Author's response to reviews

Title: Preliminary results, methodological considerations and recruitment difficulties of a randomised clinical trial comparing two treatment regimen for patients with headache and neck pain

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Preliminary results, methodological considerations and recruitment difficulties of a randomised clinical trial comparing two treatment regimen for patients with headache and neck pain

Dear Editor,

Dear Reviewers,

we thank you for the interest in our article and for the constructive remarks. We have read and analysed all remarks carefully.

Below we present a point by point reply to each of the reviewers comments. Each time we present the remark by the reviewer in normal typewriting, followed by our response in italic. Changes in the text are highlighted in yellow.

We hope this revised version meets your expectations and are looking forward for your comments.

Yours sincerely,

On behalf of all authors,

Willem De Hertogh
Reviewer 1

Compulsory changes

1. Given the inclusion at time of headache severe enough to seek care, by definition one would expect during follow-up to see improvement. The abstract suggests that both types of treatment have an effect, whereas one could also argue that both treatments do not add anything to the natural course. To provide more insight, substantially more information is needed on the actual UC delivered. If this turns out to be ‘wait and see’ (as contrast to the intervention arm with similar co-interventions in both arms) than the abstract should be reformulated.

   Additional information about the content of UC is provided in the abstract. Also later on in the ‘Interventions’ paragraph more details are provided. We believe this additional information makes clear it is not a ‘wait and see’ approach.

2. With regard to the use of the HIT-6 cut-off value of 56 points, I would like to see information included on natural prognosis, if available. Does one expect a certain improvement whatsoever?

   Concerning the natural course/ prognosis of the headache complaint: The reported frequency and long duration of headache in our recruited sample as displayed in table 1 suggest that our patients had chronic headaches (>15 days/month). Chronic headaches often develop from an infrequent headache (<15 days/month). The natural course or prognosis of chronic headache is largely unknown. Headache frequencies can fluctuate. For instance, Wiendels et al. reported reductions as well as increases of the headache frequency over a period of 5 months [1]. Midgette and Scher report various partial remission rates over more prolonged periods (one year follow-up or more) of chronic daily headaches to more ‘normal’ frequencies [2]. Accurate information on the natural prognosis of chronic headache is lacking and additional research is needed.

   Patients in similar studies describing physiotherapy interventions also reported high frequencies at baseline and long histories of the headache complaint [3, 4]. Therefore we think improvement in the health status of chronic headache patients can be expected.

3. The flow chart suggest that informed consent was (partly) collected after randomisation, since in the UCMT group 8 persons did not receive the intervention. Information on informed consent procedures should be described in the recruitment paragraph. The discussion should present more background what really has happened here, could this have been avoided?

   The information on the informed consent and enrolment procedure is extended. It can be found on page 6 lines 5-9.

   The reasons why 8 patients in the UCMT did not follow the treatment they were allocated to are discussed in the Discussion, on p. 11 from line 28 to p. 12 line 4. Various factors could be considered as ‘external factors’, such as the discouragement to participate by the physicians of two patients. We believe it is very hard to avoid them. We have added this to
the discussion. We also included information as provided by Vernon et al. who likewise encountered huge recruitment difficulties [5].

4. I am not entirely convinced that a one-way ANOVA is the appropriate technique for analysis, since one would like to adjust for baseline values and well-known prognostic factors. The analysis should demonstrate the change over time, preferably per measurement period, and the difference between both arms at each measurement period. This difference will determine effectiveness. The comparison of FU week 26 relative to baseline, as used in tables 3 and 4, is confusing when not adjusted for baseline value.

   In the revised version a repeated measures ANOVA is used to adjust for baseline values. Additional information is provided in the section 'Data reduction and analysis' (see also reply on the remarks of reviewer 3).

5. The value of the manuscript is in its candid discussion about failing enrolment. Many reasons are presented, but I would like to see more expert judgement here as to the core reasons: was it lack of patients, was it lack of practical effort of physicians (could be partly remedied by involving nurse assistant etc) etc. Also, the drop out of patients in the intervention arms is quite alarming...

   We discussed multiple factors that were in our opinion of influence for the recruitment of participants and provided recommendations for future research. Patients were recruited in primary care settings where nurse assistants are less available. Since the first submission of our manuscript, a study has been published which also encountered recruitment difficulties [5]. Apparently, it is hard to recruit chronic headache patients for clinical trials in primary care settings and to maintain these patients within the boundaries of a treatment protocol. The discussion on this topic has been extended.

Minor changes
1. I am not entirely sure how this RCT differs from previous RCTS on MT, in combination with exercise therapy. What is the underlying rationale why this specific MT RCT is required?

   In previous RCTs physio/ or MT approaches were compared with a control group [4] or another physio/ MT regimen [3].
   This RCT differs because it is a pragmatic trial investigating the additional value of MT as an adjuvant therapy to the usual care.
   This is more clearly formulated on p 10 lines 25-26.

2. I like to remarks in the introduction about current guidelines, but it is not always clear if guidelines across countries differ and whether the same patient definition is applicable, e.g. the RCTs references 5-8 on different headache types, do this types include neck pain and/or stiffness?
The cited guidelines are designed for primary care and consequently address the management of the headache types which are most frequently seen in primary care, being primarily tension type headache and migraine. With regard to the headache types and neck pain: neck pain often accompanies headache, regardless of the headache diagnosis. This has been rephrased at the beginning of the ‘Background’ section on p 4 lines 3-6.

3. The Dutch protocol for usual care is not very clearly described as to actual treatment decisions

Additional information has been inserted on p 7, lines 24-26.

4. Table 4, last 4 lines, the description does not match the presentation, eg absenteeism proportion absent/not absent..figures are not proportion, maybe except the last column.

The table has been adapted.

5. I am not sure how power calculations have been conducted, eg it is simply impossible that in the current sample size the absenteeism has a power of 0.86 (beta). In fact, all dichotomous variables will have a power substantially below 0.50 when comparing both arms.

Power calculations were performed using the PS program by Dupont and Plummer. In response to the remark of reviewer 3, the a posteriori power calculations are omitted in the revised version and confidence intervals are included.

Reviewer 2

Abstract:
Minor essential revision:

The authors should indicate that this is a report of a stopped trial and that the results presented are preliminary. The should indicate that their goal in publishing these results is to aid future systematic reviews and meta-analyses.

The information has been inserted in the abstract. It can be found on page 2 lines 11-13. The remark regarding the meta-analysis is included in the discussion on p 10, lines 12-14.

Background:
Minor essential revision:
1. Para. 1, line 4- are the references [2,3] cited to support the notion that TTH, migraine and CEH are the most prevalent headache types in primary care, OR, that (from the sentence above), they are often accompanied by neck pain and stiffness. There are no references for the latter statement. Please provide appropriate references here.

The formulation has been changed to the following:
Irrespective of the headache diagnosis it is often accompanied with neck pain and movement stiffness [6]. This combination of clinical signs occurs frequently in Tension-Type Headache (TTH), Migraine and Cervicogenic Headache (CEH), which are among the most prevalent headache types in primary care [7, 8].

2. Line 6: Please find a more appropriate term than "merely" to describe the treatment...etc.

   The term "mainly" is used in the revised version.

3. Line 9: Please find a more appropriate term than "careful" to describe the positive effects of treatment...etc.

   The term "potential" has been used.

Methods:
Minor essential revision:
1. Under "Randomisation and blinding": Please justify why 'gender' was not used as a stratification factor when it is known that there is a strong gender bias in primary headaches.

   Headache affects more women than men. We did not stratify for gender in the original protocol. As there is no statistical difference in the male/ female ratio in both groups, it was not of influence in this study. For future studies it could be indicated to stratify for gender in order to obtain an equal amount of females/ males in every treatment group.

2. Under "Interventions": While the trial design has been published previously, I think some additional detail on the method of "spinal mobiisations" is necessary.

   This information has been added on p 7, lines 17-20.

3. Were multiple therapists used for the treatment? Were multiple sites used? The authors should describe how they trained these therapists and standardized the delivery of the therapy.

   Patients were free to contact a therapist in their region. As mentioned on page 7, a letter with recommendations for the treatment was provided to be handed over to the treating therapists. This to standardise MT treatment. In the discussion on page 12 lines 9-12, we indicate that no previous training was organised and that a training period could be useful for future trials.

4. Some additional information on the methodology of the "step-up theapy" used by GP's should be included: medication types, dosages, side effect monitoring.

   Information on the content of UC has been added on p 7, lines 24-26.
5. There is no indication in the Methods that adverse events / side effects were monitored. Please add some explanation here.

Additional information is added on p 12 lines 19-20.

Results:
1. See below re: medication prescription AND adverse events.

   We do not fully understand the suggested remark of the reviewer. Concerning the adverse effects we refer to the response above.

Discussion:
1. Para.2: The authors should briefly recap what the main positive results were, rather than simply say that both groups "evolved in a positive sense".

   The information has been added.

2. Under "Treatment effects": the authors indicate that the US groups received more medication on prescription. However, this was not reported in the Results section. In order to make the claim here that UCMT offers a potential advantage in that it achieves the same level of improvement with fewer medications, the authors should provide sufficient data in the Results. Otherwise, they should remove this statement.

   On p 8 lines 24-26 we indicate that subjects from the UC group use more NSAIDs and triptans. Both types of medication are only available on prescription. We have included this in the text.

3. Only in the Discussion do the authors indicate that no side effects or adverse events were reported. This should be reported in the Results section first, then commented on in the Discussion.

   No side effects or adverse events were reported. However, the study protocol did not specifically include a monitoring. Therefore we report in the discussion the following: "No side or adverse effects were reported by the participants, but more pro-active monitoring of potential adverse effects in either treatment arms is recommended for future trials."

Reviewer 3
Statistical Review
Methods
1. In the section "Data reduction and analysis" the authors state that "Differences between successive follow-up measurements within a treatment group were analysed using a one-way ANOVA." A one-way analysis of variance is appropriate when comparing several independent groups. In the present situation the SAME patients are observed at several occasions, so this is
clearly NOT a comparison of independent groups. The correct analysis is a repeated measurements ANOVA.

*In the revised version we have used a repeated measures ANOVA. A detailed description of the procedure can be found in the ‘Data reduction and analysis’ section: "Comparisons between both groups at the follow-up measurements were made using a two-factor repeated measures ANOVA (group X time) to adjust for baseline values. Differences between successive measurements within a treatment group were analysed using a one factor repeated measures ANOVA."

2. Three lines further down we learn that

"A posteriori, power calculations of the achieved results were performed". Power calculations are useful/necessary when the study is planned. Once the data are collected, confidence intervals are the appropriate way to describe the information in the study. The full version of the revised CONSORT statement [1] gives the following advice (p. 670): "There is little merit in calculating the statistical power once the results of the trial are known; the power is then appropriately indicated by confidence intervals"

*The a posteriori power calculations have been omitted in the revised version. Confidence intervals are provided with the results.*

Results

3. This is a randomized trial and the results section should focus on comparison of the primary (and secondary) endpoints between the two treatment groups. Time trends in one of the treatment groups are less interesting. Time trends should also be compared between groups.

*The method of analysis was adapted. A repeated measures ANOVA was used with the allocated group as between-subjects factor in order to compare the time trends between groups.*

4. Why was the study terminated before the necessary number of patients was included?

*This has been specified on p 10 lines 4-6.*

Table 2

5. Nineteen patients were randomised to UC and 18 to UCMT. Apparently, some patients drop out during follow up. This is not explained.

Some patients may have more than one health care contact. The table would be more informative if also the number of patients with no contacts was shown.

*In figure 1 (flowchart) the number of subjects lost to follow-up is displayed. The drop out of subjects is discussed at the bottom of p 11 and top of p 12. Some patients had multiple contacts, as can be seen in the column of UCMT at week 7: 14 subjects and 22 contacts.*
Headache related health care contacts is one of the secondary outcome measures. In the discussion we have added the following: “For future trials we recommended to use a headache diary. This can provide more complete and day by day information allowing a more profound recording of outcome measures.”

Table 3
6. Give confidence intervals for the comparisons (difference of proportion, difference of means)

They have been inserted.

7. Here we have 18 patients in the UC group in follow-up week 12. The number was 17 in Table 2.

This was a mistake. The results of 18 subjects in the UC group were analysed on week 12.

Table 4
6. Give confidence intervals for the comparisons (difference of proportion, difference of means)

They have been inserted.

8. Absenteeism follow-up week 26: "2/99"??

This needs to be 2/9 and has been adapted.

Table 5
9. The table gives no information about the alternative hypothesis for which the power is computed. As explained above, a posteriori power calculations are not useful, but they become completely useless when the value of the parameter under the alternative hypothesis is not specified.

Table 5 has been omitted.

References

