Author's response to reviews

Title: Evaluation of the effectiveness of manual chest physiotherapy techniques on quality of life at six months post exacerbation of COPD (MATREX): a randomised controlled equivalence trial

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Author's response to reviews: see over
Dear Sir/Madam

Thank you for your latest comments, please find our responses to these below

Response to reviewer 2

The main issue it that the authors are confusing the terms RCT and equivalence study. I think that this was designed as RCT (as stated in the Abstract / Methods), which had adequate power to detect only a very small difference between groups. This is not the same as an equivalence study. As stated previously, an equivalence trial - compares a new treatment, against a control or comparator treatment that has previously been demonstrated to be effective. This requirement is explicitly stated (as follows) in the following methodological papers (i.e. by experts in the field):

Equivalence and noninferiority trials should be undertaken only when a well-proven standard therapy exists (i.e., when the intended control [treatment] is accepted as the standard of care for the particular indication). Investigators should be confident that the efficacy of the control [treatment] was proven to be superior in a previous placebo-controlled trial and that this efficacy will be preserved under the conditions of the current trial (i.e., the control [treatment] has an established, predictable and quantifiable effect). Doubts about the validity of these assumptions mean uncertainty as to whether the two [treatments] in the current trial, which are allegedly equivalent, really are effective to a similar degree, or are equally ineffective, or cannot be evaluated definitively because the trial design was inadequate to demonstrate the real differences between the two [treatments].

A key methodological consideration that we elaborate upon later is the choice of the standard treatment. Neither an equivalence nor a noninferiority design can be appropriately used without a consistently effective treatment to serve as the active control. Although the existence of a standard treatment is necessary for the use of these designs, it is not sufficient justification. As previously mentioned, these designs cannot be used without a well-established standard treatment to use as the active control (ICH, 2001). There must be convincing prior evidence of the effectiveness of the active control compared with placebo; its effectiveness must be consistently demonstrated. It must be clear that the active control is effective in the specific application, ideally with the specific population, used in the current study.

The following is a suggested minimal set of criteria against which to judge reports of clinical trials in which the equivalence of two treatments is claimed.

?There should be adequate evidence on the rigour of the trial and of the similarity of important features of design to those of earlier comparative trials which showed useful clinical effects.

This is not the case with this study. Neither ACBT+MCP nor ACBT instruction have been demonstrated to be effective at conferring gains in HRQL 6 months following hospitalisation for AECOPD and this would be a major flaw if it was designed as an equivalence study. However, as the study was designed as an RCT - which aimed to determine the effectiveness of ACBT+MCP and used ACBT instruction as the control, I suggest that the word ?equivalence? be omitted where referring to the study design.

I think that authors should speculate why they thought ACBT+MCP may improve health-
related quality of life. Although they may have been in clinical equipoise, they still would have developed hypotheses (and had a rationale for why ACBT+MCP might work). I think that the null and alternate hypotheses should be stated and rationalised.

Response:

The issue here appears to be if the trial can be considered to be an equivalence trial or not. Given that most trials as currently reporting using the consort statement which defines an equivalence trial as “...equivalence trials aim to determine whether one (typically new) intervention is therapeutically similar to another, usually an existing treatment.” [1] This does not state the necessity for the other treatment to be effective simply that it has to exist. Using the paper quoted by the reviewer by Pater (2004) says “.equivalence and non inferiority trials should be undertaken only when a well-proven standard therapy exists (i.e., when the intended control drug is accepted as the standard care for the particular indication).” In this particular case no well-proven therapy exists but there was an accepted standard treatment. We would certainly agree with both Jones et al (1996) and Greene et al (2008) if there was a well-proven therapy, but there was not. In that case we decided that it was better to plan an equivalency trial, which would be larger than a superiority, and give us enough power to either say that the two treatments arms were equivalent or if one was superior to the other. In addition this project was peer reviewed by the HTA panel and reviewers before the grant was awarded and by peer reviewers when the full report was published neither of which raised this issue, but agreed that it was an appropriate choice of design.

[1] "Reporting of Noninferiority and Equivalence Randomized Trials: An Extension of the CONSORT Statement" Gilda Piaggio, PhD; Diana R. Elbourne, PhD; Douglas G. Altman, DSc; Stuart J. Pocock, PhD; Stephen J. W. Evans, MSc; for the CONSORT Group published in JAMA.2006;295(10):1152-1160. doi: 10.1001/jama.295.10.1152

The most confusing part for me is the interpretation of the results. In their response to the Reviewers, they state. This study has shown equivalence of the two treatments. They may both be very effective or totally ineffective.the effectiveness as this can only be judged by a randomised controlled trial?. But your aim was to determine the effect and you describe this as a RCT (in the Abstract and Methods). In my view, this study shows that ACBT+MCP are ineffective at changing HRQL. The changes from baseline (in both groups) reflect an improvement in the clinical condition between acute exacerbation and clinical stability. This should be stated.

Response:

The effectiveness of any treatment can only be discussed in terms of the comparator group used in a RCT. In this case we had no placebo or “no” treatment group hence we are unable to comment on the effectiveness of any one treatment versus placebo and can only comment on the comparative effectiveness between the two treatment.

Although the authors state that this was not a trial of ACBT but of MCP they describe the intervention group as receiving guidance for ACBT (together with MCP) and the control group as receiving ACBT instruction. This does not appear to be the same thing the intervention group appeared to receive 'hands-on' instruction and the others were just told what to do. In order to confidently ascribe any change (assuming that there was one) to the
use of MCP, it would be been essential that both groups received identical ACBT. So, I think this shows that ACBT+MCP are ineffective.

**Response:**
Each group received instruction regarding ACBT during their first interaction with the physiotherapist. In the treatment group this was augmented by MCP. The difference would have been as minimal as possible however it must be acknowledged that the intervention group would have received the instruction with the therapist’s hands on the patient. This was the only option as in order to do the MCP they needed to place their hands on the patient. Confusion perhaps arises by the use of different words in the text, instruction/ guidance. To avoid this confusion the word guidance will be used on both occasions.

Given that this is a negative RCT ? the statement ?Our results suggest that a short teaching session on ACBT might be equally effective in terms of QOL after six months as several sessions of ACBT performed with support from the physiotherapist? is misleading.

**Response:**
We stand by our original statement but are happy to change it to “Our results suggest that a short teaching session on ACBT and several sessions of ACBT performed with the support from a physiotherapist have the same effect on QOL after six months.”

Regarding the implications for healthcare ? the statement ?One of its defined remits is to ensure that when someone is admitted to hospital, the time is used effectively to avoid recurrent admission? ? how does this study help address this issue ? the primary outcome was not related to re-admissions?

**Response:**
Re-admissions were studied as part of this project and reported in the full report which is referenced in the article.