Reviewer's report

Title: Reliever salbutamol use as a measure of exacerbation risk in chronic obstructive pulmonary disease

Version: 2
Date: 17 December 2014

Reviewer: Megan Hardin

Reviewer's report:

Dear Editor,

Thank you for the opportunity to review the manuscript by Jenkins et al, “Reliever salbutamol use as a measure of exacerbation risk in chronic obstructive pulmonary disease.”

In this retrospective cohort analysis, the use of rescue inhaled short acting bronchodilators was assessed as a predictor of exacerbation in subjects with moderate to very severe COPD. This is a well-written manuscript that addresses an important knowledge gap, the ability to identify COPD subjects who are at risk for exacerbations. Overall, while I think that this paper does a good job addressing this issue, I would not recommend acceptance in its current form. However, after addressing the issues below, I would find this a potentially useful analysis.

Major compulsory revisions

1. Study population:
   The authors wish to examine the utility of recent rescue inhaler use as a marker of future exacerbation risk. However, I am concerned that the study population that they are using does not represent the general COPD population and therefore limits interpretation and overall generalizability. I would recommend the authors address the following issues regarding their study population both in the methods and discussion:
   
   2. The subjects were enrolled in a study in which they were asked to discontinue their usual COPD medications, and start LABA or LABA/inhaled CS. Prior data suggests discontinuing inhaled CS could predispose to exacerbations, and in fact the LABA alone group did seem to have more exacerbations, as was noted in the original paper. Additionally, the single use of just LABA in severe to very severe COPD is not recommended by treatment guidelines, and therefore this does not represent ‘real world’ standard of care. These facts limit the interpretability of findings in the LABA group. Could the authors limit their main analysis to the BUD/FORM group alone?

   3. The subjects at baseline appear to have a very high frequency of rescue inhaler use, suggesting poorly controlled COPD. Standard of care would be to add additional COPD medication at the point that rescue inhaler use reaches greater than 4x/day, but it is unclear from this manuscript if subjects did
experience escalation of care at that point. The authors could report medication use prior to study enrollment, or again, limit their analysis to just those subjects on BUD/FORM. A further sensitivity analysis might include only those subjects who had < 4 rescue inhaler uses/day at initiation of study.

6. Statistical analysis:
It is unclear how the authors identified the inhaler use cut-off points, and how many subjects were in each cut-off. Could the authors perform a propensity score analysis or some other method that would allow them to identify cut-off points in an unsupervised manner, and then test the validity of these cut-off points as predictors of exacerbation in another population? Alternatively, is there a certain threshold that would predict future exacerbations? The authors’ extensive clinical expertise should not be discounted, however it may introduce some bias in to the analysis.

Minor essential revisions
2. Study design and methods:
Lines 103-114-Please clarify which subjects were included in this analysis, including how their COPD was staged.

2b. Did the authors adjust for additional covariates in their analysis such as smoking or age?

3. Results p 10, lines 153-156; Table 1:
The authors report that there were no baseline differences between the BUD/FORM and BUD groups, however they do not present P values in this table.

4. Table 1: Could the authors present the number of subjects who fall in to each arbitrarily defined rescue inhaler cut-off point at the beginning of the study?

5. Figure 2b is confusing, and I would suggest an alternate means of presenting this information.

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**
I declare that I have no competing interests