Peer Review File

Reviewer A

This is a review article of pulmonary hypertension clinical trials. The concept of the work and data presentation are useful and allow for a global look at the problem of PH treatment. The article needs some revision, as suggested below.

1. Line 78: I think it's an overgeneralization that PH was first observed in 1891, this is the date of the first publication on the subject (by Ernst Von Romberg)
Reply: Changes in the text: The "observed" is replaced by "described".
2. Line 79: The first clinical classification of PH, initiated by the WHO, was established in 1973.
Reply: Changes in the text: The "1998" is replaced by "1973".
3. Table 1. - In the last "paragraph" (percentage content of PH groups) the sum of the groups does not match - probably the columns have been swapped.
Reply: Because some studies have included multiple WHO Group pulmonary hypertension, the combined total exceeds 100%.
4. Figure 2. - Where does the number of studies for developing and developed countries come from for figure B (n=32 and n=180) and figure D (n=70 and n=184)??
Reply: Due to missing data, the total number for each parameter may vary.
5. Please check carefully references.
Reply: We have checked the references.
Summarizing the review, in my opinion there is some discrepancy between the emphasis placed on PAH (survival in PAH, specific treatment, subtypes of PAH) and the presented statistical data, which apply to all types of PH. In my opinion, these are such different groups of patients, due to etiology, symptoms, treatment, survival, etc. that it would be worth better characterizing not only group 1. PH, which will certainly improve the substantive value of the work.

Reviewer B

1. **"Rephrase this sentence"** Line 147-150.
   Reply: change in the text "Trials conducted both in developed and developing countries were categorized as "developed and developing countries", and those only in developed countries as "developed countries" line 153-156.

2. "Correct grammatical error" Line 174.

   Reply: change in the text "We tested the differences between trials in developed countries and those in developing countries in ……" in Line 174.

3. "Why trial sponsored by developing countries was excluded?" On line 209

   Reply: Because the number of study sponsored by developing countries was only one, we were unable to conduct further analysis, so we excluded it.

4. "Mention the percentage of trials" Line 213.

   Reply: We have added "nearly 90%) on Line 213.

5. "Rewrite this sentence for clarity. Whether non-group 1 PH pediatric patients were recruited by developed countries?" on L241-242

   Reply: change in the tex "In addition, non-Group 1 PH pediatric patients were only recruited in developed countries." Line 239-240.

6. "Rephrase this sentense" on L248-249.

   Reply: change in the text "Of the 23,402 study participants, 557 pediatric patients (<17 years old) were invovled in clinical trials without any adult participation." on Line 245-247.

7. "Rewrite for better clarity" on L259-243.

   Reply: change in the text "In developed and developing countries, PPR was highest in clinical trials involving both adults and children, while PPR of clinical trials showed homogeneity in developed countries independent of age." on line 257-260.

8. " Grammatical error" on Line 311.

   Changes in the text: "is"was replaced by the "was" word.

9. "Provide reference" on Line 397-400.

   Reply: we have added references 30-31

   30. Meloche J, Lampron MC, Nadeau V, Maltais M, Potus F, Lambert C, et al. Implication of Inflammation and Epigenetic Readers in Coronary Artery Remodeling in Patients With Pulmonary Arterial Hypertension. Arterioscler Thromb Vasc Biol. 2017;37(8):1513-23.

   31. Nappi F, Avtaar Singh SS. Distinctive Signs of Disease as Deterrents for the Endothelial Function: A Systematic Review. Metabolites. 2023;13(3).
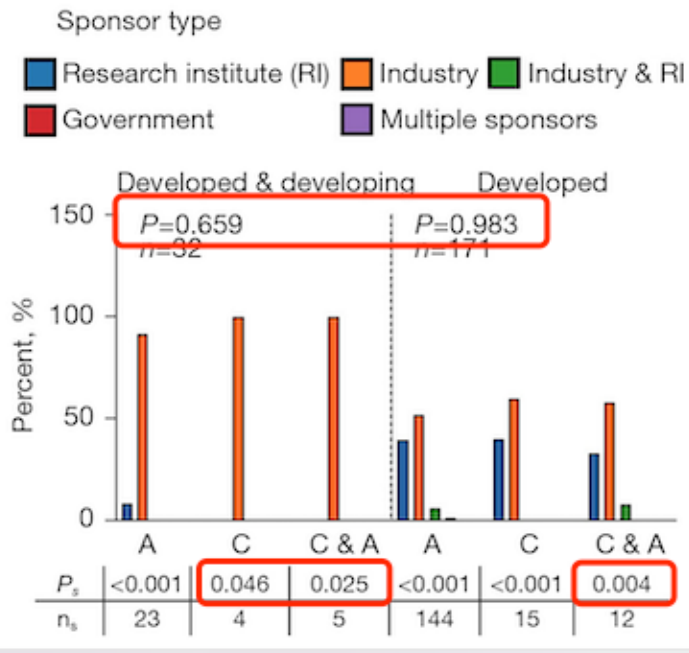
1. Figure 2

Not all the p value in figure 2C are <0.001, please check.

246   sponsor type, followed by research institutions (**Figure 2C**) (all $P<0.001$). As shown in

C

Sponsor type

- Research institute (RI)   Industry   Industry & RI
- Government   Multiple sponsors

Reply: we have deleted the "all P < 0.001"

2. Figure 4

Please explain WHO in the legend.

Reply: we have added: World Health Organization" in the legend.