Author's response to reviews

Title: A 5 item version of the Compliance Questionnaire for Rheumatology (CQR5) successfully identifies low adherence to DMARDs

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Author's response to reviews: see over
We thank the reviewers for their careful read through the original draft of this manuscript and their insightful comments and suggestions. We have carefully taken into account these considerations and made some modifications to the manuscript which we feel help to clarify the importance of the results. The changes have been highlighted for ease of reviewing. We have also responded to the reviewers’ comments which are itemised below, along with our responses which we hope adds clarification.

Referee #1 (dated 13th February 2013)

1) There were too much methods information given in the text which might be shortened and avoid repeating.

We thank the reviewer for their thoughts on the reporting of the methodology and this is an area where we welcome comments. The way in which we reported the methodology was thought about very carefully and we tried to pitch the level of technical detail for the likely audience; i.e. rheumatologists and related clinical staff rather than statisticians. The psychometric evaluation that was employed necessarily involves a relatively high level of technical statistical detail, and the fact that we have reported three related and complementary tests in one manuscript compounds the technicality. In order to convey the most important information in a concise and coherent way, we have attempted to include necessary methodological information only and explain it in a direct and manageable way. We therefore feel that we have included the minimum amount of information necessary to successfully and transparently describe the study and could not reduce the methodology without compromising the quality of the report. We realise that for the likely audience, the results of this study will probably be of more interest than the methodology and therefore we have tried to emphasise a suitable reporting style whilst signposting interested readers to relevant references.

2) There was no information about power analysis. Is the number of patients sufficient for this research?

The issue of sample size and power is contentious for exploratory and confirmatory factor analyses, in part because these estimates rely heavily on the number of factors, standard errors, correlations and factor loadings which vary from model to model (MacCallum, Widaman, Zhang & Hong, 1999). Some early rules of thumb included minimum sample sizes of 100 (Kline, 1979; Gorsuch, 1983) to 250 (Cattell, 1978). More recently, ratios of cases per predictor have been proposed but these are also wide ranging from 5 to 20 cases per predictor (MacCallum et al., 1999). Most exploratory factor analyses use a ratio of 10:1 and confirmatory factor analyses 20:1; however, it is important to note that Chi² tests (on which factor analyses are based) are susceptible to sample sizes over 100 and therefore simply adding more cases per predictor will not guarantee a more reliable result. The sample size in this study was 225 for the exploratory factor analysis and 187 for the confirmatory factor analyses, resulting in a cases-per-predictor ratio of 12:1 and 18:1 respectively. Based on the rules of thumb above and the standard sample size in similar studies of 100-200, we believe that 225 cases are adequate to provide confidence in the results shown. Some more information on the sample size has been added to the results section to explain our justification.
3) **No characteristics besides sex, disease duration and ages of RA patients were given in the table. It would be appropriate to give number of different DMARDs to be used by patients and activity level of patients.**

We agree that activity level would potentially be interesting to consider in this analysis, but was not recorded because the focus of the study was on adherence to DMARDs. Activity levels have been used in other studies as a proxy measure of adherence, on the basis that those patients with high adherence should have improved disease control and therefore higher activity levels. However, the relapsing/remitting nature of RA means that the adherence-activity relationship is unlikely to be causal in every case and could be bi-directional. As this was a cross sectional study, it would not be possible to determine the direction of the relationship, therefore patient activity was not recorded.

As many RA patients are exposed to polypharmacy and it is not unusual to be prescribed more than one type of DMARD, the wording of the questionnaires was “your DMARD medication” in order to capture usage of all types of DMARDs. Evidence suggests that intentional non-adherence is related to perceptions about the illness and treatment which is unlikely to differ among different DMARDs, therefore if a patient is adhering to one type of DMARD, it is most likely that they are adhering to all of their DMARDs. For this reason, in order to reduce confusion when patients completed the questionnaires, the number of separate DMARDs was not recorded.

4) **A table which gives the selected items of the 5 itemed questionnaire would be suitable.**

We agree with the reviewer that an indication in the table of CQR questions of the final 5 items would be beneficial and was an oversight on our part for which we apologise. Table 1 now includes an indication of the final 5 items and reference to this has been made in the results section (second paragraph under the heading “Confirmatory Factor Analysis of CQR11”).

5) **No information was given for the ability of the shortened questionnaire to give an idea to the doctor what makes the non-adherence of the patients which was possible with the long one.**

We agree with the reviewer that an indication as to the reasons why adherence may be low would be particularly beneficial, and indeed is part of the benefit of using self-report questionnaires as opposed to objective measures such as eMEMs or biomarkers. However, we argue that the final 5 items not only give an indication as to the reasons behind non-adherence, but that the procedure of reducing and validating the CQR5 demonstrates that the 14 removed items do not in fact explain adherence, and therefore could not give an indication of areas for intervention. This is particularly evident during the first reduction stage (section “Exploratory Factor Analysis of CQR19”) as the removal of 8 items led a reduction in the amount of explained variance of adherence of only 11% and the removal of 5 redundant factors.

Although we have shown that the CQR5 can act as a screening tool for potential non-adherence, the focus of adherence research now is to identify the determinants of non-adherence and target them for intervention. The aim of this study was to identify the factor structure of the CQR19 and
determine the reliability and validity of the scale, and therefore it is not possible from these data to identify why some patients are not adhering to their medication. However, a lot of work is currently being done in this area and there are some promising results that are starting to recognise common psychosocial and cognitive factors that explain non-adherence in RA and have been successfully targeted for intervention (e.g. de Thurah et al., 2010; Petrie et al., 2011; Treharne et al., 2004). We have made this distinction clearer in the discussion and have made the following change; “As was found by de Klerk et al. [12], the CQR5 is most predictive when used as a weighted discriminant equation. This is the optimum combination of weighted questions to classify patients as either high or low adherers, and is the function that should be used when implementing the CQR5. The structure matrix indicates that Q3; “I definitely don’t dare to miss my anti-rheumatic medication” is the most indicative of high or low adherence as high adherers tend to “agree” whereas low adherers tend to “disagree”. It may therefore be possible to get an indication of the overall result from the answer to this question with a positive (answer 3 or 4) response indicating high adherence and a negative (answer 1 or 2) response indicating low adherence. The main benefit of using self report questionnaires is to attempt to identify the determinants of non-adherence in order to target for intervention. Although the CQR is not designed for this purpose, it does allow for the latent variable of adherence to be measured alongside validated measures of adherence predictors. Questionnaires such as the revised Illness Perception Questionnaire (IPQ-R) [24] and the Beliefs about Medications Questionnaire (BMQ) [22] have shown promising strides in identifying determinants of non-adherence in many illnesses including rheumatoid arthritis [23-26]. The CQR5 can be used in future research as a short, parsimonious, uni-dimensional adherence scale to successfully identify the most useful areas for intervention with the ultimate aim of improving patient outcomes.”

In order to aid the reader in using and understanding the CQR5 most effectively, we have made a calculator available as supplementary material that allows users to enter answers to each question (on a scale of 1 to 4) into an excel spreadsheet which will automatically calculate the discriminant function and give an indication as to whether an individual patient is likely to be a “high” or “low” adherer.

Referee #2 (dated 9th April 2013)

1) The principle psychometric analyses involved exploratory and confirmatory factor analysis. It would have also been informative to use Item Response to cross-validate the findings derived from classical test methods.

In order to fully test the factor structure of the full CQR19 and subsequent reduced version, we used a range of statistical techniques from item response theory and classical test theory. Exploratory and Confirmatory Factor Analysis was used in relation to item response theory to test how well each item measures the latent construct of adherence. Item response theory stipulates that the “S” shaped Item Characterisation Curve (ICC) denotes the difficulty and discrimination of the item. In this instance, the ICC for each item demonstrates the probability that a respondent with low behavioural “adherence” (difficulty) will respond positively to the item that measures the latent construct of adherence. The discrimination of the item (to detect adherence) is related to the steepness of the curve. Both exploratory and confirmatory factor analysis are based on item response theory and allow for more subtle analysis of interval scales such as the “agree-disagree” scale which the CQR is based upon.
In addition, we employed a number of reliability and validity measures to the reduced CQR. For example, the Cronbach’s alpha of the CQR5 is reported in the “Confirmatory Factor Analysis of CQR11” section as being acceptable at 0.85 and in the same section, we report that the goodness of fit indices remain adequate in a bootstrapped sample of 500 randomly selected samples from the dataset. We agree with the reviewer in that a graphical representation of how responses to each item impact on the overall explanation of the items to explain adherence would be informative, but in the interests of brevity, we have excluded this in favour of the discriminant analysis and path diagram for the CQR5. The path diagram shows the factor loadings for each item which represent the amount of variance explained in the latent variable of adherence and therefore provide important information on the likely mechanisms behind adherence.

2) The sample size was rather small.

We have provided a detailed account of the sample size in response to referee 1’s second point. We believe that the sample size is standard for this type of analysis and demonstrates a good cases-per-predictor ratio of 12:1 for the exploratory factor analysis and 18:1 for the confirmatory factor analysis, particularly for a unidimensional scale with high correlation.

3) The authors did not seem to give consideration to features of item score distributions in selecting items, i.e. Item means and standard deviations and ceiling and floor effects.

The reviewer has made a correct observation here. In reducing the number of items in the questionnaire, we did not consider the measures of central tendency and spread or floor or ceiling effects. There were two reasons for this; firstly, this is the first step when developing a new measure and therefore had been carried out by the original authors. Secondly, we focused our analysis on the basis that in this case, adherence was being treated as a latent variable; i.e. by using a self report measure, adherence behaviour is not directly observed and measured. Therefore, in order to identify which individual items of the CQR best explained the variance in the latent variable of adherence, we used correlation and communality via exploratory and confirmatory factor analysis.

4) What was the ratio of the first to second eigenvalue? It would have been informative to present the results of the exploratory factor analysis in a table... If the KMO indicated a weak factor structure, did this not suggest that perhaps alternative methods of item reduction should be pursued?

We agree that the results of the factor analysis would be useful if presented as a table and have added this to the manuscript (Table 3). We thank the reviewer for this suggestion as we feel that this helps to make the results of the exploratory factor analysis clearer. We have also made the factor matrices available as supplementary material so that those with a particular interest in the process of reducing the questionnaire have access to this data without adding more technical detail to the article. The KMO of the CQR19 was low at 0.79, indicating that the factor structure was weak, but was above what would be considered appropriate for carrying out factor analysis (generally this is >0.5; Tabachnik & Fidell, 2007).
5) The manuscript should provide more transparent details on the regression model given by de Klerk so the methods and results of the manuscript can stand on its own.

We thank the reviewer for this suggestion. However, we feel that in order to fully explain the discriminant function that de Klerk et al. (2003) developed in the context of the reduced version of the questionnaire would require substantial space in order for it to be useful to the reader. As the original authors explained the technique and resulting equation very comprehensively in the appendix of the article, we have chosen to direct the reader to the original source for review. This is mainly because, although we have taken Erik de Klerk’s lead in producing the most useful method of execution for the CQR, as we are proposing a shorter, more parsimonious version of the questionnaire, we do not feel that presenting the full background and discriminant equation for the CQR19 is conducive to the understanding of the CQRS and could lead to confusion if two unrelated equations are presented. However, we are happy to concede this point if it is felt that it is essential for the original equation to be included and will add the relevant information.

6) The CQR items are worded very awkwardly.

The CQR items were developed by de Klerk et al. (1999) from patient interviews and focus groups. Following pre-testing with a small number of patients, items were reworded to their final form to aid clarity. As the CQR has been validated in its current form and was reported in English, we have not altered the wording in order to prevent any unintended (and untested) biases that this may introduce.

References


Petrie, K. J., Perry, K., Broadbent, E. & Weinman, J. (2011) A text message programme designed to modify patients' illness and treatment beliefs improves self-reported adherence to asthma preventer medication. *British Journal of Health Psychology*
