Author’s response to reviews

Title: A SYSTEMATIC REVIEW OF GUIDELINES FOR MANAGING RHEUMATOID ARTHRITIS

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Author’s response to reviews:

REVIEWER TWO (EDITOR)

Comment 1

This manuscript describes a literature review of guidelines for management of RA. It is clearly written and easy to understand. Overall it is of some interest and draws some interesting conclusions but there are methodological details lacking which detract from the manuscript. The results are also not described in the detail and precision that would usually be expected in a systematic review. Overall the most disappointing aspect is a clear research question(s) that the results specifically answer. As it stands it is not clear what we are meant to take away from this work.

Response 1

We are grateful for the generally supportive comments. We accept that it is always preferable to have clear research questions and that, in retrospect our aims were potentially too broad. We have modified the introduction to include the specific aims of assessing recommendation about disease assessments and management targets, which were the reason we undertook the review. However, the general issues about guidelines needs to be included within the rationale for undertaking the work.

Modification To Manuscript - Introduction

Our overall aims were to evaluate the range and nature of guidelines currently available, to assess the variations in their recommendations about RA management, and highlight any divergence in their perspectives. The specific questions we considered were: (a) to examine their recommendations about composite assessments of disease activity; (b) to identify their management targets with drug therapy; (c) to define the categories of drug treatments considered. As a consequence of these assessments we sought to provide insights into the value and relevance of different guidelines.

Comment 2

The terms systematic review is included in the title and methods. For best practice systematic review an appropriate methodological framework should have been adopted and presented clearly throughout, in this case probably scoping or umbrella review. It would have been preferable to see a protocol registered a priori (or at least a protocol available on request) and reference to appropriate reporting
methodology (which does come late – but not clear enough up front). Also although questions are posed in the introduction, specific research questions would be preferable i.e. what the questions this work was specifically answering are.

Response 2
We accept the need for a clear and appropriate methodological framework and have modified the methods section to take this into account. Reviews of guidelines do not fit into any of the current general classifications of systematic reviews. They are not scoping or umbrella reviews. They are not mentioned on the PRISMA website. They appear to have a distinct but somewhat different place. There have been several other systematic reviews of guidelines published in the last year or two; in retrospect we appreciate the potential benefits from register protocols for systematic reviews of guidelines. However, it was unclear when we were planning this work some years ago, that registration was relevant for this type of review. We have added a comment on these issues in the discussion.

Revision 2 - Discussion
Fourthly we have focussed on issues in the guidelines we consider to be of most importance. Other experts may have considered different aspects of the guidelines in more detail and overlooked some of the matters we have dealt with. Finally, systematic reviews of guidelines are not one of the current PRISMA extensions [http://www.prisma-statement.org/], though we anticipate they will be included in subsequent updates. Consequently we did not register our protocol; however, several other recent systematic reviews have evaluated different guidelines using similar approaches to our own, such as the report by Jollife et al on stroke rehabilitation guidelines [Jolliffe L, Lannin NA, Cadilhac DA, Hoffmann T. Systematic review of clinical practice guidelines to identify recommendations for rehabilitation after stroke and other acquired brain injuries. BMJ Open 2018; 8: e018791]. Systematic reviews of guidelines differ from both scoping [Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. BMC Med Res Methodol 2018; 18: 143] and umbrella reviews [Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P.Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. Int J Evid Based Healthcare 2015; 13: 132-40].

Comment 3 - Methods
3a. Were search terms informed by assistance of research librarian, and suitable for both databases. Why only two databases? Which specific international societies were viewed for guidelines – in general sufficient detail should be supplied so it would be reasonably expected that another author could undertaken the same screech and come to same results – I do not think sufficient detail is supplied.

3b. Also what a - Eligibility would be better expressed as inclusion and exclusion criteria

Screening of abstract title and full text is not described in sufficient detail. – reduplicating, which software used etc.

3c. How was template for data extraction developed? How do these categories related to purpose of the study?

3d. Assessment of quality – was this extracted into the data template – not clear.
3e. The method of analysis by narrative synthesis seems reasonable but I would have liked this to be related back to specific research questions? (Which would seem to be related to the 3 “predefined areas” but this is not made clear why these were of most interest)

3f. Finally came to mention of PRISMA guidelines – this should come earlier. I would also recommend REPORTING according to PRISMA guidelines – and noting where deviated from expectations (e.g. protocol registration etc.).

Response 3

3a We have provided more information about the search methods and have revised the results section accordingly. The use of two databases was based on considerable discussion about what was appropriate. A similar approach has been taken in other guidelines reviews (for example Jolliffe L, Lannin NA, Cadilhac DA, Hoffmann T. Systematic review of clinical practice guidelines to identify recommendations for rehabilitation after stroke and other acquired brain injuries. BMJ Open 2018; 8: e018791) and we therefore consider it appropriate. Clinical guidelines provide synopses of expert opinion and are somewhat different from clinical trials and other interventional studies, and therefore search strategies are not directly comparable between them.

3b. We have revised the section on eligibility into inclusion and exclusion criteria in the updated methods section.

3c. The template relates to the purpose of the study, which is outlined more clearly in the revised introduction. We assessed the nature of the guidelines (summarised in Table 1) and the different questions (summarised in the text and in Tables 2-4).

3d. We were interested in the quality assessments the guideline developers had adopted rather than in our assessment of the quality of the guidelines. We have clarified this point in the methods section.

3e. We have revised the methods section to show how we evaluated the research questions, which we have outlined more clearly in the introduction.

3f. We have moved the section on PRISMA guidelines higher up the methods section and modified it to note deviations from the guidance.

Revision 3a Methods

We searched Medline and Embase databases using the terms ‘clinical practice guidelines’ and ‘rheumatoid arthritis’. We also searched national bodies including the Scottish Intercollegiate Guidelines Network (SIGN) and the National Institute For Health and Care Excellence and national and international specialist societies including the British Society for Rheumatology, the American College of Rheumatology and the European League Against Rheumatism. Finally we searched lists of references from identified guidelines.

Revision 3b – Methods

Inclusion And Exclusion Criteria

Our inclusion criteria comprised: (a) publications that identified themselves as guidelines; (b) guidelines that provided recommendations on the general management of RA; (c) guidelines that included a range of different drug treatments; (d) guidelines published from January 2000 to January 2017; (e) guidelines published in English. Our exclusion criteria comprised: (a) guidelines and
appraisals that dealt with specific areas of management, such as safety monitoring of drugs; (b) guidelines or appraisals of single drugs or technologies. When there were several versions of guidelines from the same organisation, only the latest guideline was included.

Revision 3c – Methods
Screening And Data extraction
Two researchers (AM, DLS) independently assessed studies for eligibility and extracted data onto a predefined template. The data included: (a) year of publication; (b) format (who was involved); (c) quality method followed; (d) systematic review of evidence; (e) patient groups considered; (f) area of management included; (g) composite activity assessments; (h) prognostic assessments; (i) treatment targets; (j) and range of treatments considered. When there were differences between assessors, they reviewed the reports together and came to a joint conclusion.

Revision 3d – Methods
Assessment Of Quality Methods
We sought evidence that individual guidelines had followed nationally or internationally accepted quality methods in their development; we did not assess their quality as part of this report.

Revision 3d - Discussion
The limitations of clinical guidelines have been described in detail [49-52]. We do not intend to consider the relative strengths and weakness of guidelines in general. However, one particular challenge with the current published guidelines is that only 8/22 specifically followed a nationally or internationally agreed approach to ensure they were of high quality. Future guidelines ought to explicitly adopt one of these quality methods.

Revision 3e Methods
Methods Of Analysis
The guidelines were very heterogeneous in terms of the areas covered, the approaches taken in their development and the presentation of their recommendations. Consequently we undertook narrative assessments of their recommendations. Initially we assessed the areas covered by the guidelines, whether they included statements of principles and needs, their intended audiences and their overall structure, including whether they dealt with specific questions or recommendations. We then focussed on three predefined areas related to our specific aims. These comprised; (a) recommendations about composite assessments of disease activity and other assessments; (b) management targets with drug therapy including the impact of prognostic assessments; (c) and the categories of drug treatments considered. We considered this approach would enable us to assess the variations in their recommendations about RA management and identify divergences in their perspectives. We did not set out to produce any single optimal set of recommendations for RA management from our analyses of these guidelines. We considered management from the perspective of conventional disease modifying anti-rheumatic drugs (DMARDs) like methotrexate, biologic DMARDs like tumour necrosis factor inhibitors, Janus Kinase (JAK) inhibitors and glucocorticoids (steroids).
Revision 3f - Methods

Methodological Approaches

We followed the general PRISMA recommendations [9] and other approaches for systematic reviews [10], although none of these specifically deal with reviews of guidelines. We also followed methods recommended for reviews of systematic reviews [11] and approaches taken in previous systematic reviews of guidelines [12,13]. As PRISMA does not specifically include systematic reviews of guidelines we did not pre-register our protocol; this was omitted in other systematic reviews of guidelines [12].

Comment 4 - Results

4a Since used PRISMA guidelines, would expect reporting with a PRISMA flow diagram including how all manuscripts identified including abstract/title and full text screening etc. Where guidelines are mentioned in results – reference required

4b Frequently results state “many” or “majority” or “most” or “in the main” or “some” – needs to state actual number and proportion on every instance – what does “many” mean? Anytime a number is mentioned, the denominator should also be mentioned.

4c Boolian should be Boolean

4d “Steroids” should probably be “glucocorticoids”

4e Might wish to consider terms conventional DMARDS (cDMARDs) and biologic DMARDS (bDMARDs) as “biologics” seems a bit loose – could mean biologics for any condition!

4f Make sure all abbreviations are explained on first use in the text – even if common and even though list provided.

Response 4

4a. We have revised the first part of the results to conform with PRISMA guidance in describing the guidelines assessed and have referenced individual guidelines throughout the results section when mentioned.

4b. We have clarified all general terms such as many or most with exact numbers in parenthesis.

4c. We have changed Boolian should be Boolean throughout the text

4d. The term “Steroids” remains complex. Clinicians generally use steroids in routine practice. One
reviewer suggested corticosteroids and the other glucocorticoids. We have opted to say glucocorticoids
(steroids) in the revised text.

4e. The description of conventional DMARDs and biologics is complex. Some experts use the
acronyms cDMARDs and bDMARDs for these drugs, though this is not reflected in routine practice.
To avoid confusion we have termed them conventional DMARDs and biologic DMARDs in the revised
manuscript.

4f. Abbreviations have been defined fully when first used throughout the revised text.

Revision 4b - Results
Features Of Guidelines
These are summarised in Table 1. Groups of expert rheumatologists were reported as drawing up 21/22
guidelines; the only exception was the British Columbia guidelines, which did not specify who was
involved in their construction [18]. There were variable levels of patient involvement; 12/22 guidelines
specified there was patient involvement [14-16, 19-24, 31, 34]. There were also variable levels of
contributions from other experts, such as nurses, other allied health professionals, experts in systematic
reviews and a range of other areas; such experts were involved in 12/22 guidelines [14, 16, 19-23, 29-
32, 35].

Assessments
18/22 guidelines [14, 15, 17, 21-35] recommend regular assessments using a variety of clinical
assessments based on the Outcome Measures in Rheumatology (OMERACT) core dataset [39] using
composite indices. These all recommended using the disease activity score for 28 joints (DAS28) [40].
In addition 14 also recommended simple disease activity index (SDAI) and 13 recommended Clinical
Disease Activity Index (CDAI) [41]. Two guidelines recommended other assessments – the Patient
Activity Scale (PAS) [42] and Routine Assessment Of Patient Data Index (RAPID3) [43]. None of the
guidelines specifically recommended one composite index over another. The importance of assessing
disability was considered by most guidelines. The recommendations varied more widely on how to do
this and 10/22 guidelines recommended regularly assessing disability [15,17,21,25-27, 29, 31-33]; 9 of
these recommended using the Health Assessment Questionnaire (HAQ) [44]; the Canadian guidelines
did not specifically suggest assessing HAQ regularly [21].

Comment 5 - Discussion
5a. Given results are described so generally, discussion is a less credibility. No specific research
questions are answered.

5b. Limitations related to lack of application of PRISMA guidelines are not addressed. This manuscript
does not suggest how guidelines could be improved on in the future.
5c. Not clear what the TITRATE programme etc. given after the manuscript mean? Relevance

Response 5 - Discussion

5a. We have revised the initial part of the discussion to outline in more detail the relationship between the results and the main research questions.

5b. We have provided more comments on limitations in relation to the PRISMA statement, including details about the challenges of systematically reviewing guidelines (see response 2). Commenting on how to improve guidelines in future is challenging, but we have highlighted several relevant issues in the revised discussion.

5c. The funding statement indicates that NIHR supported our work through a programme grant with the acronym TITRATE. However, it is sensible to explain the relationship between the TITRATE programme and this systematic review in the revised discussion. In brief, TITRATE was a programme of research assessing the benefits of intensive management in patients with moderately active established RA. The research was commissioned because English guidelines concluded this was an area in which there was insufficient evidence to make recommendations. Interestingly most guidelines recommend intensive management of moderate disease even though the research evidence assessed by all of them is the broadly similar. We have commented on this issue in the revised discussion.

Revision 5a - Discussion

Our overview of 22 different RA management guidelines shows that several general principles transcend the majority of them. Firstly DMARDs should be started as soon as possible after the diagnosis has been established. Secondly disease activity should be regularly monitored using composite indices such as DAS28, which relates to our initial aim which was our initial specific question. Thirdly methotrexate is the best initial treatment, and that this can be usefully supplemented with short-term glucocorticoid (steroid) therapy. Fourthly biologic DMARDs should be given to patients with persistently active disease who have already received methotrexate and, in some instances another conventional DMARD. These principles relate to another of our specific questions. Fifthly remission or low disease activity is a suitable target and that treatment can be tapered in patients who have achieved sustained remissions. This principle relates to our final specific question. We consider that applying these general principles to RA management in all clinical settings is likely to achieve good overall clinical outcomes.

Revision 5b and 5c – Discussion

We anticipate that many of the existing guidelines will be updated in future years. We believe it important to do so to maintain their relevance to clinical practice. The frequency of review will reflect the timing of new clinical information. Looking back at the earliest guidelines from the 1990s [1-3] shows just how much clinical practice has changed over the years, indicating the need for guidance to be updated. We consider there are two ways in which the process of developing guidelines could be improved. Firstly, there guideline development should conform with one of the published quality standards; whilst there is no reason to prefer one standard over another, it seems worthwhile to adopt one of them. Secondly, guidelines should incorporate divergent views, when there is no universally
agreed answer. The controversy about the value of combinations of conventional DMARDs highlights this issue.

One important role of guidelines is to suggest potential future research questions. Our own research in the TITRATE research programme, of which this systematic review in a single component, was based on the absence of evidence on the benefits of intensive management in moderately active RA [Martin NH, Ibrahim F, Tom B, Galloway J, Wailoo A, Tosh J, Lempp H, Prothero L, Georgopoulou S, Sturt J, Scott DL; TITRATE Programme Investigators. Does intensive management improve remission rates in patients with intermediate rheumatoid arthritis? (the TITRATE trial): study protocol for a randomised controlled trial. Trials 2017; 18: 591). Interestingly, though the clinical research evidence has changed little on this aspect of treat to target, current guidelines often recommend treating moderately active RA intensively, showing the way in which guidelines interpret the evidence in very different ways.

REVIEWER 1 (JOHANNES J RASKER)

General Comment
This is an interesting article as it compares guidelines, showing that apparently there are many truths in the treatment guidelines for RA and these are determined in different ways, not only scientific. It is remarkable that the local cost and refunding appear to be reflected in the guidelines.

General Response
We are grateful for the positive perspective of the reviewer.

Comment 1
My first question is: for whom is this article aimed? And what is the value for a clinician reading the article? That should be made clear in introduction and discussion. Page 3 line 37: In your conclusions you mention "Five general principles transcend most guidelines…etc.

Response 1
Guidelines have several purposes. In particular they indicate where there is agreement on management strategies and where there is uncertainty, for which further research is needed. We consider that these issues are relevant for both clinicians and clinical researchers. We have highlighted these points in the revised introduction; the revisions are shown in Response 1 to Referee 2.

Comment 2
Would it not be time to conclude: the time has come to agree to one worldwide e.g. WHO-ILAR guideline now apparently most agree with these five principles? Why everyone does needs to invent the wheel? Page 4 line 16-23 you write: "The existence of multiple guidelines raises several questions. First, as they have all had access to the same research data, albeit at different time-points, are there recommendations similar or are there substantial differences between them? Second, why are there..."
different guidelines dealing with the same issue - how best to treat RA? Thirdly, what is the impact of these guidelines on clinical practice? Finally, what guidelines will be needed in future years?"

Comment 3

These four questions are very fundamental, but your article does not or hardly give an answer to these, especially not to points 2, 3 and 4. Please try to include the answers in the article. Page 4 line 30-34: 'As a consequence of these assessments we hope to provide some insights into the value and relevance of the different guidelines.'

Response 2 and 3

We are grateful for the referee indicating the need to relate the discussion more closely to the introductory comments. We have combined our response to these issues as they are inter-related. We revised the discussion to take account of the points raised by the reviewer.

Revision - Discussion

Our analysis shows several things. Firstly, the recommendations in the guidelines are broadly similar, though they differ in some points of detail; for example the use of combinations of conventional DMARDs. Such minor variations most likely reflect the challenges in balancing evidence of benefits against evidence of risks. Secondly, although guidelines deal with the same issue, they bring together different groups of experts and it is likely the production of guidelines enhances clinical practice. Consequently multiple guidelines appear to be needed. Thirdly, although it is difficult to judge accurately the impact of guidelines on clinical practice, there is evidence that RA outcome have improved significantly during the last 10-20 years and in part this is likely to reflect the impact of guidelines in improving the quality of clinical practice. Finally, as new treatments are introduced, particularly new JAK inhibitors, guidelines will need to be continually updated and, potentially produced by different groups.

Comment 4

I cannot find this in your results and discussion sections, please add. Are the British guidelines better than the ones from the other side of The Channel or the Atlantic? Page 9 line 6-16: "The importance of frequent assessment is stressed in most guidance. Some guidelines gave relatively specific suggestions. For example EULAR guidelines recommend assessing patients every one to three months, at least in the early stages of their RA. Many guidelines indicated patients should be assessed by rheumatologists at least annually. The English (Royal College of Physicians) guideline gives a very specific recommendation for annual review. The ACR guideline recommended annual assessments of function"

Response 4

The guidelines are generally written to reflect national and international policies about medical practice, which change over time. Clinical practice is arranged quite differently in Britain compared to North America and part of the variation is a consequence of these differences. British guidelines may be best for British practice, but aspects of them are unlikely to be relevant in North America. We have changed the discussion to take account of these issues. We have also included more detail about
specific recommendations in the results section.

Comment 5
Please add the choice of the documents in these guidelines. Was the HAQ used to measure function by the ACR? Page 9 line 23-27: “Two guidelines (British Columbia and BSR established disease) specifically recommend aiming to suppress joint inflammation, without specifically defining what this implies”

Comment 6
Do they perhaps mean the number of inflamed joints as measured for example in the DAS-28? It is a generally accepted aim as to suppress joint inflammation as the inflamed joints are the most incapacitating ones and probably also related to joint destruction Peg 9, line 54-55: "Sixteen guidelines include assessments of prognostic factors. They varied in the degree of detail they consider prognostic features”

Response 5 and 6
Disability assessments were considered as part of prognostic markers (see response to comment 7). They were not specifically mentioned in the ACR guidance, though HAQ is part of RAPID3 assessments, which are one disease activity measure within the ACR guidance.

We have revised the results section on the guidelines recommending suppression of inflammation to provide more information about what was specifically written in the British Columbia and BSR guidelines. We consider they most likely mean suppressing joint inflammation to control the disease and prevent joint damage.

Revision - Results
Two guidelines recommend aiming to suppress inflammation: the British Columbia guideline [18] concluded that the objective of treatment is to “suppress all inflammation”, implying this is joint inflammation; the British Society For Rheumatology established RA guideline [19] recommended “suppressing inflammation” indicating this was to limit disease progression.

Comment 7
Please specify these prognostic features. X-rays? MRI? Lab tests? Page 10 line 16-21: "When there are contraindications to methotrexate or if there are clinically significant adverse events to methotrexate most guidelines recommend considering alternative conventional disease modifying drugs” and also in page 10 line 34-50 and 56-58

Response 7
(a) We appreciate the need to give more details about prognostic markers. We have revised the results section accordingly and amended Table 2 to provide details on prognostic markers. We have moved this
section of the results so that it comes immediately after the section on assessments. (b) We have also
given more details about recommendations for treatment when methotrexate is contraindicated (see
response 8).

Revision – Results
Prognostic Assessments To Guide Treatment Decisions
Sixteen guidelines specifically included assessments of prognostic factors to help guide management
decisions about treatments [15-18, 21-28, 31-33, 35]. All these 16 guidelines recommended using anti-
citrullinated protein antibodies (ACPA); 14 guidelines recommended using rheumatoid factor (RF) [15-
17, 21-28, 31-33]; 15 guidelines recommended using x-ray erosion [15-16, 21-27, 31-33,35]; and 9
guidelines recommended using high disability or extra-articular disease [21, 25-28, 31-33, 35]. These
recommendations are summarised in Table 2. The guidelines including prognostic assessments all
recommended considering more intensive treatment with conventional DMARDs and biologic
DMARDs in those patients with poor prognostic features. They gave variable details of exactly how
this should be achieved.

Table 2. Recommended Composite Disease Activity Assessments And Prognostic Assessment To Guide
Treatment

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<td>2. APLAR [15]</td>
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Comment 8
Please specify which drugs and combinations are mentioned. For a clinician this is insufficient to be clear. Is it SASP? Hydroxychloroquine? Corticosteroids? Azathioprine? Page 11 line 28:

Response 8
We have listed the main combinations of conventional DMARDs in the revised text.
Revision 8 – Results

Initial Conventional DMARD Recommendations

Twenty one guidelines dealt with the management of early RA; all of these recommended starting conventional DMARDs as soon as possible after diagnosis. Methotrexate, which is often described as the “anchor” drug for RA, was recommended for most patients in 19/22 guidelines [14-17, 20-29, 31-35] (Table 4). In 13/22 guidelines there was consideration of the relative benefits and risks of oral and subcutaneous methotrexate [14, 17, 20-24, 27, 29, 31-33, 35]; however, the approach taken to this issue varied considerably and there was no obvious consensus across guidelines about when best to use parenteral methotrexate.

When there are contraindications to methotrexate or if there are clinically significant adverse events to methotrexate all 19 guidelines that suggested methotrexate as initial treatment recommend considering alternative conventional DMARDs. Sulfasalzine, leflunomide and hydroxychloroquine were all considered potentially appropriate; there was no consistent pattern in these recommendations. Other rarely used conventional DMARDs, such as azathioprine, though not excluded were not specifically recommended.

Three guidelines considered DMARDs generically without giving recommendations about which drugs to use; these were the British Guidelines for established [19] and early RA [20] and the EULAR treat to target guidance [34]. These three guidelines focussed on the overall strategy for managing RA rather than the best individual treatment options and so consequently did not provide recommendations about specific drugs.

Combinations Of Conventional DMARDs

Twenty guidelines considered the use of combinations of conventional DMARDs; 19 of these guidelines recommended using them in some patients [14-18, 20-21, 23-33, 35]. They were recommended when patients failed to respond fully to DMARD monotherapy and that biologics were not necessarily indicated. Specific Combinations of conventional DMARDS were recommended by 12/22 guidelines [14,15,17,21,23-28, 31, 33]: these combinations comprised methotrexate with sulfasalazine and hydroxychloroquine or methotrexate with leflunomide in 9 guidelines; 2 guidelines omitted leflunomide from combinations [23,33] and one guideline recommended chloroquine instead of hydroxychloroquine [31]. One guideline, from England, recommended initial combinations of conventional DMARDs [29], though it did not specify which drugs to use.

Comment 9

Steroids should be corticosteroids Page 11 line 36: "The EULAR treat to target guideline implied steroids should be used within the treatment strategy in some patients but did give any recommendations about specific therapies".

Response 9

As one reviewer suggested corticosteroids and the other glucocorticoids, we have opted to say
glucocorticoids (steroids) in the revised text.

Comment 10
You mean did not give any recommendations? Page 13 line 47: "consider the relative strengths and weakness of guidelines in general. In RA the overall the degree ……"

Response 10
We have revised this section of the discussion as indicated in Responses 5a-5c to Reviewer 2.

Comment 11
Typo - Two times the end adding your comments to the authors.

Response 11
We have tried to remove all typos from the revised paper.