Author's response to reviews

Title: Action Plan to enhance self-management and early detection of exacerbations in COPD patients; a multicenter RCT.

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Version: 3 Date: 29 October 2009

Author’s response to reviews: see over
Date 29 October 2009

Subject: Cover letter and revised manuscript:

‘Action Plan to enhance self-management and early detection of exacerbations in COPD patients; a multicenter RCT’.

Dear editor,

We are pleased to submit our revised paper ‘Action Plan to enhance self-management and early detection of exacerbations in COPD patients; a multicenter RCT’ for publication to ‘BMC Pulmonary Medicine’.

We would like to thank the reviewer for the positive appraisal and constructive criticism. All comments and our revisions (Font red.) are listed below this cover letter and changes are highlighted in the manuscript.

We hope these revisions sufficiently address the comments of the peer feedback and we are looking forward to your response.

Yours sincerely

on behalf of all co-authors,

Jaap Trappenburg, MSc
Reviewer's report

Title: Action Plan to enhance self-management and early detection of exacerbations in COPD patients; a multicenter RCT.

Version: 1 Date: 2 October 2009

Reviewer: Rodolfo Dennis

Reviewer's report:
I think that the protocol has merit, and if carried out satisfactorily will no doubt provide an important addition to the current level of knowledge in this field. I also think that the current manuscript (only on the methodology) may be innovative enough to be of sufficient interest to journal readers. The "postponed informed consent procedure" is interesting to assure patient blinding on their group allocation in the context of this study, and other aspects such as the description of the action plan, choice of outcome, and sample size, is different from previous studies (as the authors correctly point out), and may also be of sufficient interest to readers. I think the architecture of the RCT conforms to CONSORT statement standards, and authors provide sufficient information in general so that readers may be able to replicate results if the effect size is of clinical importance.

- Major Compulsory Revisions
1. Authors should discuss the assumption that a 70% symptom-based exacerbation rate will be seen over 6 months in the study population is a valid assumption, within the inclusion criteria postulated. Perhaps another inclusion criteria based on a minimum number of exacerbation events within the past 12 months may add validity to the assumption.

Added third paragraph of sample size section:
To optimize generalizability, pre-study exacerbation rates are not part of the inclusion criteria. The number of patients needed to obtain 73 exacerbations per arm depends on the expected 6-months symptom-based exacerbation incidence. Symptom-based exacerbation incidence has shown to be at least 50% higher compared to exacerbations based on healthcare contacts (1-3). Different prospective cohorts studies using similar symptom-based algorithms in average populations found (median or mean) exacerbation rates ranging from 2.53 (IQR 1.33–3.80)(4), 2.7 (± not-reported), 3.5 (± 2.7)(5) to 5.0 episodes (IQR, 4.0 to 7.0)(3) per patient per year. Based on these rates, the proportion of patients experiencing at least one episode is expected not to be less than 70 % and subsequently a safe boundary.

2. It seems that following an action plan, as is the hypothesis, may impact on exacerbation rates and other secondary outcomes, but it seems that it may be somewhat labor-intensive on the health care provider(s). That is, it is likely that it will increase both the efficacy and the health care costs (of providing the service). On the other hand, a decrease in the number of exacerbations may actually reduce health care costs. Authors should discuss why not including a health economic component in the study, given that health care utilization will be measured.

Added secondary outcomes section; healthcare utilization

…and cost-effectiveness
The perspective of the healthcare payer is adopted for the cost-effectiveness analysis (CEA). Resource use is valued in monetary terms by multiplying the units consumed by the cost per unit(6). Two major cost categories are distinguished: program implementation and direct health care. Data on cost and outcome are brought together to estimate incremental cost-effectiveness ratios (ICERs) and subsequently calculated as costs per exacerbation-related CCQ unit prevented, per hospital admission prevented, and per health care contact prevented. Sensitivity analysis is used to test the cost-effectiveness model for methodological uncertainty and generalizability.

**Added second paragraph of data analysis section:**

Confidence intervals of the incremental cost-effectiveness ratio’s are tested using nonparametric bootstrapping (Monte Carlo simulation) drawing 100,000 samples(7).

3. Data analysis aspects seem somewhat brief. The software package to be used would also be important to include.

**Added first paragraph of data analysis section:**

SPSS 15.0 for Windows (SPSS, Inc., Chicago, IL) will be used for data analysis.

The analysis of QOL data with the SGRQ has a minimal clinical significant difference that should be mentioned in the analysis.

**Added in secondary outcome section; Health-related quality of life:**

Both between group differences in SGRQ scores will be assessed as well as the proportion of patients crossing the clinical relevant threshold of 4 points (8).

Analysis of event rates over time with patient-time as the denominator could be discussed further.

**Added in first paragraph of data analysis section:**

Number of exacerbations will be reported as weighted exacerbations rates (total number of exacerbations divided by the total person-time of follow up per group). This approach has shown to produce unbiased estimates of a weighted statistical approach adjusted for asymmetry in follow-up times by accounting for each patient’s time spent in the trial (9;10). Statistical significance of weighted rate ratio’s are calculated using a Poisson regression model including an overdispersion parameter to account for variability in exacerbation rates between patients.

- **Minor Essential Revisions**

1. The case for the action plan could be magnified if the intervention reduces exacerbations that require hospitalization, aside from health status/symptom recovery time. While I understand that such an event overtime is infrequent enough that the sample size would need to be larger, authors should discuss why such an outcome is not one of the main outcomes selected.

In the last paragraph of the discussion section, we elaborately discussed why we believe exacerbation recovery time is the most subtle and clinically relevant outcome measure for this specific research question:

…..Finally, the current study clearly differs from the other studies in the primary outcome on which the study is powered. Aiming at evaluating effectiveness of a single component intervention (AP) necessitates being reserved on powering on general outcome measures such as hospital admissions. Therefore, the current study aims at specific and accurate assessment of effectiveness of the AP on patient-centered
outcomes, in the presence of an exacerbation, since this is what the AP is developed for. In addition, a clinical relevant advantage of assessing exacerbation recovery time is that it assesses effectiveness in all exacerbation episodes and not only those followed by healthcare contacts or hospital admissions. Effectiveness in terms of decreased CCQ recovery time is equivalent to a decrease in the impact of these episodes on health status and thus highly clinical relevant from a patient perspective. Detecting an effect on recovery time of exacerbations, the primary outcome, is an essential first step before trying to prove that the intervention can increase HRQL or reduce hospital admissions....

**Added in the last paragraph of the discussion section:**

....such as hospital admissions....

In addition, a clinical relevant advantage of assessing exacerbation recovery time is that it assesses effectiveness in all exacerbation episodes and not only those followed by healthcare contacts or hospital admissions. Effectiveness in terms of decreased CCQ recovery time is equivalent to a decrease in the impact of these episodes on health status and thus highly clinical relevant from a patient perspective.

2. 15% expected loses to follow-up seem somewhat high for a 6 month trial, aside from drop-outs. Authors could discuss more why this proportion has been selected, and if differential loses to follow-up are to be expected.

**Added third paragraph of sample size section:**

Since symptom-based exacerbation recovery is the main outcome measure, dropout is defined as premature and for any cause interrupting or ending daily symptom registration, for at least 3 weeks. Data on dropout rates in similar randomized trials using daily symptom monitoring are relatively scarce. Two studies documented a dropout rate of 14 % (5) and 12 % (11) respectively.

3. There are minor spelling mistakes that can be corrected with a final review of the manuscript.

After accurately re-reading by all co-authors some minor spelling corrections have been made.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:** no competing interests
Reference List


