PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	EARLY ASSISTED DISCHARGE WITH COMMUNITY NURSING FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATIONS: RESULTS OF A RANDOMISED CONTROLLED TRIAL
AUTHORS	Utens, Cecile ; Goossens, Lucas; Smeenk, Frank; Rutten-van Mölken, Maureen; van Vliet, Monique; Braken, Maria; van Eijsden, Loes; van Schayck, Onno

VERSION 1 - REVIEW

REVIEWER	Dr. John Newell Senior Lecturer in Biostatistics, HRB Clinical Research Facility and School of Mathematics, Statistics and Applied Mathematics National University of Ireland, Galway,Ireland No competing interests.
REVIEW RETURNED	19-Jul-2012

THE STUDY	The primary response is a change in a score where the score is on a scale from a 0 (best) to 6 (worst). The analysis used is described as a repeated measures model with an unstructured covariance matrix. Presumably a linear mixed model for a continuous response was used? If so some justification as to the appropriateness of using this model (which assumes a continuous response) for analyzing a change in a discrete score should be given. The variable selection techniques are justifiable however there is a strong case for including the centre (i.e. hospital) in each model regardless of its significance given that it is a component of the design. A statement as ti whether Hospital should be treated as a random or fixed effect is needed. There is no mention of the standard deviation used in the sample size calculation and it needs to be included to justify the sample size. In order to arrive at the sample size as presented the standard deviation will have been estimated to be around 0.9. This is close to that observed in the summary statistics for the primary response at baseline and hence the sample size calculation appears justified. A reference to the software used to fit the repeated measures model is needed.
RESULTS & CONCLUSIONS	The analysis focuses on the change in CCQ. As the change is calculated as change from baseline a reduction in CCQ is an improvement. This needs to be made clearer, indeed reversing the sign and using the word 'Improvement in CCQ' as the vertical axis

	label would make Figure 2 easier to interpret.

REVIEWER	Vittoria Tibaldi Geriatrician, MD, PhD Hospital at Home Service, San Giovanni Battista Hospital of Torino No competing interests to declare.
REVIEW RETURNED	23-Jul-2012

THE STUDY	1) How a diagnosis of "COPD exacerbation" was performed? 2) In the exclusion criteria: what do you intend for "major uncontrolled comorbidity"? I think it should be better to specify the comorbidities considered for exclusion; jow did you evaluate the "mental instability"? 3) Please, therapies that cannot be given at home in your trial 4) In the inclusion criteria, it is not clear, in my opinion, what do you intend for "diagnosed with COPD at least GOLD stage I and 10 pack years of smoking" 5) Who is involved in the data collection? Study nurses? 6) I think it should be better to move the period "To detect a difference of 0.4.....sample size was 165" (page 9, lines 23-27) to the statistical analysis 7) ABSTRACT: please, specify the nature of the disease under consideration in the "Objectives"; please, erase "acute COPD" from line 23, page 4 8) Please, give more details on the CCQ (instrument for primary outcome evaluation) and the study protocol, if possible
RESULTS & CONCLUSIONS	1) Page 10, lines 43-49: "Three patients in the early.....immediately after randomisation": total number of patients that withdrew consent is 10 but in Figure 1 is 13 -> please, verify the correct number 2) Please, verify numbers in FIGURE 1: the total number for "not eligible" is 892 or 863 as stated?; the total number for "signed informed consent on day 3 of admission" is 251, derived from 508 - (168-refused to sign informed consent + 89-not asked to participate) 3) Page 13, line 5: ".....CCQc scores of both groups scores were....." -> the term "scores" is repeated (modify) 4) TABLE 2: indicate numbers and percentagas as "n (%)"; "comorbidity score of 1" 60% + "comorbidity score > 1" 39% = 99%, instead of 100% 5) It should be interesting to know the GOLD stage (I-IV) of participants prior to admission. We do not have any information on functional and respiratory status of study patients on admission (and on subsequently changes) 6) Is it possible to know when patients had their first readmission? long or not long after discharge? 7) Why the treatment failed in 5 patients? It sholud be interesting to have details. (complications?) 8) Why only 118 patients completed the questionnaire at T+4 days? according to Figure 1 only 10 paticipants, from 139, withdrew < day 7 of treatment. And why only 101, from 115, at follow-up? 9) SUPPLEMENT FILE 1: in the title, specify "...Values represent mean (SD), unless stated otherwise"
GENERAL COMMENTS	Very interesting paper in the field of home care but is important to have data on costs.

VERSION 1 – AUTHOR RESPONSE

Response to comments of reviewer 1:
Reviewer: Dr. John Newell
Senior Lecturer in Biostatistics,
HRB Clinical Research Facility and School of Mathematics, Statistics and Applied Mathematics
National University of Ireland,
Galway, Ireland

Comment: The primary response is a change in a score where the score is on a scale from a 0 (best) to 6 (worst). The analysis used is described as a repeated measures model with an unstructured covariance matrix. Presumably a linear mixed model for a continuous response was used? If so some justification as to the appropriateness of using this model (which assumes a continuous response) for analyzing a change in a discrete score should be given.
Reply: We performed a linear model with correlated errors for the repeated measures model, and not a linear mixed model as the reviewer presumed. We made it more clear in the statistical analysis section which analysis we performed.
Furthermore the reviewer states that we used a discrete score in the analysis. However, we did use a continuous score, which is, as the reviewer mentions, assumed in the repeated measures model we used. We made it more clearly in the methods section of the manuscript that the (change in) CCQ score is a continuous score.

Comment: The variable selection techniques are justifiable however there is a strong case for including the centre (i.e. hospital) in each model regardless of its significance given that it is a component of the design. A statement as to whether Hospital should be treated as a random or fixed effect is needed.
Reply: As the reviewer states, the analysis model we used is justifiable. We excluded hospital as covariate because we wanted a parsimonious model, without covariates that do not influence the estimates of the treatment effect. For reference we performed the analysis with hospital as covariate, but this had no significant influence on the outcomes. Therefore we decided not to change the current analyses. This explanation has been added in the discussion section of the manuscript.

Comment: There is no mention of the standard deviation used in the sample size calculation and it needs to be included to justify the sample size. In order to arrive at the sample size as presented the standard deviation will have been estimated to be around 0.9. This is close to that observed in the summary statistics for the primary response at baseline and hence the sample size calculation appears justified.
Reply: The sample size calculation is described in the article on the research protocol (reference 19). However, for clarity we incorporated the standard deviations used for the sample size calculation in the statistical analysis section, as requested by the reviewer.

Comment: A reference to the software used to fit the repeated measures model is needed.
Reply: A reference to the software package used for the analyses has been incorporated.

Comment: The analysis focuses on the change in CCQ. As the change is calculated as change from baseline a reduction in CCQ is an improvement. This needs to be made clearer, indeed reversing the sign and using the word 'Improvement in CCQ' as the vertical axis label would make Figure 2 easier to interpret.
Reply: The reviewer is correct that the scale of the CCQ with 0 being best score and 6 being worst score makes it difficult to interpret the changes in CCQ score described in the text and displayed in figure 2.

As suggested by the reviewer we changed the sign of the scores and now positive number or increasing line can be interpreted as an improved score. For clarity we added a comment in figure 2 to remind readers that improvement in practice means decrease in scores.

Response to comments of reviewer 2:
Reviewer: Vittoria Tibaldi
Geriatrician, MD, PhD
Hospital at Home Service, San Giovanni Battista Hospital of Torino

Comment: How a diagnosis of "COPD exacerbation" was performed?
Reply: We added that the diagnosis was made by the reviewing physician. We believe it lies out of the scope of the paper to describe the clinical differential diagnosis process in more detail.

Comment: In the exclusion criteria: what do you intend for "major uncontrolled comorbidity"? I think it should be better to specify the comorbidities considered for exclusion; how did you evaluate the "mental instability"?
Reply: In order to make it more clear which comorbidities could be reason for exclusion, we incorporated the most important ones in table 1. However, although the trial is not a real pragmatic trial (it has quite tight inclusion- and exclusion criteria), we tried to reflect current practice of assessing patient as near as possible and the final decision for inclusion was made by the reviewing physician.

Comment: Please, therapies that cannot be given at home in your trial
Reply: Specification is added in table 1.

Comment: In the inclusion criteria, it is not clear, in my opinion, what do you intend for "diagnosed with COPD at least GOLD stage I and 10 pack years of smoking"
Reply: As suggested by the reviewer we specified in table 1 that COPD was defined as at least GOLD stage 1 with 10 smoking pack years. We intended to exclude asthma diagnoses and mixed asthma/COPD diagnoses from the study and therefore defined a diagnosis of COPD as being at least a GOLD 1 stage and 10 smoking pack years.

Reply: Comment: Who is involved in the data collection? Study nurses?
The data collection process has been described in more detail in the research protocol. In the manuscript is referred to this separately published research protocol for readers who want more details (reference 19).

Comment: I think it should be better to move the period "To detect a difference of 0.4.....sample size was 165" (page 9, lines 23-27) to the statistical analysis
Reply: Correction made as reviewer suggested.

Comment: ABSTRACT: please, specify the nature of the disease under consideration in the "Objectives"; please, erase "acute COPD" from line 23, page 4
Reply: Disease under consideration is specified in abstract. Extra COPD has been deleted as reviewer suggested.

Comment: Please, give more details on the CCQ (instrument for primary outcome evaluation) and the study protocol, if possible.
Reply: The reviewer asks for more details on the CCQ and the study protocol. We added information on the number of questions of the CCQ that needs to be answered in order to produce a valid overall score (see also the reply to comment 8 of this reviewer below).Other references to the main publications on the CCQ are included in the manuscript for interested readers (references 20 and 21). Additional information on the research protocol can be found in the separately published research

protocol. A reference to this research protocol (reference number 19) is included in the manuscript.

Comment: Page 10, lines 43-49: "Three patients in the early.....immediately after randomisation": total number of patients that withdrew consent is 10 but in Figure 1 is 13 -> please, verify the correct number.
Reply: The reviewer has accidently mixed the number of patients that refused randomisation with the number of patients that was randomised but who were not satisfied with the outcome after randomisation. This number is 10 as can be observed in figure 1.

Comment: Please, verify numbers in FIGURE 1: the total number for "not eligible" is 892 or 863 as stated?; the total number for "signed informed consent on day 3 of admission" is 251, derived from 508 - (168-refused to sign informed consent + 89-not asked to participate).
Reply: The reviewer is correct. We incorporated the wrongly screened patients (N=29) in calculation of the number of eligible patients instead of the number of ineligible. This has been corrected. The number of eligible patients is 479, which is in line with the number of patients who signed informed consent (N=222) +the number of patients who were not eligible for randomisation (N=70) and the number who refused randomisation (N=13).

Comment: Page 13, line 5: ".....CCQ scores of both groups scores were....." -> the term "scores" is repeated (modify).
Reply: Repetition of scores is deleted.

Comment: TABLE 2: indicate numbers and percentages as "n (%)"; "comorbidity score of 1" 60% + "comorbidity score > 1" 39% = 99%, instead of 100%
Reply: Corrections made as reviewer suggested.

Comment: It should be interesting to know the GOLD stage (I-IV) of participants prior to admission. We do not have any information on functional and respiratory status of study patients on admission (and on subsequently changes)
Reply: The reviewer is right that we do not have data on lung function at admission. We choose not to measure lung function at admission, as dyspnoea at admission is too severe to perform spirometry in most patients. Other argument why we did not collect pre hospitalisation would be biased because of differences in time between most recent lung function measurement and the hospitalisation under study.

Comment: Is it possible to know when patients had their first readmission? long or not long after discharge?
Reply: In the table with number of readmissions (in revised manuscript table 5) an additional row with the average number of days to the first readmission has been added.

Comment: Why the treatment failed in 5 patients? It should be interesting to have details. (complications?)
Reply: We specified the reasons of treatment failure in the text.

Comment: Why only 118 patients completed the questionnaire at T+4 days? according to Figure 1 only 10 participants, from 139, withdrew < day 7 of treatment. And why only 101, from 115, at follow-up?
Reply: The reviewer deservedly makes this comment, as it is not clear. The differences in the numbers can be explained by the design of the CCQ questionnaire. This questionnaire consists of 3 sub scores for symptoms (4 questions), functional state (4 questions) and mental state (2 questions). In order to produce a valid overall score the patients needs to complete 3, 3 and 2 questions, respectively, of the domains. Some patients did not meet this criterion and their score could not be

used in the analysis. However, they continued to participate in the trial (consent was not withdrawn) in order to contribute to the other analyses and to produce a valid score at other measuring points. This approach fits with the intention-to-treat principle and the repeated measures analysis. We included the information on the number of questions that needs to be completed on the CCQ in the methods section and in explained the difference in number of patients in the CCQ analysis and the total number of patients in the trial in the results section.

Comment: SUPPLEMENT FILE 1: in the title, specify "...Values represent mean (SD), unless stated otherwise"
Reply: Correction made as reviewer suggested. In addition, we added the number of patients in the GOLD groups instead of only providing the percentage in table 3.