Author's response to reviews

Title: Management of Headache Disorders: Design of a Randomized Clinical Trial Screening for Prognostic Patient Characteristics [NCT00298142]

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Authors reply to the reviewer’s report

Title: Management of Headache Disorders: Design of a Randomized Clinical Trial [NCT00298142]

Brussels, March 12th 2007

Dear editor,

Dear dr. Burdorf,

We thank you for your interest in our manuscript “Management of Headache Disorders: Design of a Randomized Clinical Trial [NCT00298142]” (MS: 6304477911224394)

We thank the reviewer for his critical and constructive remarks. We have read and analysed all remarks carefully. We provided additional information and modified the manuscript according to the reviewer’s comments were needed.

Our responses to the remarks are presented below: the reviewers remarks are each time cited in normal typewriting, our responses in italic. The page numbers and lines refer to the new version of the text.

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

Yours sincerely,

Willem De Hertogh
In general

We have the impression that the primary goal of the study, i.e. the search for prognostic patient characteristics, was not sufficiently emphasized and as a consequence the message was not fully transferred. In the revised version we therefore made the following adaptations:

- The title was changed into: Management of Headache Disorders: Design of a Randomized Clinical Trial Screening for Prognostic Patient Characteristics [NCT00298142]
- At the end of the introduction we reformulated the aims and research questions, emphasizing the primary and secondary goal.

Rationale for RCT

The rationale could be strengthened by included the systematic reviews from Cochrane, I identified at least one suitable review.

We agree with this remark and have included a recent Cochrane review (update begin 2007). We also included two recent references: a study by Lawler et al., describing the effect of massage therapy in the treatment of migraine patients [1] and a comment from Detar et al., on the study from van Ettekoven et al. [2, 3]. In this comment the importance of the article for general practice, neurology and physical rehabilitation is highly scored. See p. 4 line 16.

We believe these additions strengthen the rationale of the study.

Patients

Please specify whether the intervention is aimed at chronic/recurrent or subacute patients, the 2 months period is rather at odds with current definitions.

In the Headache Classification of the International Headache Society [4], the distinction between acute/subacute/chronic is not made in the same way as in musculoskeletal classifications.

In the IHS classification, the term subacute is not used for the description of headache types, but rather for the description of potential causes of secondary headache types, e.g. headache associated with subacute ocular inflammatory disorders, subacute encephalopathy or subacute haematomas.

A headache is labelled as chronic after an evolutionary process from an episodic headache to one with a more chronic pattern. Chronic does not only reflect the duration but also the frequency of the headache. This is for instance the case in chronic migraine and tension headache, who are labelled as such when subjects experience more than 15 headache days a month (frequency) since at least three months (duration).

For this trial we established our criteria in the line of those used in the study from Jull et al. [5]. They included subjects with a headache frequency of at least one per week over a period of 2 months to 10 years. We slightly adapted our criteria into headache since at least two months and at least twice a month. This to ensure the selection of patients with a substantial headache frequency and duration without focussing solely on the chronic (IHS) patients.

We will label our patients as having recurrent headaches, and have added this specification in the abstract (p 2 line 14) and in the text (p 7 line 11).
Intervention
Lacks a detailed description on how administered (2x/week, sessions of 20 min ?), what content (what is exercise therapy ?), etc. The section contains statements on effectiveness, literature etc that should be included in the introduction rather than the description of the intervention per se.

*We have included a more detailed description of the treatments that are administered (Starting p 12, line 23 to p 13 line 6). The information concerning the effectiveness is transferred to the introduction (p 4 line 14 to line 21).*

Outcomes
The GPE score is only mentioned at follow-up!

*In the methods section we make the subdivision in baseline and follow-up measurements. As the Global Perceived Effect can only be measured in the follow-up measurements it is located here. Therefore we believe this position in the text is justified.*

Randomization
Suddenly, one reads that a pre-stratification is being used, that was not taken into account in the power analysis. When this is an important prognostic factor, one can analyse its influence on effectiveness of the intervention, but this may require a larger sample size. When one is simply interested in adjusting for potentially confounding, then this pre-stratification is in general not a very good idea (may result in underestimation of the variance).

*We used the pre-stratification to avoid potential confounding of the factor ‘headache diagnosis’. It would be a minus point to allow the allocation of a larger proportion of subjects with symptoms of one particular headache type (e.g. migraine) to one treatment group. The pre-stratification ensures an equal distribution of subjects with the same diagnosis over the two treatment groups, and that both groups are matched for the factor ‘headache diagnosis’. If ‘headache diagnosis’ turns out to be a determining factor, the power will be re-analysed with the acquired sample.*

Blinding
A protocol needs explicit description of blinding procedures

*In the section ‘Study Design’ we have added the use of blinded assessment and unblinded treatment (p 6 line 16). Additionally we inserted the blinded assessment in the section of the ‘Baseline measurements’ (p 8 line 10,15 and 17) and in the ‘Follow-up measurements’ section (p 12 line 14 and 16).*

Prognostic study vs RCT
A prognostic study may be included in an RCT, but this will raise specific questions that need to be addressed:

- selective selection and participation

*One of the confounding factors for the inclusion of subjects is indeed treatment preferences of both participating doctors and patients, possibly resulting in selective*
selection of participants and participation of subjects. We tried to avoid this as much as possible by providing detailed information (personally) to both participating doctors and patients. In this way we tried to motivate them to participate and to reduce this selectivity to a minimum.

Using a randomised study protocol, can be a barrier for doctors or therapists to collaborate or to adhere to the treatment protocol. A non randomised study could be an alternative (longitudinal cohort study) with its limitations. An example for this rationale is the study from Pfeiffer et al. [6]. In case the total number of referred and included patients is too low, a cohort study can be considered as a next step. We have addressed this issue in the discussion (p 17, line 8 to 21).

- interference with intervention

As in any study, there is indeed a risk of additional therapies (e.g. self medication), interfering with the treatments which are prescribed in the study protocol. This is hard to avoid. Using the Headache Inventory List we can analyse the additional therapies that have been used in the last 4 weeks. This will enable us to map the use of additional therapies. If patients look for extra treatments or take extra medication, this is also a finding of the study which will be reported. We have added this in the 'Methods' section following the description of the Headache Inventory List (p 10 line 4-5).

- relevance of prognosis for effectiveness of intervention

    The aim of this trial is double: the primary aim is to look for prognostic patient characteristics. The secondary aim is to look for the effectiveness of each of the treatments.
    We have strengthened this statement at the end of the introduction (p6 line 6 to 13).

- sample size (e.g. 4 or 5 prognostic factors will easily need 100 subjects)

    Our sample size calculation resulted in 93 subjects in each treatment group, resulting in a total of 186 subjects. We have added the sample total in the text (p 14 line 19).

In general concerning the statistical analyses and power calculation:

    We analysed the manuscript from Steyerberg et al. [7]. In our analyses we will not start with a full regression model, but will include a priori two known prognostic factors, derived from the study from Jull and Stanton [8]. Those two factors are 'light-headedness' and 'joint pain on palpation'. Consequently we will use a backwards stepwise selection, including the two known factors in the smaller models. We will explore the possibilities of the adapted p-values (p > .05). The plausibility of the signs will be considered to check the logical contribution of the factor in the model.
    The power of the obtained models will be analysed via the area under the ROC-curve. In the new section 'Statistical analysis, power and sample size calculation', this information is provided (p 14 line 1 to 21).
Power analysis
The statement that a power analysis on a longitudinal study with dichotomous endpoints (i.e. logistic regression) cannot be conducted is a too crude remark. See eg Harrell et al Stat Med 1996;15:361-87 and Steyerberg et al Med Decis Making 2001:21:45-56.

See our general reply on the statistical analyses above.

Statistical analysis
A section should be included on the intended analyses, eg intention-to-treat vs per-protocol analysis?, Subgroup-analyses stratified by likelihood of good prognosis? How is dealt with differences in baseline characteristics? A priori inclusion of important prognostic factors in the effectiveness analysis?

At the end of the ‘Analyses’ section we inserted the following: The results of all subjects will be analysed, regardless of their treatment adherence (intention-to-treat analysis).

There is no information available concerning the likelihood of good prognosis. Information on important prognostic factors is scarce. We base this statement on the following: the effects of non-invasive physical treatments have been documented in various headache types (see background/ introduction) and we pre-stratified both groups to avoid confounding of the factor ‘headache diagnosis’. An analysis of the data from a headache trial performed by Jull et al. identified only two prognostic patient characteristics [9]. Therefore these two factors will be included a priori, followed by a backwards stepwise selection of factors (see above). Differences at baseline will be included in the regression models as potential prognostic factors.

These remarks were clarified in the section ‘Statistical analysis, power and sample size calculation’ (p 14 line 1 to 21).

REFERENCES

2. Detar DT, Chessman AW: Physiotherapy plus a craniocervical training programme was better than physiotherapy alone in tension type headache. Evid Based Med 2007, 12:14.
