Author’s response to reviews

Title: The prevalence and types of discordance between physician perception and objective data from standardized measures of RA disease activity in real-world clinical practice in the US

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Author’s response to reviews:

Editor comments

COMMENT: In addition to reviewer comments, I have some difficulty with the term "overstatement" as it refers to discordance between the rheumatologist's assessment (or gestalt) of remission in contrast to the value of the chosen composite disease activity measure definition of remission. In the literature around patient-clinician discordance of disease activity measure, the term "positive" discordance has been adopted whereby the patient rates themselves as having higher disease activity than the provider. One could consider a similar term of "positive" discordance around the assessment of remission whereby the rheumatologist rates a patient with higher disease activity than the composite measure of remission. Something to consider as "overstated" is a somewhat awkward term. Other questions/comments for clarification:

RESPONSE: The term ‘overstatement’ has been replaced with the terms ‘positive discordance’ to describe cases where rheumatologists rate a patient with higher disease activity than the objective measure and ‘negative discordance’ where the objective measure rates a patient with higher disease activity than the rheumatologists. This change has been made throughout.
COMMENT: 1) methods - were the healthcare professionals given an incentive to complete the DSP survey? What were "DSP inclusion criteria" as referred to on page 5, line 104?

RESPONSE: A statement regarding physician compensation has been added to the methods section. The inclusion criteria described in the Methods sections has been clarified.

COMMENT: 2) discussion - I agree with the reviewer 2 that the discussion can be made much more concise

RESPONSE: The discussion and much of the text in general has been rewritten as advised to be more concise.

COMMENT: 3) conclusion - would specify in the first sentence that this applies to the DSP sample and not globally across the US (see recent report of RISE registry, Yazdany, J., et al., Rheumatology Informatics System for Effectiveness: A National Informatics-Enabled Registry for Quality Improvement. Arthritis Care Res (Hoboken), 2016. 68(12): p. 1866-1873.) In RISE, 55.2% of clinicians recorded disease activity over their recording period.

RESPONSE: The first sentence of the conclusion in the abstract and main body have been rephrased to make them more DSP-centric.

Kaneko Yuko (Reviewer 1)

COMMENT: Many important index were missing, which is the major drawback. Although DAS28-three variables has been validated, it is known that there is some discrepancy between DAS28 (4) and DAS28 (3). The 298 patients who were included in the CDAI analysis had patient VAS so that the authors should be able to calculate DAS28 (4). The supplementary data by DAS28 (4) would corroborate the authors' conclusion.

RESPONSE: We accept DAS28(4) is the preferred measure over DAS28(3) due to its incorporation of the patient self-reported element, however, if we incorporate the patient VAS the patient sample for DAS28(4) drops to 249 compared with the 531 patients with DAS28(3). Forty-nine of the patients for whom we have the VAS do not have a reported ESR. The use of DAS28(3) over DAS28(4) is mentioned as a potential limitation in the Discussion.
COMMENT: The high proportion of biologic agents use should be discussed. The patients included might not represent overall rheumatoid arthritis population.

RESPONSE: We have reported potential data biases and identified the population as DSP-specific rather than representative of the US population as a whole.

COMMENT: Table 1 should include DAS28 (3)

RESPONSE: DAS28 (3) has been included.

COMMENT: How were the marginal bone erosion and the synovium inflammation assessed? By ultrasonography?

RESPONSE: Physicians responded to a direct question regarding these symptoms, they were not asked how the symptoms were assessed. A sentence has been added to Methods to explain this.

COMMENT: Figure 1A would be better expressed by a pie chart.

RESPONSE: Figure 1a has been replaced with a pie chart as suggested.

COMMENT: Figure 2 is a bit confusing. It seems that DAS28 of a part of patients in the concordant - both not remission group is less than 2.6, that of several patients in the concordant - both remission group is more than 2.6, and so on. Should those be not clearly separated?

RESPONSE: This is a function of the smoothing in the kernel density function which results in the plot crossing the line shown when in fact there are no patients in the incorrect groups. A footnote has been added clarifying this for the reader.

Ricardo J. O. Ferreira, PhD student (Reviewer 2)

1) Title
COMMENT: Despite being clear and concise, it does not refer to the analyses of factors associated to the overstatement of remission by physicians. I would suggest a title such as: "Factors associated with rheumatologist overstatement of remission compared to DAS28 definition in rheumatoid arthritis: a clinical practice, cross-sectional study". To study the factors requires to assess the differences first and this might be more informative.

RESPONSE: The title has been changed to “The prevalence and types of discordance between physician perception and objective data from standardized measures of RA disease activity in real-world clinical practice in the US”.

2) Abstract

COMMENT: The sample (101 rheumatologists and 843 patients) is presented in methods. Please consider to move this info to results.

RESPONSE: Population size has been moved from Methods to Results of the abstract and main text.

COMMENT: 2.2. Please clarify why do you considered 101 rheumatologists and 843 patients if in the results section (page 11, line 240) it is stated: "A total of 531 RA patient records from 78 rheumatologists had all the information needed to calculate the DAS28(3)-ESR score for the analysis on concordance between remission according to rheumatologists' evaluation and according to a standardized measure"

RESPONSE: Overall, 101 rheumatologists and 843 patients were available for the initial descriptive analysis (figure 1a–c), however only 531 patients (provided by 78 rheumatologists) met the inclusion criteria for the discordance analysis. An attrition figure (Fig. 2) has been added to demonstrate this. A description of rheumatologist attrition has been included in the manuscript body (attrition due to having no patients meeting the inclusion criteria).

COMMENT: 2.3. may the conclusion be more informative regarding the results?

RESPONSE: Greater detail with regards to the results has been provided in the conclusion. Please see revised version.

3) Background
COMMENT: Well written and supporting the study. Ref 1 is not the most updated version of T2T recommendations, which is the reference 11. Was this done to be like this?

RESPONSE: While we realize that reference 1 is not the most recent version of these guidelines they were the guidelines in place at the time of data collection and so are referenced here. We have highlighted this however in the manuscript.

4) Methods

COMMENT: 4.1. the n is presented in methods and results. I would prefer to see it only in results.

RESPONSE: The n-number has been deleted from the methods.

COMMENT: 4.2. Page 6 of the manuscript presents some examples of repetition of information that can be improved. For instance: line 115 "All data were de-identified in adherence with...", line 120 "Prior to receipt for analysis, all data were fully deidentified", and even line 121-122 "no personal identifiable information was collected". Also, the term "de-identified" is not written in the same way. Another clear example of over-repetition of information is presented in line 118-119: "The analyses carried out in this study were conducted on an existing database. All analyses were conducted on the existing database;"

RESPONSE: This section has been edited to reduce repetition.

COMMENT: 4.3 It is not clear how rheumatologists classified remission: was a yes or no question? (page 7, line 149-150) Or did they answered in a VAS (0-10cm) scale (EGA), which allows also to assess CDAI? (page 8, line 172)

RESPONSE: Physicians responded to a direct question “Is this patient currently in remission?” yes / no. This is the question that was used in the primary analysis to compare against DAS28(3) remission. Physicians also answered a VAS (0–10 cm) scale – this was used in the calculation of CDAI. Clarification has been added to Methods.

COMMENT: 4.4. The cut-off of 2.6 was used to determine remission based on the DAS28ESR(3v) definition. However, more strict cut-offs were recently proposed by Fleishman et al for DAS28 using CRP and ESR. Why did the authors not used this new cut-off for primary
or for sensitivity analyses? Furthermore, in the discussion (Page 15, line 325-328) the "stringency" of DAS28 is also compared, as a limitation, with other definitions: "It is also less stringent than CDAI, SDAI, or Boolean remission." This should be stated as a limitation or included in the analyses. Fleischmann R. et al. How much does Disease Activity Score in 28 joints ESR and CRP calculations underestimate disease activity compared with the Simplified Disease Activity Index? Ann Rheum Dis. 2015 Jun;74(6):1132-7. doi: 10.1136/annrheumdis-2013-204920. Epub 2014 Aug 20. Fleischmann RM et al. DAS28-CRP and DAS28-ESR cut-offs for high disease activity in rheumatoid arthritis are not interchangeable. RMD open 2017;3:e000382.

RESPONSE: Since the rheumatologists completed the questionnaires based on the cut-off points proposed at the time of the data collections, we are concerned the recalibration based on the new cut-off would be incongruous due to the fact that physicians were not applying those updated criteria when providing their evaluations. A sentence has been added to the limitations section of Discussion.

COMMENT: 4.5. The description of "CDAI (sensitivity analysis)" is another example of overwriting, with too many details and words to describe something simple. Examples: a. "CDAI was evaluated as an alternative measure of disease activity to DAS28(3)-ESR [28]. In the current study, CDAI was included in the sensitivity analysis as it is an alternative disease activity assessment that does not require measurement of an acute phase reactant." - The first sentence can be deleted. b. "and its definition of "remission" is more stringent than that of DAS28(3)-ESR". This was also referred in background and is in the discussion. c. "CDAI was calculated for patients with RA in the sample", in is not need, at all, to say that was in this RA sample... d. defined as .... defined as .... (lines 174-175). I think that the 9 lines of this section can be easily reduced to less than half.

RESPONSE: a. The first sentence has been removed and the reference moved to the next sentence. b. This text has been removed as it is in the Discussion. c. Text “in the sample” has been removed. d. This text has been revised.

COMMENT: 4.6. Might the section "remission concordance" be reduced as well?

RESPONSE: The authors feel that this is a really important part of the study’s methodology and reducing this section may reduce clarity for the readers.
COMMENT: 4.7. The McNemar's paired chi-squared test referred at page 13 line 238 is not mentioned in methods. The comparison being made and reported in this section was also not explained in methods. I do not see the need for this comparison.

RESPONSE: This test has been removed from Results.

COMMENT: 4.8. "Variables with a P value < 0.05 were considered to have a significant association with either rheumatologist overstatement of remission or concordance" (line 216) - is this information really needed?

RESPONSE: This sentence has been removed and replaced with the following: “A 95% significance level was used throughout.”

COMMENT: 4.9. "Analysis was performed both for the primary concordance variable (using DAS28(3)-ESR) and the sensitivity concordance variable (using CDAI)." (line 218) - Is this information really needed? A separate section exists only for the "sensitivity analysis".

RESPONSE: This sentence has been removed.

5) Results

COMMENT: 5.1. The table 1 was initially very difficult to read because it has too many information and also because it should have 3 main sections: overall, concordant and discordant. The overall seems to be together with the concordant due to the top horizontal line. For different reasons I think that this table can be split in two or arranged in a different way. For instance, the statistical comparison is being made only between the 3rd and 4th column but this turns clear only when reading all results section, even being stated the note "a" in the bottom. It is not clear why some much information (variables and columns/sub-groups) are presented. I would prefer a table with the overall characteristics and a table with the 3rd and 4th columns.

RESPONSE: Edits have been made to Table 1.

COMMENT: 5.2 Also in the table 1, what do the authors consider by "TJC/SJC/ESR most recent"? Was it possible to include clinical data - with upmost relevance for the study aims - from previous consultations? This was not reported in the methods.
RESPONSE: These data have been removed from Table 1, however, edits have been made to Methods to clarify that the test results and disease activity scores had been calculated either at the current or an earlier visit.

COMMENT: 5.3. Also in the table 1, how were the number of flares in the last 12 months assessed? is this information relevant for the study?

RESPONSE: Flares data have been removed from Table 1 and the manuscript.

COMMENT: 5.4. Still in Table 1, The inclusion of "marginal bone erosion, Synovium inflammation, osteoporosis, and non RA-related bone/joint inflammation" variables are not clear. The first time I saw them was in the table and I did not know how they were assessed and their direct relevance to the study. Only latter (page 14, line 296) I was informed about that: "They were more likely to have experienced a higher level of pain and had more joint inflammation and damage (e.g., destruction of cartilage, thinning of bone, and/or synovium inflammation) (P < 0.005)."

RESPONSE: Information has been added to Methods to explain how marginal bone erosion, synovium inflammation, osteoporosis, and non-RA-related bone/joint inflammation were assessed.

COMMENT: 5.5. Is Fig 1 a really needed? It presents only 2 complementary percentages. It is also not the proper graphic representation. Reference to values in text only seems enough. Also, remember the (possible) discrepancy in the n.

RESPONSE: Figure 1a has been changed to a pie chart as suggested by Reviewer 1.

COMMENT: 5.6. In the end of the first section of results "Rheumatologist self-reported behaviors in use of standardized measures" the authors present a statistical test comparing hospital and office-based practice. This should be presented in the proper section.

RESPONSE: This text has been removed, as this is already covered in the section “Patient and rheumatologist characteristics associated with Rheumatologist negative discordance of RA disease remission vs Concordance – in remission cohorts”
COMMENT: 5.7. The sentence in line 240-242 is one more example of not needed words: "A total of 531 RA patient records from 78 rheumatologists had all the information needed to calculate the DAS28(3)-ESR score for the analysis on concordance between remission according to rheumatologists' evaluation and according to a standardized measure." Info after DAS28(3)-ESR score can be deleted.

RESPONSE: Text has been deleted.

COMMENT: 5.8. Info in line 246-247 is also not needed "from the analysis of DAS28(3)-ESR concordance because of missing at least one component required to calculate DAS28(3)-ESR scores."

RESPONSE: Text has been deleted.

COMMENT: 5.9. Please consider to present the comparison of the characteristics of patients included from the exclude in supplementary files and refer only if they were similar or not. Or be more concise in the description.

RESPONSE: A supplementary table has been added for the patient characteristics of included versus excluded patients, which has been highlighted in the discussion. However, when a comparison was made between characteristics of patients who had been included in the study vs those who had been excluded due to missing data, only severity at diagnosis was shown to differ significantly between the groups, with included patients being more severe at diagnosis (Suppl. Table 1).

COMMENT: 5.10. The second paragraph of page 12 is a complete description of Table 2. It should be more concise. The info in the table should not be all reported in the text.

RESPONSE: This paragraph has been edited to include just the key information from Table 2.

COMMENT: 5.11. the 3rd par of page 12 (lines 261 - 2669 includes discussion in my perspective. Should be reduced. It report to fig 2. I'm not sure if all the 4 sub-groups of patients should be reported in the graph or only the discordant. But it can be like it is. The description in the text could be shorter. It is logical that if both assessment are concordant in remission, the patients will be below 2.6 cut-off etc.
RESPONSE: This section has been reduced, however, given Reviewer 1’s comments on this figure we feel that some clarification is still required.

COMMENT: 5.12 line 267-268 - % can be presented and "as an alternative standardized measure to DAS28(3)-ESR." can be deleted.
RESPONSE: Text has been deleted.

COMMENT: 5.13 - the n in lines 268-270 may not be needed
RESPONSE: These have been removed as suggested.

COMMENT: 5.14. Lines 270-279 - over-description. Should be more concise
RESPONSE: The paragraph has been edited to be more concise.

COMMENT: 5.15 - lines 280 - "The percentage of rheumatologists overstating remission when using DAS28(3)-ESR (25.8%) was lower than that obtained when using CDAI (35.6%)." seems discussion to me.
RESPONSE: The text has been edited.

COMMENT: 5.16 - lines 281-284. As referred above, the McNemar’s test and the comparison between rheumatologist overstatement compared with DAS28 and with CDAI was not explained in methods. the percentage in all patients was 25.8 (DAs28) and 35.6% (CDAI) and only for patients with data for both was 24.1 and 31.7%, respectively. So what seem relevant is that the % do not change to much. What authors compare is the difference form DAS to CDAI and this seems redundant as it is known - and stated by the authors - that CDAI is more strict.
RESPONSE: This analysis has been removed from the paper.

COMMENT: 5.17. paragraph from line 288-292 is not easy to read/understand and seems that come info are for methods
RESPONSE: This paragraph has been edited to improve readability.
COMMENT: 5.18 - Please clarify the reader in Fig 1c that more than 1 rheumatologist could have used more than 1 and thus more than 100% is possible when summing the figures.

RESPONSE: Text has been added to Results and Fig. 1 to clarify this.

6) Discussion

COMMENT: 6.1. line 313-314 - Is this first sentence needed? Why not begin with the highlights of the study?

RESPONSE: This sentence has been deleted.

COMMENT: 6.2. - line 321-322 "Although the literature suggests an increase in rheumatologists' use of standardized RA assessment measures, such as HAQ or DAS28" please include references.

RESPONSE: This sentence has been removed as part of the comment to reduce the length of the Discussion.

COMMENT: 6.3. the sequence of arguments/topics in the discussion does not seem logical. The 2nd par. of discussion is about limitations, but limitation are addressed in the end (page 18). So lines 325-336 could be deleted or moved to other place (more concisely). the decision to select DAS28(3)-ESR is explained in the methods, does not need to be repeated in line 328-329. Also authors refer that using DAS283v may be a limitation because it does not include PGA, but PGA accounts only 0.014 for the score... so this was not a limitation. They used the CDAI with takes into account much more the PGA...Still about this paragraph, the topic being introduced in lines 332-334 (PGA being affected by comorbidities etc) does not relate with the discussion being done here, bit with the factors that might influence discrepancy.

RESPONSE: This sentence has been edited and moved to the limitations section of the discussion.

COMMENT: 6.4. paragraph 337 to 341 could be better summarized.
RESPONSE: This paragraph has been edited and length reduced to improve readability.

COMMENT: 6.5. The size limitation of understated remission cohort could be discussed in the limitations section.

RESPONSE: A sentence has been added to Discussion.

COMMENT: 6.6. The following sentence is confusing to me (lines 347-349): "Regardless, the factors associated with rheumatologists’ overstatement of remission were expected to inform future identification of patients or rheumatologists where overstatement of remission was more likely, and thus ensure that patients are not undertreated."

RESPONSE: This sentence has been reworded to improve clarity.

COMMENT: 6.7. lines 350 to 357 - please see Fleishmann cut-off mentioned above. Also, after reading this paragraph, the question is: "So what?".

RESPONSE: This paragraph has been removed as this is discussed elsewhere in the discussion.

COMMENT: 6.8. It is not clear what is being discussed with lines 358 to 361. It misses a clear connection with the results of the present study: "A meta-analysis of six studies performed between 1995 and 2009 showed that close monitoring of RA based on disease activity outcomes, combined with protocol-specific treatment adjustments, is associated with better outcomes than usual care [38]. The frequent assessment of RA disease activity with a standardized measure is an integral component of this approach."

RESPONSE: This sentence has been revised.

COMMENT: 6.9 - The info in lines 362 to 367 is also not new and stated in the background. The link with the present results is also lacking

RESPONSE: We agree with the reviewer and have removed the sentence from the discussion and left it in the background section only as it adds useful context.
COMMENT: 6.10. line 405-406: "Thus the generalizability of our results to all rheumatologist practice may be influenced by willingness to participate." I would suppose that rheumatologists more willing to participate use more the disease activity indexes, thus the argument would be other way around. Could you please discuss this?

RESPONSE: A sentence has been added to the Discussion to address this point.

COMMENT: 6.11 lines 409-410 - "...only severity at diagnosis was shown to differ significantly between the groups, with included patients being more severe at diagnosis" - This information seems new to me. Was it presented in the results?

RESPONSE: Linked data has been provided in a supplementary file.

COMMENT: In summary, the two major issues of this paper that might need a reformulation of analyses is: A) the n being considered for analysis: 101 or 78 rheumatologists B) the cut-offs of the DAS28-ESR(3v)

RESPONSE: Thank you for your comments. These have been addressed as outlined above.