Author’s response to reviews

Title: Randomized Controlled Trials of Pharmacological Treatments to Prevent COPD Exacerbations: Applicability to Real-life Patients

Authors:
Laurie Pahus (laurie.Pahus@aphm.fr)
Pierre-Régis Burgel (pierre-regis.burgel@aphp.fr)
Nicolas Roche (nicolas.roche@aphp.fr)
Jean-Louis Paillasseur (jean-louis.paillasseur@effi-stat.com)
Pascal Chanez (pascal.chanez@univ-amu.fr)

Version: 1 Date: 09 May 2019

Author’s response to reviews:

Dear Editor and Reviewers,

We really appreciate the time you have dedicated to the review of our manuscript.

Below is a point-by-point response (R) to the comments (C). The revised version of the manuscript has been submitted with changes highlighted in yellow.

Simon Brill (Reviewer 1):

Major comments:

C1. Statistical analysis.

In view of the small numbers of trials included, I think statistical analysis only has limited application here. For example, "With a mean eligibility rate of 10.3%, phase IV trials (n=5) do not have a higher rate of eligibility than phase III trials (19.3%, n=11) from a statistical perspective (p=0.31)." The proportions are very different and the small sample size means that the absence of statistical difference is not necessarily meaningful. I think this is qualitative research and should be presented as such. For me the conclusions drawn will be no less meaningful.
R1. We agree with this comment. Accordingly, we have updated the method and results sections to present the results as qualitative. The text mentioned in this comment has been updated to:

“Eligibility rates in subgroups of trials

Phase IV trials (n=5) have a mean eligibility rate of 10.3% while phase III trials (n=11) have a mean eligibility rate of 19.3%. These results are shown in figure 4 along with eligibility rates by pharmacological class of tested agents and starting year of RCTs.”

C2. Alongside this, I think it would be nice to produce a 'headline figure' - how many patients were eligible for all trials after all inclusion criteria were applied (i.e. the most stringent criteria). It may also be worth applying Herland's fictive criteria (reference 17) for comparison. My feeling is that clinicians considering prescribing a treatment for their patients do not consider the differing exclusions in different trials and therefore this would be useful to report.

R2. We respectfully tend to disagree with the idea of a fictive RCT. We think that one strength of our study is to demonstrate the poor eligibility rates of real, existing trials. Some criteria are required in all trials but the thresholds may vary (in part due to different study aims), making it difficult to identify a “typical criterion”. We however understand in the comment the need for information about the number of patients eligible for each trial in order to make comparisons. Hence we have added to table 1 a column with eligibility rate of each trial.

C3

2. Missing data

Reference is made to missing data, but the proportion of missing data is not given. This is important and should be included. It would also be worth running a sensitivity analysis with any missing data excluded and reporting whether the findings differ when only complete case records are included. I do however accept the authors' argument that - by assuming eligibility in the case of missing data - the conclusions presented here are not weakened.

R3. The reference made to missing data in table 2 may be misleading. This data is missing for 100% of patients because this was not collected in the iBPCO database. As a clarification, we have replaced in this table and in the text the term “missing data” by “uncollected data”.

C4.

3. Discussion
I felt personally that the discussion was over-long. I think the impact of this paper would be considerably strengthened by reducing the length here and focussing on key messages. Within this, I would like to see a little more specific discussion about comorbidities, as I was surprised by the low ineligibility proportions due to comorbidity (11.5%, 16.1%). This should be done with reference to the scope of the Initiatives-BPCO database.

R4. Discussion has been shortened and modified. A statement has been added to acknowledge the low ineligibility proportion due to cardiovascular comorbidities in our cohort as follow:

“If allergic status and diabetes rates are consistent with previous epidemiologic studies, we found lower cardiovascular comorbidities proportions in our cohort than previously reported (30, 31) while these were not exclusion criteria to enter the initiatives-BPCO cohort. Only arterial hypertension, heart failure, myocardial infarction and arrhythmias were collected in our database.”

C5

4. Definition of tertiary care

This may differ between countries and should therefore be better defined here. The authors mention that these were 'university hospitals' - but (for example) in the UK sense, 'tertiary care' for COPD implies the existence of a regular formal multidisciplinary meeting, access to subspecialist therapy e.g. LVRS, transplant etc. Anything less than this would be a secondary care population, albeit in an academic centre. It should be clarified exactly what this means so that the population in the Initiatives-BPCO database can be better understood.

R5. The reviewer is completely right when pointing this out; in France, tertiary care is hospital care (primary being general practice and secondary private specialized practice). Therefore we replaced tertiary care university hospitals by “academic centres”, which has a more universal meaning.

Minor (discretionary) comments:

C6. Table 1 - it would be useful to also include a column with the numbers of patients in each included trial, for ease of reference.

R6. A column has been added in table 1 with this information.

C7. The legend for Figure 4 could be a bit more informative.
R7. Figure 4 title has been updated to:

“Figure 4. Eligibility rates in subgroups of trials differing by their development phases, pharmacological class of tested agents and starting year.”

C8. I felt there was some over-referencing in the introduction; for example, four references are not needed to illustrate the statement that exacerbations decrease survival, a now widely accepted concept.

R8. Agreed. We have shortened the reference list related to this part of the manuscript.

Hannah Whittaker (Reviewer 2): Pahus and colleagues present their work on eligibility of "real world" COPD patients in RCTs aimed at reducing exacerbations. Using the Initiatives-BPCO French cohort and previous RCTs, the authors aimed to: i) identify the number of patients who meet each RCT criteria to determine the most frequent criteria; ii) identify how many patients meet the set of inclusion criteria from each RCT; and iii) compare eligibility rates between different types of RCTs. The main outcome suggests that very few "real world" COPD patients meet the inclusion criteria for RCTS assessing interventions on COPD exacerbations. This paper is clearly written and aims to investigate a clinically important research questions.

Below are my comments and questions:

Discussion

C9. The point on the exclusion criteria is important and should be expanded on. The authors should note that eligibility numbers would be even smaller.

R9. Actually we have not distinguished between inclusion and exclusion criteria and we refer to both in the manuscript when we write “eligibility criteria”.

C10. Variables within the cohort were collected via a questionnaire. This should be mentioned in the limitations.

R10. In the Initiatives BPCO cohort, data are collected in case-report forms through both questionnaires, tests (e.g., spirometry, blood tests) and examination of medical files (e.g., for comorbidities). This has been made clearer in the methods section as follows:
“Briefly, a case-report form was used to collect in patient’s medical file demographic data, smoking history, physician-diagnosed comorbidities, symptoms, dyspnea (modified Medical Research Council scale), results of pulmonary function tests, and the number of exacerbations and hospitalizations in the previous year.”

C11. A paper by Rothnie et al (2018) found that 50% of "real world" COPD patients did not exacerbate in the first year of follow-up. This could be referenced to further highlight the point that RCT eligibility criteria is not generalizable.

R11. Thank you for this reference we missed. We have updated the discussion as follows:

“We focused on RCTs aiming at decreasing the exacerbation risk, which makes it appropriate to enroll patients with a history of exacerbation(s). We must however mention that considering the study primary efficacy endpoint is crucial in the extrapolation of study results to an individual patient. Rothnie and colleagues recently showed that almost 52% of COPD patients do not exacerbate in the first year of follow up and that up to 26% do not exacerbate during a 10-year follow up. Treating these patients with medications that only proved their efficacy on exacerbation rate would not be relevant, but it remains difficult if not impossible to predict the risk of exacerbation accurately on an individual basis.”


FORMATTING CHANGES:
C12 Please rename 'Introduction' to 'Background'.

R12 Done

C13 Please rename 'Material and Methods' to 'Methods'.

R13 Done
C14 Please remove the figure legends embedded within the figure files. All figure titles/legends
should be listed and placed at the end of the main manuscript, after the References, and not
within any of the figure files.

R14 Figures have been removed from the main document. A “figure legends” has been added at
the end of the main document.

C15 Figures should be attached to the manuscript as separate files, and each figure of a
manuscript should be submitted as a single file.

R15 Figures have been submitted as separate files.