Author’s response to reviews

Title: Factors that Influence Rheumatologists’ Anti-Tumor Necrosis Factor Alpha Prescribing Decisions: A Qualitative Study

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Author’s response to reviews:

Please find our responses the specific reviewer comments below. Amendments to the manuscript have been highlighted in yellow.

Reviewer 1 (Liana Fraenkel)

Authors’ response: Many thanks to Reviewer 1 for their thoughtful comments on our manuscript. We have addressed each comment below and highlighted where amendments to the manuscript have been made. We believe that these amendments have addressed the reviewer’s concerns and will improve the manuscript substantially.

Reviewer comment 1: The authors address an important topic in this paper. My main criticism relates to the methods of recruitment. It is unclear how participants were purposefully sampled. It does not appear that an effort was made to ensure that rheumatologist were recruited to ensure representation of diverse backgrounds, practice settings, and experience.

Authors’ response: Our study specifically recruited senior rheumatologists in England because we believed that (i) they had the most experience of prescribing anti-TNF agents for people with rheumatoid arthritis and (ii) they had the most knowledge of NICE recommendations. The sample was dispersed evenly across England; we reported this using aggregate geographic regions (north, midlands, south of England), rather than reporting the specific local-level region, to preserve anonymity of the participants. We agree that an alternative method to achieve our aim could have been to recruit a sample that was representative of the diverse backgrounds, practice settings, or experiences of rheumatologists in England. However, recruitment of a representative sample to produce generalisable results for England was not the objective of our study and, more generally, is not necessary for robust exploratory qualitative research. The
following sentences have been included to clarify how participants were sampled and that alternative sampling methods were possible.

Amendment (Methods Section; P 6): The target population comprised senior rheumatologists who had experience of treating RA. This target population was chosen because they were expected to have good working knowledge of the key NICE recommendations that guide practice and extensive experience of using anti-TNF agents to manage people with RA.

Amendment (Methods Section; P 6): The role of principal investigator was indicative of seniority and extensive experience of managing RA using biologic anti-TNF agents. Individuals in the sampling frame were based at different hospitals across the country (one individual per hospital).

Amendment (Discussion Section; P 22): The decision to purposefully sample rheumatologists with extensive experience of using anti-TNF agents may have masked the factors that influence rheumatologists from different practice settings or who have lower levels of experience. Future research could investigate whether the external environmental and internal hospital factors influence junior rheumatologists to the same extent that their senior colleagues have described.

Reviewer comment 2: Most importantly, recruitment did not include an approach to ensure thematic saturation.

Authors’ response: There was no stopping rule to recruitment with respect to saturation because the sampling frame for the study was finite. However, saturation was achieved as a consequence of the framework analysis method (ie. the construction and application of a framework of themes to all earlier and subsequent interview transcripts until no new themes were identified). A figure (Figure 3) has now been included which illustrates the dispersion of themes identified in each transcript. The accompanying text has been amended to explain that new themes were not identified by the final interview.

Amendment (Methods Section; P 7): Recruitment continued until all individuals in the sampling frame who agreed to participate were interviewed.

Amendment (Methods Section; P 9): The dispersion of themes that were identified in each transcript was evaluated after all interviews had been conducted to interpret the extent of thematic saturation within the sample.

Amendment (Results Section: P 10): Figure 3 illustrates the dispersion of subthemes reported by each rheumatologist. A mean of 10 subthemes (range: 8 to 12 subthemes) were identified in each transcript. Unique subthemes were not described by the rheumatologists after the third interview which was indicative of thematic saturation in the sample.
Reviewer comment 3: There are numerous papers describing multiple reasons why physicians do not adhere to guidelines. It is not clear what specific gap in the literature this paper addresses or whether the results add significantly to what is already known.

Authors’ response: Many thanks for highlighting concerns about whether our study addressed a specific gap in the literature or whether the results significantly added to what was already known. The introduction section described the specific gap in the literature which we now summarise here:

The health care system in England has a single-payer and routine clinical decisions are made with reference to uniform national recommendations made by NICE. One objective of NICE recommendations is to minimise regional variation in health care; however, national clinical audits for rheumatology and specific quantitative studies have identified that regional variation in care for people with rheumatoid arthritis is pervasive in England. This study used qualitative methods to explore factors that may influence this observed regional variation in anti-TNF prescribing decisions. No study to date has used qualitative methods to explore this phenomenon in England. Our findings were discussed in the context of the results from similar studies in different countries. Our study adds to this literature by highlighting that, even in England where national uniform recommendations are in place to mitigate regional variation in care, differences in factors that influence anti-TNF prescribing decisions (at 3 distinct levels) may drive regional variation in care for people with rheumatoid arthritis. We have made the following amendments to make the specific gap in the literature and the significant contributions more explicit to the reader.

Reviewer comment 4: Moreover, the interview appears to assume that physicians are aware of the guidelines and are able to access cost information. These may in fact be important barriers, likely perhaps to be experienced by those who did not wish to participate in the study.

Authors’ response: Thank you for identifying an area for clarification within the manuscript. There is a difference between NICE guidelines (which are advisory) and NICE recommendations based on the results of a technology appraisal (where the provision of a treatment is mandatory for patients defined by the recommendation unless a clinical exception can be made). In England,
NICE recommendations will be known to all NHS health care professionals within a specific disease area because they mandate (i) which treatments can be used and (ii) when each treatment can be used. The following has been included to clarify that health care professionals within England will be aware of NICE recommendations:

Amendment (Introduction Section; P 4): Health care professionals will be aware of the specific recommendations for treatments made during the NICE technology appraisal program because, for the majority of cases, their implementation is mandatory within 3 months [2]. For example, the NICE technology appraisal program has produced…

Authors’ response: All rheumatologists in England can access information about the cost of specific treatments by using the British National Formulary (BNF). NICE provide health care professionals with a hard-copy of the BNF for free and this information can also be accessed online. In addition, local commissioners may negotiate a lower cost for a specific treatment (as reported in the study); these costs will be known at the local-level. The following been included to clarify that health care professionals will be able to access cost information:

Amendment (Introduction Section; P 5): Rheumatologists in England have access to the cost of treatments because they are reported within the British National Formulary which is made available for free (hard-copy and online access) to health care professionals [16]. Commissioners of health care may also negotiate the cost of a biologic agent at the regional-level which will be communicated to prescribers [17].

Reviewer 2 (Mark Harrison)

This is an interesting and well-written qualitative study of the factors that influence the prescribing of anti-TNF treatments in the context of UK rheumatology services. The findings suggest the existence of three key spheres of influence which exist at the internal environment, external environment and at the individual level. These findings are then nicely placed in the context of other studies of prescribing patterns and their variation. I have a few comments and suggestions that I would welcome consideration by the authors.

Reviewer comment 1: 1. The thematic analysis with the six outlined stages are well described and seem reasonable and the citations for the approach look appropriate.

Authors’ response: Many thanks. No action required.

Reviewer comment 2: 2. There is no need for an estimated sample size required for this type of research, but I wasn't clear from reading what the rule to stop recruitment rule was e.g. saturation. I think the authors should provide a definition of saturation and also how they knew they'd reached it.
Authors’ response: Many thanks for this suggestion. Reviewer 1 had a similar suggestion and we have now included the following text to explain that recruitment continued until participants in the sampling frame who agreed to participate were interviewed. The following text and figure have been included to explain how the extent of thematic saturation in the sample was evaluated. The dispersion of subthemes across each transcript and the lack of new themes after the third interview were indicative of thematic saturation.

Amendment (Methods Section; P 7): Recruitment continued until all individuals in the sampling frame who agreed to participate were interviewed.

Amendment (Methods Section: P 9): The dispersion of themes that were identified in each transcript was evaluated after all interviews had been conducted to interpret the extent of thematic saturation within the sample.

Amendment (Results Section: P 10): Figure 3 illustrates the dispersion of subthemes reported by each rheumatologist. A mean of 10 subthemes (range: 8 to 12 subthemes) were identified in each transcript. Unique subthemes were not described by the rheumatologists after the third interview which was indicative of thematic saturation in the sample.

Amendment (Figure 3): Figure 3. Distribution of Themes and Subthemes Identified in each Transcript

Reviewer comment 3: 3. The gist statements like 'most' and 'many' are used frequently in the reporting of results. I understand that this is acceptable in qualitative reporting. I have also seen a few papers using qualitative methods which have included actual counts of how many participants shared an experience, perception, or attitude. Did the authors consider this approach to support these statements?

Authors’ response: A count for the frequency of a theme’s occurrence within each transcript was not included due to the exploratory nature of the study and it was not necessary for the framework analysis method. No action required.

Reviewer comment 4: 4. I would also be interested to know, or hear the authors describe the presence/absence of given themes in the sample of participants (especially absence if there was evidence that suggested it should be present), if there were differences in themes between subgroups, and whether there were any conflicting attitudes/experiences among participants (and within individuals). This might be interesting to include and add depth to the findings currently presented.

Authors’ response: We have taken this recommendation into account and have now described conflicts in the sample (interpretation of NICE recommendations; consideration of cost in prescribing decisions) and themes that appeared to coincide with each other. The following text has been added:
Amendment (Discussion Section; P 20): One conflict between participants in this study was the extent to which NICE recommendations were interpreted as flexible (advisory) or inflexible (mandatory).

Amendment (Discussion Section; P 20): The extent to which the cost of treatment was described to influence the rheumatologists’ routine prescribing decisions also conflicted between the participants. At one extreme, cost was said not to influence routine prescribing decisions to the advantage of the patient with RA who will receive treatment; at the other extreme, cost was explicitly considered in order to sustain resources for other patients being treated elsewhere in the health care system.

Amendment (Discussion Section; P 21): The rheumatologists who perceived their commissioners as an enforcer of NICE recommendations also had a tendency to describe stricter systems to ensure compliance with those recommendations at the hospital-level and fewer opportunities for patients to be involved in prescribing decisions at the individual-level.

Reviewer comment 5: 5. On one occasion I don't agree with the description of a quote - it says "…we don't give them options of five agents…you don't want to bewilder patients" and this is described as 'patient influence.' It sounds more like physician influence to me (provider behaviour/perception of patients rather than patient influence), and there is a category under the same 'patient influence' section where physicians skepticism over patients’ abilities to make informed treatment decisions is listed - I'd think it sat more comfortably there. Consider moving or describing more clearly why it is classified as patient influence. It may be that the themes need to be described more clearly for the reader so that the direction of influence isn't misinterpreted.

Authors’ response: Thank you for making this suggestion. We have moved this quotation as suggested, replaced it with a different quotation to demonstrate that some patients have no influence on the choice of anti-TNF, and included the following text to clarify the interpretation of these quotation.

Amendment (Results Section; P 16): The rheumatologists described three different approaches to patient influence in the choice of anti-TNF: (i) complete freedom to choose any anti-TNF; (ii) freedom to choose an anti-TNF from a subset of agents; and (iii) no ability to choose an anti-TNF.

Amendment (Results Section; P 16): K: “For rheumatoid at the moment…we don’t really give them a choice [of anti-TNF].”

Reviewer comment 6: 6. Quite a lot of interpretation of results relies on knowing what the NICE criteria are for starting an anti-TNF treatment (e.g. what the DAS28 score has to be to determine eligibility, how many times it has to be &gt;5.1 etc), think this would be a worthwhile addition. Table 3 relies on this
Authors’ response: We agree that this is an important addition to the manuscript. The following amendments have been made to inform the reader of the NICE criteria for stating anti-TNF treatment.

Amendment (Table 3): The criteria by NICE to determine eligibility for anti-TNF therapy was to have two DAS28 assessments of at least 5.1 one month apart [34].

Amendment (Results Section; P 18): NICE recommendations specify that the DAS28 [33] is used as part of the criteria to determine a patient’s eligibility for anti-TNF therapy. The specific criteria for eligibility at the time of the interviews was to have a DAS28 assessment of at least 5.1 on two occasions one month apart [34].

Reviewer comment 7: Linked to point 6, when I got to Table 3 I didn't understand how the #3 "Only perform one DAS28 assessment" helps in the absence of some explanation clarification of the NICE criteria - is this because need an average &gt;5.1 so if you suspect patient not very active and you get one &gt;5.1 you stop there?

Authors’ response: Thank you for highlighting that this was not clear. We have now included the following sentence to explain the NICE criteria with respect to this point.

Amendment (Results Section; P 19): For example, a single DAS28 assessment could be performed, instead of the two assessments required by the NICE eligibility criteria, to (i) reduce the time to prescribing an anti-TNF and/or (ii) avoid the risk of the second DAS28 assessment being less than 5.1.

Minor

Reviewer comment 8: 1. Background, paragraph 2: Sentence starting "For example, in 2015/16, 60% and 73% of patients commenced cDMARDs within 6 weeks…" is important but the way it is written currently seems to be difficult to under. Could be written more clearly to emphasize the point here e.g only 60% in Midlands/Eastern compared with 73% in South

Authors’ response: The following amendment has been made to clarify this sentence:

Amendment (Background Section; P 4): For example, in 2015/16, 60% of patients in the midlands/eastern regions of England commenced cDMARDs within 6 weeks of referral compared with 73% of patients in the southern region.

Reviewer comment 9: 2. Backrorund, page 5, paragraph 1: Re: "1.5. Start treatment with the least expensive drug (taking into account administration costs, dose needed and product price per dose)" [5, p.5]." Is it immediately clear to physicians what the least expensive is - I assume this would be in the BNF?
Authors’ response: Thank you for identifying this point of clarification. Reviewer 1 made a similar comment and we have added the following sentence to explain that cost information is available to the rheumatologists:

Amendment (Introduction Section; P 5): Rheumatologists in England have access to the cost of treatments because they are reported within the British National Formulary which is made available for free (hard-copy and online access) to health care professionals [16]. Commissioners of health care may also negotiate the cost of a biologic agent at the regional-level which will be communicated to prescribers [17].

Reviewer comment 10: 3. Page 14, line 44: minor typo - "received referrals with as DAS below 5.1.." 'As' should be 'a'

Authors’ response: Thank you for identifying this. This sentence has been amended as follows:

Amendment (Results Section; P 15): …has received referrals with a DAS below 5.1…

Reviewer comment 11: 4. Page 18, line 15 "A: "…then there's some people who don't put up their inflammation tests, their ESR/CRP" I think it's interesting that rheumatologists just don't seem to have any faith in the validity of ESR/CRP

Authors’ response: Thank you for this comment. No action required.