The Practicability of New Endpoint Measures in Pulmonary Hypertension Trials

Dear Editor,

I read with interest the thoughtful article by Hassoun et al.¹ titled “Updating clinical endpoint definitions.” One of the primary tasks in my role as a pulmonary hypertension (PH) research nurse coordinator is to identify PH patients in our clinic who are eligible and willing to participate in research studies. This is not always an easy task.

As Hassoun et al. point out in their article, PH studies historically have run 12 weeks, requiring several hundred patients, based on a primary endpoint of 6-minute walk distance (6-MWD) test, an endpoint which has fallen out of vogue in the PH community. More recent studies have used morbidity/mortality as primary endpoint. These types of studies require very large numbers of patients (some 1,000 or more) and take many years, some five or more years, to complete. At the recent American Thoracic Society meeting in Philadelphia, vocal PH experts declared this endpoint the be-all-end-all solution to future PH studies. The worrisome scenario that comes to my mind is that in the near future, when a truly novel and potentially curative agent comes to phase II/III testing, there will be no eligible, willing, and available PH patients left to enroll because most will be committed to years-long morbidity/mortality trials. Given the rarity of PH, requiring morbidity/mortality outcomes for all clinical trials may have the unintended consequence of suppressing innovation of novel therapies in the field, thereby reducing any progress in this disease. Progress will come to a slow crawl.

While I do not claim to have the answer for what should be the best endpoint of study, I suggest that there could be a compromise between a historic 12-week outcome measure like the 6-MWD test and a multiyear outcome measure like morbidity/mor-

talidity. Practicability ought to be taken into account. I can only hope that regulatory agencies, along with the PH physician community and pharmaceutical companies, consider recruitment implications and keep the best interest of the PH patient in mind when determining the future of drug trial design in this patient population.

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REFERENCES

1. Hassoun PM, et al. Updating clinical endpoint definitions. *Pulm Circ* 2013;3(1):206–216.

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Updating clinical endpoints in pulmonary arterial hypertension: when challenges are welcome

We thank Ms. Deborah McCollister for her feedback on our recent article titled “Updating clinical endpoint definitions.” McCollister judiciously points out some of the challenges raised with the recent trend among investigators and pharmaceutical companies involved in pulmonary arterial hypertension (PAH) clinical trials to move away from the 6-minute walk distance (6MWD) as a primary outcome in favor of a more composite endpoint, such as time to clinical worsening (TTCW), which includes elements of morbidity (such as hospitalization, clinical worsening, and need for additional therapy) and mortality.