Author’s response to reviews

Title: Treatment of Idiopathic Pulmonary Fibrosis: A network meta-analysis.

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Author’s response to reviews:

The following letter has also been uploaded in Word format entitled "Response to BMC editors".

January 13, 2016

Dear Dr. Alam and Editors at BMC Medicine,

Thank you for your review at BMC Medicine of our manuscript, "Treatment of Idiopathic Pulmonary Fibrosis: A network Meta-analysis." We appreciate the chance to improve our work. Herein, we respond to the Editor's comments and Reviewers' comments. Our detailed responses to your specific suggestions are preceded by ** and in blue font, below. We have uploaded a marked up and clean copy of the revised manuscript.
Reviewer reports:

Reviewer #1: The paper is well written and the information (although as honestly recognized by the Authors some weak points are present and for me also unavoidable) provided can be extremely useful for the medical community dealing with IPF patients

Reviewer #2: Congratulations on completing your work.

This is a very well-done study, and the results are presented very nicely.

I have only two very minor critiques:

1. Page 4, line 20: the sentence starting "Acute exacerbations..." needs modification. The sentence suggests only survivors of AEx's often experience a step-wise decline in PFT parameters, when in fact, the step-wise decline is present in many patients from the time of diagnosis.

   **This sentence has been revised. It now reads:**

   “Patients with IPF often experience a step-wise decline in pulmonary function test parameters and clinical symptoms and acute exacerbations are associated with increased mortality.”

2. Page 4, line 45: regiments should be regimens.

   **Thanks for picking this up – we have revised.

Reviewer #3: General comments on statistical methods:

1. The choice of network meta-analysis is entirely appropriate.

2. The methods used are appropriate, thoroughly described and appear to be correctly applied.
3. Results are generally very well presented.

Discretionary revisions:

4. PRISMA guidance recommends inclusion of an example of the exact search strategy for one of the databases, including all search terms, synonyms, Boolean operators, exclusions, etc. The systematic nature of the literature search forms the basis for the meta-analysis, so this is an important element to include as supplemental material.

**We have now included the MEDLINE search strategy in the appendix.

5. I would have liked to have seen more transparency in the assessment of any inconsistency, as this is an important element in interpreting results. The authors have already done this analysis as part of the GRADE assessment, but it would be good to have the separate information on which this was based.

**Following GRADE principles, overall certainty in evidence is judged based on the domains inconsistency (including incoherence), imprecision, risk of bias, indirectness, and publication bias. Inconsistency of the pooled estimate is evaluated following a few strategies which include: similarity of point estimates from included trials, extent of overlap of confidence intervals, and statistical criteria including tests of heterogeneity (eg Chi square) and the I-squared value (for reference see Guyatt et al. GRADE guidelines: 7. Rating the quality of evidence – inconsistency. Journal of Clinical Epidemiology 2011).

Applying this to network meta-analysis is slightly more complex. Therefore, GRADE has suggested an elaborate and extended approach for Network Meta-Analysis (A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis) which was cited in our manuscript (Puhan et al, BMJ 2014 DOI 10.1136). Direct estimates are assessed for inconsistency following the criteria listed above (as would be applied to a standard pair-wise meta-analysis). Indirect estimates are lowered for inconsistency if one of the direct comparisons that make up the indirect loop were judged to be inconsistent.
As our analysis only included indirect estimates, the overall NMA estimate was lowered for inconsistency if the indirect estimate was inconsistent. Following these rules, none of our NMA point estimates were judged to be inconsistent.

This overall approach is consistent with the one outlined in the BMJ publication by the GRADE working group cited above.

6. Likewise it would be good to have the assessment of publication bias (e.g. funnel plots in supplemental material) presented. Risk of bias is already presented in table 1, with at least the reasons for low scores provided.

**Although we would have liked to assess for publication bias in the direct comparisons, the small number of studies included made this impractical based on statistical criteria. Most direct comparisons had only 1-2 studies included which does not allow for any formal assessment. Publication bias is a domain that is separate from risk of bias (as per Cochrane) or limitations in study design or execution. However, we believe that given the small number of studies and the for-profit interest publication bias is a possible concern. But we did not believe that this concern is sufficient to further downgrade the quality. We noted this in the revised manuscript. The following two sentences were added to the GRADE description within the methods section:

“Publication bias could not be formally assessed based on statistical criteria due to the small number of studies included in the direct comparisons. Although the potential for this bias is real given the small number of studies and the for-profit interest, we did not believe this concern was sufficient enough to further downgrade the certainty in the evidence.”

7. In my downloaded pdf of the article the symbols used for the grade scores looked a bit messy. Hopefully these can be tidied up for publication.

**The version we uploaded to the BMC website the GRADE symbols looked fine. However, we will wait to hear from the publisher as if this is the case we can produce a higher quality version. Thanks for pointing this out.
Editorial Requests

Please note that all submissions to BMC Medicine must comply with our editorial policies. Please read the following information and revise your manuscript as necessary. If your manuscript does not adhere to our editorial requirements this will cause a delay whilst the issue is addressed. Failure to adhere to our policies may result in rejection of your manuscript.

Ethics:

If your study involves humans, human data or animals, then your article should contain an ethics statement which includes the name of the committee that approved your study.

If ethics was not required for your study, then this should be clearly stated and a rationale provided.

**We have added a statement that ethics approval for this systematic review and network meta analysis was not required.

Consent:

If your article is a prospective study involving human participants then your article should include a statement detailing consent for participation.

If individual clinical data is presented in your article, then you must clarify whether consent for publication of these data was obtained.

**This is not relevant to our study and therefore not included.

Availability of supporting data:

BioMed Central strongly encourages all data sets on which the conclusions of the paper rely be either deposited in publicly available repositories (where available and appropriate) or presented in the main papers or additional supporting files, in machine-readable format whenever possible.
Authors must include an Availability of Data and Materials section in their article detailing where the data supporting their findings can be found. The Accession Numbers of any nucleic acid sequences, protein sequences or atomic coordinates cited in the manuscript must be provided and include the corresponding database name.

**We have now included the search strategy in the appendix.**

Authors Contributions:

Your 'Authors Contributions' section must detail the individual contribution for each individual author listed on your manuscript.

**This was included in our initial submission.**

We are grateful for the opportunity to improve the presentation of our work and hope that we have addressed the suggestions and concerns raised through the peer-review and editorial review process.

Sincerely,

Bram Rochwerg
Holger Schünemann
On behalf of all authors