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

Authors:

jane l cross (j.cross@uea.ac.uk)
frances elender (f.elender@uea.ac.uk)
gary barton (g.barton@uea.ac.uk)
allan clark (allan.clark@uea.ac.uk)
lee shepstone (l.shepstone@uea.ac.uk)
anne blyth (a.blyth@uea.ac.uk)
max o bachmann (m.bachman@uea.ac.uk)
ian harvey (i.harvey@uea.ac.uk)

Version: 3 Date: 13 December 2011

Author's response to reviews: see over
Reviewer's report

Title: Effectiveness of manual chest physiotherapy techniques in the management of exacerbations of chronic obstructive pulmonary disease (MATREX): a randomised controlled equivalence trial.

Version: 1 Date: 11 October 2011
Reviewer: Giancarlo Garuti

Reviewer's report:
The authors present an randomized controlled trial on the manual chest physiotherapy. The intentions of authors are interesting because, about this specific argument, there are few randomized controlled trials with large series.

Major Compulsory Revisions
The question posed by the authors for this study is important but is lost during the course of the article. In fact the title of the article is about the effectiveness of these techniques, but the most out of this study is how to be the quality of life. So, I recommend two ways: 1) change the title in one which the emphasis is only on the quality of life and the use of the MCP or 2) enter more outcomes (whether in their database they are been collected) that assess physiological parameters in the short term efficacy of these techniques.

We have change the title in order to reflect the main measure of quality of life.

The methods used in this study are appropriate but poorly described by the authors: in the methods section the authors should better describe the techniques of chest physiotherapy adopted.

Space available would make it impossible to provide enough detail in the text and these techniques are described elsewhere with full details http://www.hta.ac.uk/project/1416.asp this is referenced in the text

The presented data are consistent with others in the past, but since they have a so vast case history (and, certainly more data are collected), pathophysiological data should be evaluated (eg. pulmonary function tests, blood gases samples, etc). with quality of life data. They would be more appropriate to be more specific with regard to hospital admissions, the emergency room admissions, and GP interventions after the first treatment.

These pathophysiological data area only available for the intervention group hence there is no comparator to measure effectiveness therefore they are not presented in this paper. Hospital admission data was not collected as part of effectiveness data – it is however available in the full report as part of the cost effectiveness analysis. We do not consider it appropriate to add this as an outcome measure as part of the analysis at this late stage.

Minor Essential Revisions
Title: If the authors cannot submit additional outcome measures, it would be appropriate to change the title by inserting the change of quality of life in patients subjected to MCP .
done

Abstract: it is in line with what is described in the article

Introduction:
-authors should better explain the physiological point of view and rational use of
MCP, considering to place some bibliographic references.

We consider this is covered in the introduction
- Specify the abbreviation NIHR HTA
done

Methods:
Patients and Study design:
- better explain the patient inclusion criteria and in particular the definition of acute COPD exacerbation eligible for drainage of secretions.
In line with pragmatic trials this was based on the admitting physicians diagnosis hence not specifically defined at the point of inclusion.
If it is possible, introduce, lung function tests, blood samples analysis and ml of sputum (before and after treatment)
This is not possible as these data were not collected or only collected in the intervention group hence not presented

Procedures:
- explain in detail the MCP procedures and in particular unfold better criteria by which the therapist decides
- to start and finish the procedure
- number of sessions,
- how many times a day,
- how many days
Describe what parameters are monitored during the MCP procedure.

These are described in the full report previously referenced and has been cited in the paper

Outcomes Measures:
these data do not measure the effectiveness of the action in an event such as acute exacerbation in the short term.
I eventually would split outcomes in:
- short term outcomes (pathophysiological outcomes, days of drug treatment, hospital length of stay and disease days )
- mild-term outcomes (more exacerbations, use of antibiotics after first treatment, hospital admissions)
- long-term (QoL)

As per clinical trial guidelines these were defined before the start of the trial and thus not possible to change

Statistical Analysis: good description of the statistical analysis

Results
  1) Figure 1 is missing
     This is corrected
  2) Table 1: is difficult to read remove and describe in paragraph “MCP treatment “ how many treatments have been made to patients, the average per patient, the mean saturation before and after treatment with the statistical difference and In the same paragraph put only the percentages of adverse events instead the pure number.
We do not know how to make this table any clearer.  
The reporting of adverse events has been done in accordance with CONSORT statements.  
2) Table 2: add a column for statistical significance.  
- remove female, current smoker, never smoker and smoker lines and mention these in the methods section as percentage. Put a description of abbreviations JPH, NNUH, QEH, UHA and remove these lines always putting the description in the discussion.  
Insert in the table only the MRC score mean and SD and the statistical difference.  

It is inappropriate to test for statistical significance at base line as discussed in the CONSORT statement. The JPH, NNUH, QEH, UHA have been changed to Site 1 site 2 etc.  

Discussion:  
remove MCP versus ACBT section it and mention it at the beginning of the discussion  
References reference n.3 and n.8 are the same  

The discussion is presented in a logical order chronologically for ease of reading. Ref 8 has been deleted  

Level of interest: An article of importance in its field  
Quality of written English: Acceptable  
Statistical review: No, the manuscript does not need to be seen by a statistician.  
Declaration of competing interests:  
I declare that I have no competing interests  

Reviewer's report  
Title: Effectiveness of manual chest physiotherapy techniques in the management of exacerbations of chronic obstructive pulmonary disease (MATREX): a randomised controlled equivalence trial.  
Version: 1 Date: 16 October 2011  
Reviewer: Kylie Hill  
Reviewer's report:  
This manuscript reports on the results of a large study that examined the effect of manual chest physiotherapy techniques in patients hospitalised with an acute exacerbation on disease-specific health-related quality of life, six months following randomisation.  
This study would have been an enormous, difficult and time consuming undertaking. Certainly studies that investigate the role of physiotherapy treatments during an acute exacerbation are necessary and important. Nevertheless, I strongly suspect that the design has a fatal flaw (see below) and this must be discussed and acknowledged.  
• Major Compulsory Revisions  

Introduction  
The purpose of an equivalence study is to demonstrate that a new (or experimental) treatment is as effective as one with established effectiveness. In
order to do this, there must be convincing prior evidence that the control or standard therapy group (in this case, instruction regarding ACBT) is effective compared with placebo or no treatment. Therefore, the most important issue to be addressed in the Introduction, is that ‘ACBT instruction’ is, in fact, effective (at improving health-related quality of life at 6 months). To my knowledge, there is no study demonstrating this and therefore, I believe that this study has simply demonstrated that two ineffective treatments, are equally ineffective. The authors allude to this in the Discussion (by commenting on the need for further research regarding the effectiveness of ACBT), but it is critical to acknowledge this a major flaw in this study.

We agree that the purpose of an equivalence trial is to demonstrate that one treatment is as effective as another; we do not however agree that one of the treatments needs to have been shown to be previously effective. We believe it is sufficient that one treatment is used frequently or is part of standard practice for it to be comparable. At the time of the study design this was believed to be the case in the UK.

The rationale for selecting health-related quality of life as the primary outcome needs strengthening. I appreciate that the SGRQ is a standardised patient-orientated outcome, but in the Introduction, the authors state that MCP are done with the goal of ‘improving V/Q ratios and lung function’. Therefore, it would seem that measures which reflect V/Q ratios and lung function would have been more appropriate as the primary outcomes. Are improvements in health-related quality of life really the most important goal of MCP applied during a hospital admission?

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We believe it is important to study patient related outcome measures and that this is in line with current clinical and research directions within the NHS in the UK. We find it difficult to believe that patients would appreciate changes in short term physiological outcomes although we acknowledge they may be important clinical parameters of efficacy. However they are not measure of effectiveness.

The other aspect that needs strengthening is the rationale for the length of follow-up. I appreciate that earlier work has not examined long-term effectiveness of MCP, but I would have thought that the outcome of interest with regards of long-term effectiveness of MCP would be exacerbation frequency, antibiotic use or maybe healthcare utilisation. Why did the authors expect MCP to confer benefits in health-related quality of life 6 months following randomisation?

The six month follow up was based upon the need to obtain reliable long term outcome measures in these patients. Health care utilisation was measured and is available in the full report as part of the cost effectiveness analysis.

Methods
Following the work by Gallon in the 1990s (and very early work by Campbell demonstrating a decrease in FEV1 with percussion), there is a general consensus that MCP, especially percussion, should only be offered to patients characterised by mucus hypersecretion (i.e. # 30 mls per day). Can the authors strengthen their rationale for why mucus hypersecretion was not an inclusion
criteria?

Standard practice at the time of the design of this study in the UK was for patients who met the inclusion criteria to receive either MCP or the control type interventions regardless of sputum volume. Thus the inclusion criteria are reflective of a pragmatic trial in this population. We did perform a sub group analysis of those producing more that 15 mls of sputum per day and this is now reported in the paper.

Under ‘statistical analysis’ – you use the term ‘non-superiority’ (which I am not certain is appropriate). Was the trial designed as an equivalence study, or a non-inferiority trial (i.e. powered for two-tailed vs. one-tailed analysis)?
Agreed – changed to equivalance

Why was an effect size chosen for the power calculations and not the MCID for the SGRQ?

At the time of the design we were unsure of what the standard deviation would be in our population hence we based the sample size calculation on the effect size.

When you explain how the effect size was calculated, I am not clear how the data from the control group was used (mean difference in what?)

The effect size was calculated as the mean in the control group minus the mean in the intervention group

Who collected the outcome measures – were they blinded to the aims of the study and group allocation?

The primary outcome measure was patient reported and it is not possible to blind these.

Results
It is important that the within-group results (for both the no MCP and the MCP groups) are reported.

We disagree; it is not possible to infer the effectiveness of an intervention by looking at within group differences due to issues such as regression to the mean, the Hawthorn effect etc. However the mean at base line and follow up are presented enabling change from base line to be observed.

Did either group achieve a significant improvement in the SGRQ? If not, both interventions were ineffective and this must be stated clearly.
Yes they did – but for the reasons above we have not presented this.

The data pertaining to saturation are interesting. However, I think it is important to know how many desaturated by an amount that is likely to be important (and is more than the measurement error of most oximeters). Can you please provide data on how many desaturated by # 4% to a level # 90% (i.e. criteria often cited in UK guidelines)?
We have updated the text accordingly
Under the subheading ‘MCP treatment’ – I am unclear what you mean by’ Shortness of breath reported by patients was accompanied by varying degrees of reduced oxygen saturation’. Can you please re-phrase this? Did all patients report shortness of breath?
Done

How many in each group were re-admitted over the six months follow up period?
We have included descriptive statistics in the results

I noticed in Table 1 – for the variable ‘Deviations from MCP treatment protocol’ – you have 248 (38%) for ‘one position only’ – was there an expectation to treat in more than one position?

Yes there was and was outlined in the treatment protocol, however considering the results we would amend the protocol accordingly

Discussion
I would argue that first statement under the subheading ‘MCP treatment protocol’ is not correct. There have been at least two systematic reviews recently published that evaluate the role of ‘chest physiotherapy’ in the management of an acute exacerbation and both conclude that the evidence is strongest for positive pressure devices (i.e. PEP like devices), not MCP. Therefore, I would be interested to know why the authors think that their MCP treatment was based on ‘best available research evidence’.

We acknowledge the two systematic reviews published since the finish of our study however at the time of the design of our study the MCP protocol was based upon the best available evidence of the time. Reference to these systematic reviews has been included in the conclusion

The paragraph with the subheading ‘MCP versus ACBT’ needs re-visiting. In addition to stating that ACBT is a popular treatment choice, the authors must review the evidence for this treatment. 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 (I suspect neither were effective). Can this be re-worded?

This was not a trial of ACBT but of MCP thus it is not appropriate to comment on the effectiveness of ACBT as it was included in treatment as usual and we reflect upon the need for further evidence in this population group in this paper.
The authors must include a paragraph that summarises the limitations of their study. If neither group conferred an improvement in quality of life, the authors must be transparent that this study has not confirmed equivalence of two effective treatments, but in fact, has shown equivalence of two ineffective treatments.

This study has shown equivalence of the two treatments. They may both be very effective or totally ineffective. The within group changes tell us nothing about the effectiveness as this can only be judged by a randomised controlled trial.
• Minor Essential Revisions

Abstract

Last line under ‘Methods’ – please change ‘This study is registered’ to ‘This study was registered’. Also please state which registry was used.

done

Under ‘Results’, is the word ‘evaluable’ needed? Please make it clear that the 95% CI pertains to that for an effect size, not the actual units of the SGRQ.

The word evaluable is needed to state the % of patients who gave data which could be used in the primary effectiveness analysis

There are some redundant sentences. For example, the authors state that the study looked at quality of life six months following intervention three times – (i) end of Background, (ii) last paragraph under ‘design and patients’ and (iii) under ‘outcome measures’ – this needs stating only once.

We have purposely emphasised the time point for ease of those who might wish to included this study in a systematic review.

Introduction

It would be useful to clarify if the authors actually expected a difference between the groups and why (or why not).

We did not expect a difference between treatment arms because we were in clinical equipoise otherwise it would have been unethical to randomise patients

It would be useful to move the paragraph that summarises the study objectives from the Methods section to the end of the Introduction.

We disagree and would prefer to have the detailed objectives in the methods

Methods

Was there any contact with the participants between discharge and follow-up?

Yes if they were readmitted, treatment data was routinely collected as described in the protocol

Last line of the paragraph under the subheading ‘outcome measures’ – please change ‘trail’ to ‘trial’.

done

Results

Under ‘Efficacy Analyses’ – can you please clarify that the mean differences were calculated as no MCP – MCP

Yes we can, we have updated table headings appropriately

Discussion

The opening statement of the Discussion is confusing. For readers who are not familiar with how the SGRQ is scored, it sounds as though the patients in this study had better quality of life than others. Can this be re-worded?

done

Other

References: The authors need to check their use of references. As an example, the paper by Cecins et al is cited to support the statement that “Sputum volume…is recommended as an indicator of the physiological impact of MCP” – but this study was not in COPD, used sputum weight not volume as its outcome measure, and did not investigate MCP – so does not support this statement.

This is a mistake and has been replaced

The manuscript refers to both a consort diagram (last line of first paragraph
under sub-heading ‘procedures’) and Figure 1 (first line of Results) – neither of which were available at the time of review. Were these uploaded?

Yes they were and are now available

Regarding the Tables, can the authors please carefully consider how many decimal points it is appropriate to use when expressing their data. In most instances, it would not be appropriate to use more than one decimal point. EQ5D is measured between 0 and 1; hence we have reported this to 2 decimal places for accuracy. We decided to be consistent and do the same with all outcome measures

Table 2 – the abbreviations JPH, NNUH etc – I assume that these represent the hospitals? It would be better to have these listed as Site 1, Site 2 etc.

Done

There are some inconsistencies in formatting throughout the manuscript – e.g. for some subheadings the authors have capitalised the first letter of each word and for others, they haven’t. This happens again in the Tables.

Done

Reference 24 is not formatted correctly (e.g. single spaced)

• Discretionary Revisions

In the Abstract – consider replacing the term ‘chest clearance’ with ‘airway clearance’

Done

Consider re-phrasing the statement ‘Chronic obstructive pulmonary disease (COPD) is characterised by exacerbations during which…’ to ‘Chronic obstructive pulmonary disease (COPD) is characterised by exacerbations, some of which result in increased cough…. (not all exacerbations are characterised by excessive sputum production – some are characterised more by dyspnea and fatigue).

Done

In the Introduction, where the authors state ‘However, systematic reviews of clinical trials…’ the references supporting this statement are not all systematic reviews. The authors might want to consider citing some of the very recent systematic reviews that have been done in the area of ‘chest physiotherapy’ for patients during an acute exacerbation (there are plenty of them).

We have removed the word systematic and included the newer systematic reviews in the conclusion as they were not available during the design of this study

Done

In the Discussion, in addition to the paper by Yohannes et al, the authors might want to cite the paper by Harth et al that examined practice patterns of physiotherapists who treat patients hospitalised with an acute exacerbation across Canada.

Done

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests: I declare that I have no competing interests
Reviewer 3 comments:

Title and abstract accurately reflect the work carried out although I think the words ‘management of exacerbations?’ should be changed to reflect the primary aim, ie evaluation of the effectiveness of MCP on QoL 6 months post exacerbation in COPD.

amended

The introduction:
Line 4 ‘These purpose of these is intermittently?’ needs correction.

amended

There is insufficient justification/ rationale in the introduction for the use of SGRQ as the primary outcome. It is likely that this choice of primary outcome will be contentious in Physiotherapy, the authors need to make the case for the links between the benefits expected as a result of MCP and how these may translate to improved QoL in the longer term.

We believe it is important to study patient related outcome measures and that this is in line with current clinical and research directions within the NHS in the UK. We find it difficult to believe that patients would appreciate changes in short term physiological outcomes although we acknowledge they may be important clinical parameters of efficacy. However they are not measure of effectiveness.

In the methods the authors cite the use of SGRQ as a predictor of mortality, was it anticipated that SGRQ would stand in as a ‘Proxy’ for mortality or at least for morbidity. It is reasonable, though tenuous, to suggest that short term improvements in expectoration of secretions may lead to improvements in QoL, certainly if less exacerbations were experienced as a result of the MCP treatment, this would be expected to translate to improvements in QoL. It is not a proxy for morbidity or mortality, see above.

However, I see no data on exacerbation frequency, the authors need to explain why this was not included as a secondary outcome and only hospital readmission recorded. This is a limitation of the study that should be addressed.

We agree this would have been interesting but primary care records were not available for this study so we had to rely on readmission as an indicator of exacerbation.

The authors need to be more explicit as to the proposed mechanism for change in QoL. There should also be some inclusion as to the choice of primary outcome and the limitations/ opportunities that using QoL allows us in the interpretation of the findings.

Sentences have been added to the discussion on MCP effectiveness and clarity between efficacy and effectiveness hopefully achieved.

A feature of the work that will provide useful information to the community concerns the reporting of oxygen saturations, positioning and time taken to perform MCP. In the introduction I would encourage the authors to be more specific concerning the lack of research in this area. They report that
existing studies show ?unstandardised interventions? perhaps this could be expanded to be more specific about the things this new research will bring, ie positions, frequency etc.

Methods: patients were excluded with no evidence of sputum production on auscultation- should this read sputum retention? , all humans produce sputum although clearly it is not evidenced on auscultation, perhaps they mean ?excess? sputum production.

Yes - corrected
Why was the effect size of the SGRQ chosen to determine the sample size and not the Minimum clinically important difference, this is mentioned in the discussion but not explained.
At the time of the design we were unsure of what the standard deviation would be in our population hence we based the sample size calculation on the effect size.
We note there is also some debate regarding mcid thus a small effect size was chosen

We need to know more information about the location of the patients, were any seen from critical care units. High dependency units, admission units? How many were on Oxygen and how was oxygen use monitored / addressed during the study. Obviously oxygen usage will play a bearing in the oxygen desaturation findings so is an important variable for the reader to know. I assume it was according to standard care and not changed during treatment.
Yes patients did receive standard care

I would have liked to see Figure 1, the trial profile but could not see it on the pdf provided. The authors provide an excellent breakdown of recruitment and attrition and should be congratulated on recruitment of such a large sample to the study. This study has recruited significantly greater numbers of participants than most other evaluations of MCP, however , it appears that the complete pre and post data on the primary outcome was available in 372 subjects rather than the desired 466. There seems to be no comment on this in the discussion. I am sure we are not seeing a type II error, however there does need to be some mention or justification of this (unless I am missing something since I could not see the flow chart).

Thank you this should have been included and is now appended and has been added to discussion
The statistical analysis is appropriate and well described.
Thank you
The study deserves publication in a high quality journal and provides some very interesting data, particularly on oxygen saturations during treatment, I suggest the authors reinforce the novelty of the data and the strengths of the study a little more strongly in the discussion as well as reporting a little more critically on the difficulties of recruitment to trials such as these.