Author's response to reviews

Title: Enhancing activities of daily living of chronic stroke patients in primary health care by modified Constraint Induced Movement Therapy (HOMECIMT): study protocol for a cluster randomised-controlled trial

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Author's response to reviews: see over
Dear Editors and Professors,

thank you very much for your detailed reviews. We appreciate your profound reading of our study protocol and would like to thank you for your valuable comments. Please find enclosed our answers to your questions and comments. You will find our changed text passages highlighted yellow. Moreover, we asked another native speaker to correct the manuscript again. The resulting linguistic changes are coloured and underlined. We hope that we answered all your questions satisfactorily and hope that our manuscript is now suitable for acceptance.

Sincerely yours

Anne Barzel for the authors team
Reviewer 1: Peter Sandercock

Home CIMT Major Compulsory Revisions

1. In the section ‘Novel aspects of HOMECIMT it states: ‘CIMT is a therapy shown to be effective in the treatment of stroke patients largely independent of 3 time post stroke’ and three references are cited [8, 9, 10]. However, the 2009 Cochrane review of the topic identified We 19 studies involving 619 participants and was able to include data from six trials (184 patients). They concluded ‘CIMT ... is associated with a moderate reduction in disability assessed at the end of the treatment period. However, for disability measured some months after the end of treatment, there was no evidence of persisting benefit. Further randomised trials, with larger sample sizes and longer follow up, are justified.’ The background section should include a reference to this paper, and the authors should search the literature for published reports of CIMT that have appeared since that review, to provide a more comprehensive background to the HOMECIMT study. To my knowledge, the field is moving rapidly.

Response:
You are right, the field of CIMT is moving rapidly. Since the planning of our trial in 2009, you’ll find no less than 106 hits (including 27 reviews) under the search terms 'stroke' and 'constraint induced movement therapy', with exclusion of trials concerning children. Restricting the search to our modified CIMT approach, we found 4 reviews, one of which is the Cochrane Review you mentioned. In the background section we only cite the three central papers published concerning the original CIMT and do not claim completeness at this point as the discussion of the various approaches might be beyond the scope of the background chapter of a study protocol. But you are right we should refer to the reviews, at least to the recommendations they provide for further trials.

We included the references of the reviews and added the following passage (page 5, line 4ff):

“However, in this regard the literature is inconclusive. A Cochrane review [12] and its update [13] found no evidence of persisting benefit on the outcome disability, while a more recent review [14], which focuses on the effect of CIMT and modified CIMT on activity and participation, describes evidence on hand mobility. Both reviews recommend further randomised trials with larger sample sizes, relevant measures and a sufficient follow up. Therefore HOMECIMT aims to address these requests in the conception of the trial.”

2. The Cochrane review ends with some comments on the ‘implications for research of the completed trials’, and the authors should mention how their trial addresses these points:
It is likely that additional trials investigating CIMT as a rehabilitation technique would be worthwhile if they: consider disability or arm motor function as the primary outcomes; include a validated quality of life measure as one of the outcomes; recruit a larger sample (minimum of 74 participants for arm motor function measures); involve a control group under active treatment, since CIMT involves a certain amount of exercise; explore benefits for longer follow-up periods (one year); and include all randomised patients in their analyses.

Response:
Thank you for this comment. We actually considered the recommendations of Sirtori and colleagues during our trial planning as far as possible. With the added text on page 5, line 4ff. (see above, our answer on your comment No.1) this should become more clear. To our knowledge, all of these points are described under methods and design at the corresponding points:

… consider disability or arm motor function as the primary outcomes;
Arm motor function is one of the primary outcomes in our trial.
… include a validated quality of life measure as one of the outcomes;
We chose the Stroke Impact Scale (SIS), which focuses on stroke-related quality of life and is validated as a stroke specific measurement.

… recruit a larger sample (minimum of 74 participants for arm motor function measures);
The calculated sample size of 144 patients (72 per group) lies in the recommended range.

… involve a control group under active treatment, since CIMT involves a certain amount of exercise;
The control group patients receive active treatment and the same amount of therapy as the intervention group patients.

… explore benefits for longer follow-up periods (one year);
We chose the maximum follow-up interval allowed by the 3-year funding period of the study.

… include all randomised patients in their analyses.
We will include all randomised patients in the analysis, which will be based on the ITT population.

3. In the sample size calculation, the source of the parameter estimates (e.g. intraclass correlation coefficient is given, but it is not clear that the source data will be appropriate for the population to be studied (i.e. are the patient characteristics in the cited studies similar to the planned study population comparable). Some more detail on the justification for the sample size estimates would be helpful.

Response:
The study is powered for the detection of an intervention effect of the same size as considered a minimal clinically important improvement [20]. As we did not have a pilot study to estimate the intra-cluster correlation (ICC), we assumed a moderate ICC of 0.05 (Eldridge SM, et al: Lessons for cluster randomized trials in the twenty-first century: a systematic review of trials in primary care. Clin Trials 2004, 1:80-90) because, on the one hand, we will recruit only three patients (on average) per practice, while on the other hand, the intervention aims at the patient's level. Thus, we expect the inter-practice variance will be low in comparison to the intra-practice variance, which leads to a relatively small design effect (Kerry SM, Bland JM: Trials which randomize practices II: sample size. Fam Pract 1998, 15:84-87).

4. The data analysis section sets out the overall plan. Please state if a more detailed analysis plan be prepared and finalised before the code is broken and the main analyses performed?

Response:
Thank you for this helpful advice. We complemented this point in the manuscript on page 12, line 23: “A detailed statistical analysis plan will be prepared and finalised before the code is broken.”

5. The acceptance of 15% loss to follow-up is very surprising. The CONSORT statement expects all randomised subjects to be accounted for at the end of the trial. The authors should clarify what they mean by ‘loss to follow-up’. At the very least, the vital status (dead/alive) at 6 months should be known for all participants. The strategies to maintain retention of the subjects on follow-up and methods to trace those not attending follow-up should be stated.

Response:
Actually, 15% loss to follow-up was a very conservative assumption and above what we have seen in other trials. We re-discussed this point and noticed that the sample size increase for loss-to-follow-up was not required since we intended to use ‘last observation carried forward’. In this case conservative imputation will allow an intention-to-treat analysis, as we now mention in the statistical analysis section. We added the following sentence on page 13, line 3ff:
“In case of missing follow-up values, a last-observation carried forward (LOCF) imputation will be performed, i.e. the baseline determination will be imputed as follow-up determination.”

Thus, we corrected the sample size calculation, but decided to recruit more practices than calculated, since we do not expect every recruited practice to actually part-take in the study, but we can't be sure until the study is running. Vital status will be complete anyway as an easy access by registry office data is possible in Germany.

To outline our strategies to maintain participants in the study, we added the following sentence at the bottom on the section “recruitment of practices and patients” (page 9, line 11f):

“To maintain participants in the study we provide good accessibility (telephone hotline, E-mail and fax) to the study personnel, who respond to any questions and emerging issues during the study period.”

6. Recruitment. It would be helpful to have some indication of the source of referrals to the study, and how patients were invited to join.

Response:
To point out the recruitment process in more detail, we revised the following passage (page 9, lines 1 to 7):

“The referrals to the study follow two steps to allow all eligible patients access to the study. In a first step active practices willing to participate are asked to create a list of all stroke patients currently in treatment (incident and prevalent cases, regardless to prior treatment and duration of therapy). To identify all potentially eligible patients, the inclusion and exclusion criteria (see below) of each listed patient are discussed with study personnel. All patients meeting the inclusion criteria obtain written study information from their therapists and are asked to meet study personnel for more information about the study and to obtain informed consent (second step).”

If a patient is unable to write because of their stroke, how will consent be obtained?
Response:
In case patients are unable to write with the stroke affected hand (usually the dominant hand) they will be advised to use the other hand.

7. How will the recruitment of patients to the study be securely recorded? In a trial where individual patients are randomised via a central office or computer system, the system records the moment the patient is recruited, and retains sufficient identifiers that the patient can then be traced even if the participating clinician does not return data forms. It would be helpful to have more details of the process of recording the recruitment of individual patients.

Response:
Please find more details on the recording of the recruitment process on page 9, lines 8 to 11. We added the following sentences:

“The study centre records the recruitment process for each therapy practice including the name of the study personnel, the date and the result of the patient visit (enrolment yes or no). Document and data completeness are checked by a second person of the study personnel, who also ensure that all data forms will return to the study centre.”

8. Some details on the trial oversight arrangements should be included: is there a trial steering committee?, is there a data and safety monitoring committee (I presume not, but that should be stated)?

Response:
Thank you for this question. We added information on trial monitoring on page 16, line 13ff:
"Quality control and quality assurance
The Data Management Center (DMC) is at the University Medical Center Hamburg-Eppendorf. A trial steering committee composed of the principal investigator, experts in the field of CIMT and the DMC is responsible for all decisions concerning the conduct of the study. The trial's study team (Department of Primary Medical Care, University Medical Center Hamburg-Eppendorf) will be responsible for monitoring the trial. Study employees will regularly contact the trial sites (therapists and assessors), to ensure that the rights of the trial participants are protected, the study data is documented correctly and completely, and that the trial is conducted in accordance with the study protocol and complies with GCP and legal requirements at the trial site. A Scientific Advisory Board supports the study management in scientific questions concerning study design, implementation and evaluation."

9. Reporting of results. The CONSORT statement would expect the results to be presented in the context of a systematic review of the existing RCT evidence; a mention of whether this is planned in the protocol would be of interest.

Response:
We will discuss our results in the context of current scientific literature. On page 18, line 14/15 we added the following sentence:
„According to the CONSORT statement, the results of this trial will be presented in the context of a systematic review of the existing RCT evidence."

Discretionary revisions.
In places, the English is rather awkward, e.g. 'An explicit participation-oriented therapy concept is lacking' and other places it is rather technical and difficult for the non-expert reader. If possible, a review of the writing by a native English speaker would be helpful.

Response:
Although a native speaker checked the manuscript before submission, we apologize for any inconvenience due to our poor English expression. Another native speaker has corrected the revised manuscript again.

Reviewer 2: Sandra Eldridge

Major compulsory revisions
1. I found the explanation of the underlying rationale for this trial confusing, however, and the discussion of the choice of outcomes. The discussion about the primary outcome seemed to suggest that participation was a desired outcome, but the background and the abstract seem to be suggesting that participation is a therapeutic approach. I think the background, the background section in the abstract, and the primary outcome section need rewriting to make it clear how participation is being viewed, and certainly the sentence that begins "Participation, defined as..." should be rewritten as this definition is confusing and the sentence was very unclear to me.

Response:
Thank you for your advice.
In our opinion participation is the goal of the therapy, but not the therapeutic concept itself. We wanted to point out that some therapy concepts seem to support patients better in the attainment of participation than others. In our study we hypothesize that CIMT leads to an increased arm usage in activities of daily living and thereby a pre-requisite of participation can be achieved.
As you suggested, we revised all passages dealing with the definition of participation in the three sections: the background, the background section in the abstract, and the primary outcome section.
Please find below the results:
The background section in the abstract
You mention that the definition "Participation, defined as involvement in a life situation (WHO 2001) [1], is a major therapeutic target, particularly in the long-term care of stroke patients" is confusing. These words are actually part of the official ICF definition of participation as stated by the WHO ("In the context of health, participation is involvement in a life situation. Participation restrictions are problems an individual may experience in involvement in life situations") on which we built our theoretical framework.

The citation may have been too short and our formulation unfavourable. We now revised the passage as follows (please see page 2, line 5ff):

"Stroke is the most common cause of lifelong disability in adults and leads to constant rehabilitation needs even in the chronic stage. Participation is a major therapeutic target in the long-term care of stroke patients. In the context of health, participation is defined as involvement in a life situation and is related to the execution of a task or action (activity) [1]. But, although many stroke patients receive physical therapy or occupational therapy in primary health care, treatment prescriptions generally do not specify the therapeutic goal, and particularly participation, has not yet been established as an explicit therapeutic goal in the ambulatory setting. Thus, the primary aim of this study is to evaluate the efficacy of a therapy regimen for chronic stroke patients ("CIMT at home") with impaired hand or arm function with regard to the pre-requisites of participation in everyday activities: a sufficient arm and hand function. "CIMT at home" will be compared to "Therapy as usual" (i.e. conventional physical and occupational therapy)."

The Background, page 4, line 8ff
Correspondingly, since 2001 in Germany, rehabilitation services are required by law to prioritise participation as a treatment goal, rather than merely providing social care (SGB IX,§8). Despite this, many stroke patients who receive physical therapy or occupational therapy in primary health care are provided with therapy-prescriptions that specify neither the appropriate therapeutic approach nor the therapeutic goal. So far, there are no therapy concepts concentrating solely on enhancing the patients' participation. Recent developments in treatment, such as Arm Ability Training, Constraint Induced Movement Therapy and Robot-Assisted Arm Rehabilitation, focus on the improvement of activities of daily living as pre-requisites of participation. These concepts are recommended by guidelines [6] since they have shown evidence of good therapeutic results [7] in terms of motor function improvements and effects on the dexterity of the affected arm, as well as a clinically relevant effect on the usage amount of the affected arm during activities of daily living. Whereas these therapies are now increasingly being used in (in-patient) rehabilitation, they have not yet been established in ambulatory care (e.g. outpatient physical and occupational therapy) and are not listed in the German catalogue of care interventions and modalities ("Heilmittelkatalog") [8]. In testing the Constraint Induced Movement Therapy (CIMT) in an ambulatory setting, this project provides a contribution towards an explicit participation-oriented approach to treating stroke patients in ambulatory care."

The primary outcome section, page 7, line 3-7
In this section we changed nothing, because we adjusted the statement in all other passages accordingly.

"The primary objective of this study is to evaluate the efficacy of a modified approach of Constraint Induced Movement Therapy ("CIMT at home") for chronic stroke patients with impaired hand or arm function, compared to conventional physiotherapy and occupational therapy ("Therapy as usual") with regard to the pre-requisites of participation in everyday activities: a sufficient arm and hand function."

2. In the sample size calculation I don't think the last sentence, which says the study aims to include 180 patients and 130 practices is correct - surely it is 60 practices?
Response:
Thanks for this comment, we've corrected it.

Also I could not replicate the sample size calculation exactly and think the authors should check this. If I have understood correctly, a standardised effect size of 0.5 requires 63 in each group without adjusting for clustering and the design effect with a cluster size of 3 and ICC 0.05 is 1.1. This does not result in 75 individuals being required in each group?

Response:
We did the sample size calculation with PASS 2008. As we now noticed, PASS 2008 does not calculate the sample size as it results by direct calculation using the design effect, due to rounding effects. We performed a new sample size calculation also to react on your next commentary (please see page 8, line 2ff).

"The sample size was calculated for the two primary outcomes (Motor Activity Log - Quality of Movement; MAL-QOM and Wolf Motor Function Test - Performance time; WMFT-PT). For the first primary endpoint (MAL-QOM) an effect size of 0.5 was pursued based on the reported minimal clinically important improvement of 0.50 on a scale from 0 to 5 [20]. With a power of 80% and an alpha-error probability of 5% 2 x 64 patients need to be included if the randomisation occurs on patient level. With an assumed intra-cluster correlation of 0.05 and 3 included patients per cluster, a design effect of 1.1 results was calculated increasing the sample size to 72 patients and 24 practices per group.

For the second primary endpoint (WMFT-PT) an effect size of 0.55 was calculated based on the minimal clinically important improvement of 0.60 on the logarithmic performance-time scale [21]. With identical alpha and beta design effect, a sample size of 63 patients and 21 practices per group was calculated. Since the first co-primary endpoint requires a larger sample size, the sample size was chosen accordingly. We decided to approach 60 practices for participation in the study, expecting at least 48 to actually take part in the study, which allows us to demonstrate effect sizes of 0.49 and greater for the second primary endpoint."

3. I am surprised that in the sample size calculation drop out was only allowed for at cluster level. This should be explained.

Response:
Since we will analyse the data according to the intention-to-treat principle with imputation of missing values by last-observation-carried-forward as a conservative approach, we did not provide missing values on patient level. However, we expect some of the recruited practices not to start recruiting as they promised. To cope with this problem we will overrecruit practices.

The procedures are now described in the section 'sample size' (page 8, line 14ff):
"We decided to approach 60 practices for participation in the study expecting at least 48 practices to actually take part in the study, which allows us to demonstrate effect sizes of 0.49 and greater for the second primary endpoint."

and in the section 'data analysis' (please see page 13, line 3ff):
"In case of missing follow-up values, a last-observation carried forward (LOCF) imputation will be performed, i.e. the baseline determination will be imputed as follow-up determination."

4. The inclusion criteria are clear but it would be helpful to specify who makes the judgement about inclusion - I am presuming it is the therapist? Is there any danger that later in the process the research team judge a patient ineligible? There should be some explanation about this, particularly as patients are recruited before randomisation but presumably do not have the intervention until after. Circumstances may change.
Response:
Thank you for this important advice. To avoid a (uncontrolled) selection bias of therapists, each patient is seen by study personnel prior to enrolment. At that time, the patients’ eligibility is judged. The randomisation of the therapy practices is done as soon as study personnel have seen all patients in the recruitment region. As also requested by reviewer 1, we have now described the recruitment process in more detail. Please see our answers to his comments 6 and 7 or in the manuscript on page 9, lines 1-13. We hope the added explanation provides a better understanding of this point.

5. The authors should explain how attempts are made to keep assessors blinded since it would be possible to become unblinded during home visits.

Response:
We added the following explanation on page 11, line 8ff:
“The assessors are blinded to the patients’ group affiliation. They have no access to study computers and documents and are not involved in any other study aspects except for the data collection in the patients’ homes. To keep assessors blinded, patients and non-professional coaches are prompted to give no information to the assessors, neither about their treatment nor about other experiences from participating in the study.”

6. I think the decision about the co-primary outcomes should be reconsidered, especially given the stated strategy of analysing them in sequence. This is unusual and does not seem justified. I would suggest it would be much easier to use a single primary outcome.

Response:
We agree that it would be much easier to use a single primary outcome. In fact, we discussed the issue primary outcome(s) thoroughly, and we would like to explain in detail below.

During the study planning we were looking for any primary outcome measures linkable to the activity and participation components of the International Classification of Functioning, Disability and Health (ICF) to depict activities of daily living as pre-requisites of “participation” as best as possible. However, the Motor Activity Log (MAL) and the Wolf Motor Function Test (WMFT) (both of which belong to the (ICF)-defined activity and participation measures), are two of the most common measures in other CIMT trials. We considered these as the best possible approach at the time of our study planning and decided to test the two primary endpoints (the MAL and the WMFT) as pre-described in the protocol of the EXCITE trial (Winstein et al 2003*), known as one of the high quality trials on the topic CIMT. In fact, the recent review on CIMT and modified CIMT (Peurala et al 2012**) states that the MAL and the WMFT are two of the most commonly used measurements in CIMT trials: “Altogether, 27 different outcome measures were reported (Appendix 3 on-line shows all activity and participation outcomes used). The most common measures were the Motor Activity Log, Action Research Arm Test and Wolf Motor Function Test.”
All in all, we discussed this point again extensively and would like to keep the chosen approach with the co-primary outcomes. We will discuss this point in the main report of the study results.


7. While there may be none anticipated, the authors should discuss potential unintended harms.

Response:
Thank you for this important advice. Please find the additional text below. In the manuscript, we placed this section under the newly added sub-heading "Monitoring of potential unintended harms and adverse events", page 16, line 5ff.

“During study participation hospitalizations and severe diseases will be documented as well as any adverse events. Regarding the therapy, no specific adverse events are expected, since the indication for physiotherapy or occupational therapy is mandatory for all study participants. Nevertheless, potential unintended harms may include falls, frailty, severe depression, and patients of the intervention group may perceive some of the CIMT specific conditions (e.g. the daily exercise program or the wearing of special glove) as stressful. Thus all study participants (the patients, non-professional coaches, therapists and assessors) will be encouraged to report any events. Feedback as well as events will be documented and evaluated at the end of the study.”

8. Is this an efficacy or an effectiveness trial? The authors state they want to evaluate efficacy but without a tightly controlled control group intervention I am not sure how this is possible?

Response:
HOMECIMT has characteristics of both study types. With respect to the control group the study type is not clear. On one side, together with therapists working in the ambulatory care of stroke patients, we aligned the study as best as possible concerning the ambulatory conditions to ensure the feasibility of the trial. At the same time we tried to standardize the procedures as much as possible. We also considered whether or not we should allow only one specific therapy in the control group, e.g. Bobath. However, being familiar with physical and occupational therapy, we are aware that Bobath therapy and Bobath therapy are not necessarily the same depending on the therapist. Thus, we preferred to let the therapist conduct and document their "usual" therapy, which allows us to describe the therapy actually performed. Altogether, the choice of the control seems to move the trial nearer to effectiveness. Since the choice of the control group is the only characteristic of the trial drifting towards effectiveness, the trial should possibly be characterized as an efficacy trial with a "Therapy as usual" control group.

Minor essential revisions

9. The study should be described as a 'parallel' cluster randomised trial, rather than 'prospective'.

Response: We followed your suggestion.

10. Remove the words "(at least one patient)" from line 12, page 9. These seem superfluous and do not help the reader.

Response: We agree and removed the above-mentioned words.

Discretionary Revisions

11. page 8 - recruitment section - More detail could be added about how the areas in northern Germany were selected; this is not clear.

Response:
We describe the recruitment process in more detail to clarify this point (page 8, line 18ff)
All physical and occupational therapy practices (TP) treating stroke patients are eligible to participate in the study. Because the study centre is located in Hamburg, recruitment is performed consecutively in selected areas of northern Germany that are sufficiently accessible for the study personal from Hamburg as well as for local therapy practices. Based on community numbers (geographical recruitment) we formed an area of eight related regions, each within 50 kilometres of a city. All TP with known addresses are invited to an information meeting nearby.

12. At the bottom of page 15, I did not understand the phrase “randomisation is performed regionally” since this seems slightly at odds with the earlier description of randomisation.

Response:
Since the recruitment is performed consecutively per region the randomisation is conducted per region as well. We now state that point more precisely under the issue “Randomisation” on page 9, line 15 ff:

“Therapy practices are randomly allocated to either "CIMT at home" or "Therapy as usual" in a 1:1 ratio stratified by region."

Additionally, we specified the sentence concerning randomisation under the issue “Study Timeframe” on page 17, line 12f:
“The central randomisation is stratified by region as soon as all patients of the region are included.”

In context with the now in more detail described recruitment process (see our answer to your comment No. 11 above resp. page 8, line 18 ff), we think that this point should be better understandable.