Author's response to reviews

Title: RCT Examining the Effect of Exercise in People with Rheumatoid Arthritis on Anti-TNFalpha Therapy Medication

Authors:

Angela Reid (angelatreid@hotmail.com)
Audrey Brady (audbrady@yahoo.co.uk)
Catherine Blake (c.blake@ucd.ie)
Anne-Barbara Mongey (anne.b.mongey@ucd.ie)
Douglas J Veale (douglas.veale@ucd.ie)
Oliver FitzGerald (oliver.fitzgerald@ucd.ie)
Tara Cusack (t.cusack@ucd.ie)

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Author's response to reviews: see over
Reviewer 1 Claudia Witt

<table>
<thead>
<tr>
<th>It would have been much more convenient for me as reviewer, when the authors would have highlighted their changes as it is usually done in revised manuscripts.</th>
<th>Apologies for this omission. On this occasion all changes have been highlighted in red font in addition line numbers have been added for clarity.</th>
</tr>
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<tbody>
<tr>
<td>Major Compulsory Revisions</td>
<td></td>
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<tr>
<td>Abstract: The primary endpoint and comparisons are still missing in the abstract.</td>
<td>The primary end point and comparisons have been incorporated into the abstract and have been highlighted in red font (line 22).</td>
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<td>Methods: Sample size calculation: It is not necessary to provide the formula this is common knowledge.</td>
<td>The sample size calculation has been deleted.</td>
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<td>I asked for the rational of the assumptions which were included into the formula.</td>
<td>The authors thank the reviewer for this comment and apologise that they did not fully reflect fully on this point when undertaking the initial changes to this manuscript. It is a very significant point which led to substantial revision of the sample size calculations.</td>
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<td>It is still unclear from where the SD of 0.206 is determined, if this is based on previous data this should be referenced.</td>
<td>The minimally significant clinical change was taken from work undertaken by Kosinski et al (2000) (line 402). (Kosinski, M. Zhao, SM. Dedhiya S, Osterhaus, JT., Ware JE. (2000) Determining minimally important changes in generic and disease-specific health-related quality of life questionnaires in clinical trials of rheumatoid arthritis. Arthritis and Rheumatism. 43, 7, 1478–1487) The sample size calculations in the previous draft were undertaken on the bases of the standard deviation (0.206) reported from the RAPIT study by Van den Hout (2005). However the authors have reviewed the literature in the area of the HAQ and acknowledge that the standard deviation of 0.206 is small when compared to that reported in other large scale studies that have included the HAQ (ATTAIN and AIM studies). Wells et al</td>
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(2000) reported on HAQ outcomes in these two studies ATTAIN (n=391) and AIM (n=632) the standard deviation for the HAQ ranged from 0.59 to 0.74. The sample size calculations have been revised using a standard deviation value of 0.63 (line 404-408).


In addition you provide now two times the same information about the sample size calculation (before and after the formula).

I still would like to see a clear rational which support such a large effect due to the intervention as here assumed.

The authors apologies for this oversight, the duplicated text has been removed.

This was very useful feedback which provided much discussion among the authors. The revision of the standard deviation value (0.63) that will be used in the sample size calculations has influenced the effect size that is expected (0.3). I have addressed this in the manuscript under sample size considerations and have highlighted the alterations in red font (line 404-408).

Statistics:
Two group comparisons are preplanned, and the multiple testing has to be handled not only as a post hoc procedure. The authors should discuss with their statistician the options (e.g. hierarchical test procedure, Bonferroni-Holm)

The authors have sought further statistical advice following the recommendation of the reviewers. The revised text has been incorporated under the heading statistical analysis and the changes have been highlighted in red font (line 411-440).

The statistical analysis should adjust for baseline values.

In my opinion further covariates

This point has been considered in the drafting of
are only necessary if there are relevant group differences. the statistical analysis section (line 411-440).

**Minor Essential Revisions**

**Methods, randomization:** The block size usually should not be transparent to those who perform the trial, because this influences blinding.

The block size will be predetermined but not disclosed to those conducting the trial (line 233).

Due to the nature of the intervention gym and water based exercise programmes it is not possible to blind those conducting the exercise classes. However the randomization will be undertaken by an individual not involved in the trial and the measurements will be undertaken by an independent blinded physiotherapist not involved in the conduct of the trial (line 247-253).

One point from my last review has not been answered by the authors:

Randomization: Please provide software and who generated the sequence

Apologies for this omission the following text has been inserted under the heading randomization on page 9 (line 233-237).

‘Participants will be randomised in predetermined block sizes by means of an allocation sequence generated using a random number table devised in Microsoft Excel 2003 (Microsoft Corp, Seattle, USA). The allocation sequence will be generated by one of the authors (TC) who will not be involved in the assessment of participants or supervision of the exercise groups.’

Recruitment: I don’t understand why the authors use the term “A convenience sample” if they invite patients from a computer data base they could invite a random sample which fulfills the inclusion criteria.

This is a good point, in fact all the individuals from the data base that fulfill the inclusion criteria living within a 50km radius of the rheumatology centers will be invited to participate (line 223).

**Reviewer 2 Arianne Verhagen**

Furthermore I think the formulas on sample size calculations can be deleted, because that is common knowledge.

Thank you for this comment the sample size calculation has been deleted.

**Major compulsory revisions**

**Background.** The authors do not

Thank you for this feedback it was very useful and
provide information on why the effect of exercise would be different in patients on anti-TNF-alpha medication compared with the RA patients not on this medication. Why would these patients react differently or why can we not assume that the RA patients on medication react the same as other RA patients?

The authors stated they addressed this issue. Now the background contains a lot of information in great detail about the effectiveness of exercise in RA patients and one sentence that the effectiveness is not evaluated in RA patients on anti-TNF-alpha medication.

This is not really what I meant. My comment was that the author did not made clear to me why the available evidence on RA patients could not be extrapolated or generalized to RA patients on anti-TNF-alpha medication. What makes these patients so different that the effect of exercises also needs to be evaluated in this subgroup of patients?

<table>
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<tr>
<th>• Methodology. Statistical analysis page 13. This section is not complete.</th>
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<tbody>
<tr>
<td>The authors have sought statistical advice and have revised the statistical analysis section. The alterations to this section have been highlighted in red font (line 411-440).</td>
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<tr>
<td>Authors should describe when an intention to treat analysis is performed how they will handle missing data.</td>
</tr>
<tr>
<td>Thank you for this comment. Missing data will be estimated through multiple imputation with a regression method by means of SPSS. The text indicating how missing data will be managed has been highlighted in red font (line 418).</td>
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</table>
Furthermore more information on multiple regression analysis should be provided. I assume this will be performed using the primary outcome as the dependent variable, but will it be dichotomised?

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<th>How many and which variables will enter the regression analysis? Etc.</th>
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<td>Following previous feedback in relation to this paper the authors have sought additional statistical advice. The statistical analysis component of this paper has been redrafted in line with the reviewers’ recommendations and the statistical advice received. The changes to the text have been highlighted in red font (line 431-441). The primary outcome (HAQ-DI) will be dichotomized.</td>
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<td>‘The dependent variable will be dichotomous in terms of change in the HAQ (0=change less than 0.1, 1=change greater than or equal to 0.1).’ (Line 433-435)</td>
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As a secondary analysis it is proposed to examine age, length of time since diagnosis and length of time taking anti-TNF α medication in the analysis. The detail of this proposed analysis has been included in the statistical analysis section and has been highlighted in red font (line 431-441).

The author indeed completed this section, but not according to the latest evidence on how to deal with missing data. Perhaps they need help from a statistician here? Last measure carried forward is not regarded an appropriate way of dealing with missings nowadays, we prefer multiple imputation techniques, especially when missings are selective or when the amount is over5%.

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<tr>
<td>This feedback was most helpful. Advice has been sought and missing values will be estimated through multiple imputation with regression which is available in SPSS (line 418).</td>
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<tr>
<td>Under the heading ‘Statistical Analysis’ the amended text has been highlighted in red font.</td>
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