Author's response to reviews

Title: Homeopathic Treatment of Elderly Patients - A Prospective Observational Study with Follow-Up over a two year period

Authors:

Michael Teut (michael.teut@charite.de)
Rainer Luedtke (r.luedtke@carstens-stiftung.de)
Katharina Schnabel (sumimar@web.de)
Stefan N Willich (stefan.willich@charite.de)
Claudia M Witt (claudia.witt@charite.de)

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Author's response to reviews: see over
Response to Reviewers

Dear Editor,

Attached please find the revised manuscript and our reply to the reviewers’ comments. In one file, we have highlighted the changes made to the manuscript, in the other file we have not.

We’re very grateful for the thorough review process, which was extremely helpful and has improved the quality of the manuscript.

We have to apologize because we found an error in our calculation. We re-analysed our data on the reduction of conventional medication and found a different result as reported in our first version. Patients don’t reduce their conventional medication. This error occurred because we analyzed the wrong item (medication reported by the homeopath instead medication reported by the patient). In the revised version we corrected this information (results and discussion) and deleted the discussion about the reduction in drug use.

The manuscript and its contents have not been published and are not under consideration for publication elsewhere. We do not have any conflict of interest.

We hope that our revised version is now suitable for publication.

Thank you very much for your time and consideration.

Sincerely
Michael Teut

Authors General remark to Reviewers:
We have to apologize because we found an error in our calculation. We re-analysed our data on the reduction of conventional medication and found a different result as reported in our first version. Patients don’t reduce their conventional medication. This error occurred because we analyzed the wrong item (medication reported by the homeopath instead medication reported by the patient). In the revised version we corrected this information (results and discussion) and deleted the discussion about the reduction in drug use.
Reviewer:
The data from this sub-set of patients are a novel and useful addition to the evidence base in homeopathy. The conclusions are suitably cautious and encourage new research. However, a number of concerns need to be addressed; these are all in the category "Minor Essential Revisions":

Introduction:
It is not clear what “annual expenditures” refers to precisely.

Authors:
This term has been deleted, because the whole paragraph does not fit in the revised version.

Reviewer:
Methods:
· Explain the interpretation of “maximum severity”. Does it mean the most severe the patient has ever felt, or the most severe he/she has ever experienced (with a given condition)?

Authors:
This has now been clarified (see page 4, line 103-104).

Reviewer:
Clarify that the physicians’ NRS also has the range 0–10.

Authors:
This has now been clarified (see page 4, line 110-121).

Reviewer:
· Statistics: It should be stated how many patients who died during the study did so as a result of the medical condition that had been treated with homeopathy: it would put the automatic scores of 10 in better context.

Authors:
In total, 9 patients died during follow-up. Mean survival time was 376 days (range 6 to 725 days). We added a respective sentence to the results section (see page 6, line 191-192). We do not have access to data in which the causes for deaths of our patients were documented by the physicians that diagnosed death.

Reviewer:
Results:
· The sentence “Patients received on average 6.1 +/- 5.3 homeopathic prescriptions” is unclear: is this different remedies and/or per main medical condition and (presumably) per person?
Authors:
Each patient received on average 6.1±5.3 homeopathic remedies which where not necessarily different. Placebo treatments were not counted. This has now been clarified (see page 6, line 196).

Reviewer:
· Not sure if Figure 1 is necessary; the facts would be clear enough presented in a suitable sentence.

Authors:
We would like to leave figure 1 in the paper, because it gives a clear idea that a small number of remedies count for nearly half of the prescriptions.

Reviewer:
· Are there data for conventional medication prescriptions at 3 and 12 months?

Authors:
We reanalysed our data and report now corrected data about the real medication use of patients (see page 6, line 202-203). See also initial general statement.

Reviewer:
There seems no statistical authority for the final sentence (“The SF-36...scale slightly improved at 3 and 12 months...”). Also, it is not the scale itself that may have changed in any way.

Authors:
This has been changed to ‘Overall the quality of life remained stable within the 24 months observation period’. (see page 6, line 208-213).

Reviewer:
Discussion:
· There needs to be some discussion of regression to the mean and the effect (if any) that the various statistical manipulations may have had on the data and their interpretation.

Authors:
We added information about regression to the mean (see page 5, line 163-171; page 6, line 210-213; reference 16 and 17; ).

Reviewer:
· The sentence, “...cannot be attributed to homeopathic treatment alone” should be reworded to avoid the use of the word “alone”. It will be argued by some readers that the findings cannot be attributed to homeopathic treatment at all.

Authors:
We reworded the text (page 7, 236-242).

Reviewer:
· Given the comparison between various outcome studies and the chronology of patient-reported clinical change, it might be useful to cite the work from the UK

Authors:
This reference has now been included (ref. 20).

Reviewer:
· The exact meaning of the phrase, “…but the effect was not very strong” is not clear.

Authors:
This sentence has been deleted.

Reviewer:
Abstract: Error values should be defined as SD on the first occasion.

Authors:
This has now been clarified.

Reviewer:
Tab 2: The word “Ischialgie” does not exist in English. The appropriate term might be “Sciatica”, but this should be double-checked.

Authors:
We have checked this and it has been changed as suggested (see table 2)

Reviewer:
Tab 3: In the footnote, “0 = cured” does not reconcile with the description in Methods.

Authors:
This has now been changed.

Reviewer:
Fig 2: Use linear scale on time axis.

Authors:
This has now been changed.

Reviewer:
Grammatical points:
· Title would be better phrased as “…study with follow-up over…”.

Authors:
This has been changed as suggested.

Reviewer:
· In Methods/Treatments (second sentence), delete redundant “also”; (last line,
penultimate paragraph), “adult’s” should be “adults’”.

**Authors:**
This has been done.

**Reviewer:**
· In Discussion (fourth paragraph), “Our data shows…” should be “Our data show…”.

**Authors:**
This has been changed as suggested.

**Reviewer:**
· “Author’s Contributions” should be “Authors’ Contributions”.

**Authors:**
This has been changed as suggested.

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**Reply to Reviewer 2**

**Version:** 2  **Date:** 17 August 2009  
**Reviewer:** Vinjar Fonnesbo

**Reviewer’s report:**

**Reviewer:**
**ABSTRACT:**
Major Compulsory Revisions:
1. The purpose of the study needs to be given identically in the abstract and introduction. This must be corrected.

**Authors:**
The purpose of the study is now given identically in the abstract and introduction (see page 2, line 19-21; page 3, line 66-72).

**Reviewer:**
2. Only the abstract gives the geographical location of the study. This also needs to be given in the methods section.

**Authors:**
This information has been added (see page 3, line 75-76).

**Reviewer:**
3. The abstract indicates that the physicians assessed the complaints of the patients. This is contradictory to the main text which indicates that the physicians only assessed their diagnosis.

**Authors:**
The physicians assess the severity of the diagnoses and the patients the severity of the complaints which they reported at baseline. This has now been clarified (see page 4, line 102-104 and line 119-121).

Reviewer:  
INTRODUCTION  
Major Compulsory Revisions:  
1. The last two sentences (lines 61-65) should be moved to the materials section.

Authors:  
This has been changed as suggested, although in most papers the aim of a study is described at the end of the introduction.

Reviewer:  
MATERIAL AND METHODS  
Major Compulsory Revisions:  
1. The authors need to describe how the participating physicians were recruited. From a register? A convenience sample? How many were approached, and how high a proportion agreed to participate?

Authors:  
This has been reported in the paper on the whole cohort. The most relevant information has now been added to this paper and the reference is given. (see page 3, line 75-82, ref. 10).

Reviewer:  
2. The authors need to describe here in what setting the physicians were working. This is now presented first in the results section.

Authors:  
We explain this now more in detail see page 3, line 83-88).

Reviewer:  
3. In the methods section it is indicated that the physicians were required to have "certified training in classical homeopathy". The authors need to indicate whether their practice also followed the principles of classical homeopathy.

Authors:  
This has now been clarified (see page 3, line 84-85).

Reviewer:  
4. The authors need to indicate whether some patients declined to participate in the study when approached.

Authors:  
We added the reference to the main study in which the selection process is described in detail (see page 3, line 80-82).

Reviewer:  
5. "Consecutively" recruited could be interpreted as a 100% participation rate on behalf of the patients. Is this the case?
Authors:
Consecutively means that all patients were asked to participate without the selection by the Physician, but only those patients could be included who gave written informed consent. We had a participation rate of 68% for the total cohort. This information and the reference have now been added (page 3, line 75-82).

Reviewer:
6. The authors indicate that the SF36 results are presented "in normalised scores". I can not see that in table 3, only the changes seem to be presented in both actual and normalised scores. This needs to be clarified.

Authors:
In contrast to our statements in the methods sections, the results in table 3 were not given as normalised scores with a mean of 0 and a standard deviation of 1, but with a mean of 50 and a standard deviation of 10. We corrected this and apologize for this mistake.

Reviewer:
7. The authors state that the questionnaires were distributed by the study physicians. Is this the physician that treated them, or is the study physician a separate person? Needs to be clarified.

Authors:
It is the physician that also treats the patient. This has now been clarified (see page 4, line 113-114).

Reviewer:
8. The baseline questionnaire was completed "prior to the start of therapy". How did the researchers ensure that the envelopes were sealed and sent before the patient saw the physician that treated them?

Authors:
We did our best to ensure high quality. The physicians and their nurses were trained in the in the process and a monitor visited the practice to check the process during the study. In addition we had dates on both the patient’s questionnaire and the physician’s documentation. However, there is no 100% guarantee.

Reviewer:
9. In the statistics section the authors should indicated that the 5 multiple imputed data tables relate to each participant (if that is the case).

Authors:
the respective section has been rephrased and we now clarify that the complete data tables are related to all patients (page 5, line140-141).

Reviewer:
10. In the statistics section the authors indicate that subgroup analyses were performed. This can not be found in the results section. This needs to be clarified or omitted.

Authors:
Our analysis was a subgroup analysis of a larger study, but no additional subgroup analyses were performed. Thus we omitted the respective sentence referring to subgroup analyses (see page 2, line 23-26.; page 3, line 70-72).

Reviewer:
11. The authors are writing about pooling of children's data. This study does not include children and this should be rectified.

Authors:
This was true for the total cohort, but not for this subgroup. This information has been deleted.

Reviewer:
12. The authors explain extensively how they are dealing regression-to-the-mean issues. I can not see that any results are presented in this area. This should also be rectified.

Authors:
We added two sentences to the end of the results sections which described the results of the regression-to-the-mean analyses (see page 6, line 210-213).

Reviewer:
RESULTS
Major Compulsory Revisions:
1. The second paragraph of the results describes the diagnoses made by the physician. The last sentence indicates that the patient's complaints are listed in table 2. But table 2 also only gives diagnoses. These needs to be clarified.

Authors:
This has now been clarified (table 2).

Reviewer:
2. The results indicate that the patients received on average 6.1 homeopathic prescriptions. The authors need to inform us whether some of these were given simultaneously (violating the classical homeopathy principle).

Authors:
They were not given at the same time. This has now been clarified (see page 6, line 197).

Reviewer:
3. The result text indicates that table 3 describes complaint severity (patient perspective) while the table describes diagnoses (physician perspective). Did the patients also rate the physician-generated diagnosis? This confusion needs to be rectified.

Authors:
This has now been clarified (table 3: page 4, line 102-104; page 4, line 119-121).

Reviewer:
4. Table 3 includes 40 statistical tests (possibly with 12 twin tests). Why are the
Authors using a 95% confidence interval in this situation with multiple testing?

**Authors:**
The reviewer is right, there were 28 different confidence intervals or p-values. Our results therefore might be severely affected by a multiple testing problem. As this was not a confirmative trial trying to assess the effectiveness of homeopathy in elderly but rather to provide reliable data on what is going on, we decided not to report adjusted p-values or confidence intervals. All results from our statistical models should only be interpreted descriptively (exploratory), and from our point of view adjustments for multiple testing seem to be too exaggerated for this situation. We clarified this and added a note to table 3, saying that “p-values and 95% confidence intervals could be affected by multiple testing”

**Reviewer:**
**DISCUSSION**
**Major Compulsory Revisions:**
1. The discussion needs to be reorganized in the following sections: A. Brief recap of results, B. Bias considerations, C. Comparison with previous research, D. Implications, and possibly a conclusion.

**Authors:**
The structure of our discussion has been improved as suggested.

**Reviewer:**
2. Bias considerations (both selection and information) are almost non-existent. This needs to be covered appropriately.

**Authors:**
This has now been discussed (see page 7, line 236-247).

**Reviewer:**
3. One major topic that needs to be covered is relating the findings to studies from conventional medicine on how complaints develop after conventional treatment alone at the GP office.

**Authors:**
To our knowledge there are no comparable studies from conventional medicine.

**Reviewer:**
**TABLES/FIGURES**
**Major Compulsory Revisions:**
1. In table 1 the authors need to indicate how the last 2.7% of participants are living.

**Authors:**
These are patients living together with relatives or friends for example. We do not consider it necessary to specify.

**Reviewer:**
2. In table disease severity is given. They need to clarify that this is physician-evaluated (Am I right in assuming this?)
Authors:
This has now been clarified (table 2).

Reviewer:
3. The legend to figure 1 needs to be corrected to indicate that it only relates to the study population. The legends to the other tables and figures also need to be flushed out so they are self-explanatory.

Authors:
This has been now clarified (see tables, figures).

Response to Reviewer 3: Dr Peter Fisher

Reviewer:
This a useful article, part of a series published by this group. I strongly recommend publication subject to some minor revisions, one of which is important.
Minor essential: I could find no mention of how many patients withdrew, were lost to follow up or died. This is strange since a full explanation of how such data was handled is given! These data must be included.

Authors:
This has been clarified (see page 6, line 191-195).

Reviewer:
Minor Discretionary: The study was uncontrolled and perhaps a fuller acknowledgement of the limitations of the method should be given.
Nevertheless the significant improvements and, particularly, the reduction in medication is impressive. It would be helpful to have more detail on medication reduction: presumably it was statistical significant? It would also be useful to have more detail (perhaps in another pie chart) of the classes of medication that were reduced. I would guess that hypnotics or migraine medication is more like to reduced than anti-hypertensive medication.

Authors:
We have to apologize because we found an error in our calculation. We re-analysed our data on the reduction of conventional medication and found a different result as reported in our first version. Patients don’t reduce their conventional medication. This error occurred because we analyzed the wrong item (medication reported by the homeopath instead medication reported by the patient). In the revised version we corrected this information (results and discussion) and deleted the discussion about the reduction in drug use.

However we highlighted the limitations of the study design (see conclusion and discussion section)