study was designed to mirror a clinical trial; therefore, we chose our primary endpoint to be CDAI < 10 at 12 months, which has a defined target at a particular time point. Subsequent analyses will examine sustained CDAI remission/low disease activity at 9 to 12 months.

In order to stay true to the treat-to-target design in a real-world clinical setting, where patients are quite varied, patients in this study were recruited regardless of their duration of disease or prior number of biologics received. This enrollment follows the well-established designs of cluster-randomized trials. We have revised the text on Page 9, Lines 19-20 to elaborate on patient recruitment. We plan to adjust for any baseline differences between the groups when performing our final analyses.

3.) Discussion: As the authors comment there is one important limitation of the study such as the investigator discretion regarding treatment decision. I agree with this but it is difficult to improve the design of the study to solve this problem. However there is other limitation such as the site randomization. I don’t know if there are previous studies analysing the differences in the usual care inside the centres participating in the CORRONA registry. This information would be interesting.

We thank the reviewer for this comment and can appreciate his concern. In the US, it is not feasible to mandate that physicians give a certain intervention or treat a certain way. Physicians would not participate in the study if they were forced to give care they were not comfortable with; therefore, by design, we had to give healthcare providers the option not to escalate treatment if they thought changes in CDAI were being driven by noninflammatory conditions or if additional factors necessitated deviation from the study protocol (e.g., physician’s intuition based on knowledge of the patient’s history, etc). This problem is inherent in any kind of interventional study.

In our study, we are intervening at the level of the physician/site, rather than the patient. The study design should avoid contamination within each site, where one provider’s attitudes or beliefs may influence others at the same site. In addition, it would be difficult, if not impossible, for a doctor to treat patients differently based on treatment assignment—i.e., treating some patients to target while giving “usual care” to others. For these reasons, we chose to use a well-established cluster-randomized trial design described by Donner and Klar (see reference 13). As you correctly note, all of the patients at a given site will be randomly allocated to receive the same treatment, either usual care or the treat-to-target strategy. Prior work has indicated that some treatment decisions are site/physician related (Harrold LR, et al. Arthritis Rheum. 2012;64:630-8). Much like randomization by patient,
randomization by site should provide balance between the arms in treatment strategies by site. Analysis will also account (within arm) for variation of treatment by carrying out clustered analyses that adjust for the correlation within site. Please see edits on Page 6, Lines 20-22 and Page 12, Lines 6-7, 10-13.

Reviewer 2: Burkhard Leeb, MD, PhD

Reviewer’s Report: Major compulsory revision.

1.) How will the authors rule out the problem of tight therapy control and patient visits e.g. every three months?

We thank the reviewer for this comment and we agree that this should be addressed in our analysis. For this reason we will assess the visit frequency and treatment acceleration as this may be a mediator of disease control. We have clarified in the manuscript on Page 12, Lines 6-7 that this is in the list of analyses that need to be performed.

2.) How will the authors rule out problems with patients’ attitudes, expectations and wishes if they do not randomize on a patient basis but on a centre basis? Patients may be significantly different in different locations depending on socioeconomic or psychological status.

While there may be differences across sites in terms of patients’ expectations or attitudes, it was more important to randomize by centers to avoid contamination, since we are intervening on a physician level and not a patient level (see above response). Patients as well as physician treatment patterns will differ by site, but the randomization by site should provide balance in site differences much like patient randomization. Upon completion of the study, the analyses will be adjusted by site, which will account for any differences between sites (e.g., socioeconomic factors or patient-reported comorbidities, as suggested). If large differences do exist in patient characteristics by arm even after site randomization, adjustment for those characteristics can be carried out. We have added text to clarify this point on Page 12, Lines 10-13.

3.) How will the authors rule out problems evolving from applying the CDAI as the primary outcome. The CDAI does not count the feet joints, so one may have the situation that the patients is counted in remission, but is not even able to walk out the office because of "not countable" foot involvement. And, this refers to about one third of the patients.

We appreciate the reviewer’s concern and note that there are problems associated with every measure of disease activity available; however, we believe the CDAI was the most appropriate measure for our study since it is validated and utilized extensively in the US as well as listed by the American College of Rheumatology treatment recommendations as a tool for monitoring disease activity (Singh JA, et al. Arthritis Care Res [Hoboken]. 2012;64:625-39).