

Ethical Considerations for RCTs in PAH



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A roundtable discussion on ethical issues relating to the conduct of randomized clinical trials (RCTs) with pulmonary arterial hypertension (PAH) patients was held during the May 2009 American Thoracic Society meeting in San Diego. Scott Halpern, MD, PhD, MBE, Assistant Professor of Medicine and Epidemiology, Pulmonary, Allergy, and Critical Care Division, and Senior Fellow in the Center for Bioethics at the University of Pennsylvania, Philadelphia, facilitated the discussion among participants Myung H. Park, MD, Director, Pulmonary Vascular Diseases Program, University of Maryland School of Medicine, Baltimore, Maryland; David B. Badesch, MD, Professor of Medicine, Divisions of Pulmonary Sciences and Critical Care Medicine, and Cardiology, and Clinical Director of the Pulmonary Hypertension Center, University of Colorado at Denver Health Sciences Center; and Michael D. McGoan, MD, Professor of Medicine, Department of Cardiology, Pulmonary Hypertension Clinic, Mayo Clinic, Rochester, Minnesota.

Dr Halpern: Thank you for participating in what I hope is a useful discussion for all of us involved in treating patients with PAH. The goal for our discussion is to elucidate and expand upon some of the ethical considerations in the conduct of randomized clinical trials (RCTs) in pulmonary arterial hypertension (PAH) with a specific focus on novel agents, but not exclusively. The 3 general topics I envision our talking about are, first, barriers to enrollment in RCTs including the scarcity of adequate numbers of eligible patients, refusal of consent, and motivation of patients for enrollment. The second topic regards the potential for conflicts among physicians who simultaneously serve as investigators. Third, we will discuss optimal elements of study design in PAH RCTs, with a specific focus on the use of placebo controls in the modern era, both for new drug development and for comparative effectiveness research.

Let's open it up with what you perceive to be the primary barriers to adequately enrolling patients in trials of novel therapies for PAH.

Dr McGoan: I think there are multiple barriers that exist. For one thing, although we all recognize how important this disease is, compared to illnesses like coro-

nary artery disease, it is simply not that widespread. In addition, it is heterogeneous in terms of severity, symptoms, and substrates. We see the full spectrum in our clinics, but traditional enrollment criteria are very restrictive, which cuts the eligible population down to a small size that ends up not being very representative of the full spectrum of patients we treat. Consequently, there just aren't enough patients to independently partition them among all the needed trials. The end result is that with study conclusions based on populations with very specific enrollment criteria, we wind up treating people who just don't fit the demographic defined by the studies. That's an ethical issue of its own.

Dr Park: I agree. We are getting more referrals, which reflects the growing public knowledge of PAH and the need for research. However, speaking from experience in my own practice, the majority of the patients that we see do not fit the criteria for trial enrollment.

Dr McGoan: I also think that clinical drug studies may in a way be victims of our success in educating the medical community about pulmonary hypertension. There is a much higher level of knowledge about the diagnosis now than, say, 20 years ago, due to the dissemination of information about PAH thanks to organizations such as the Pulmonary Hypertension Association and the American Thoracic Society. So, while there is still room to go, pulmonary hypertension is in fact being recognized more often, but those patients are not always seen and treated in the academic medical centers where the clinical trials are being conducted. This is another obstacle to enrollment.

Dr Halpern: Given the scarcity of patients for trials, how do we as researchers prioritize enrollment in the several different trials for which they might be eligible, being mindful that some patients may receive placebo?

Dr McGoan: A corollary to the scarcity of patients is the number of questions that clinical drug studies need to answer: efficacy of new drugs, combinations of drugs, effect on various endpoints—including survival. Different investigators have their own interests. So prioritization between these interests is a big issue, since not everything can be addressed in a way that provides

meaningful results. But there are no easy answers. Often, clinician investigators are reactive—signing on to pharmaceutical-initiated studies without adequately considering whether or not they or their institution are too thinly spread to provide sufficient enrollment. Prioritization needs to begin locally.

Dr Badesch: We need to continue to encourage the referral of patients to centers of excellence where clinical trials are conducted. While placebo-controlled trials are difficult to conduct in treatment-naïve patients for ethical reasons, current studies are often conducted on the background of other therapies, and in that situation, randomization to study drug vs placebo is often a reasonable option.

Dr McGoon: Agree. I guess the first step of prioritization is at the individual patient level, by deciding whether a patient should be enrolled. This incorporates ethical and clinical considerations depending on the patient's presentation and the specifics of the study.

Dr Halpern: Would there be a role for a centralized body to adjudicate the relative priorities of different competing trial designs for enrolling these patients? Would that improve on, if you will, effective utilization of what is a scarce resource? And if there is a role for that, what would you see as potential push backs to such a body?

Dr Badesch: The possibility has been raised previously, and I honestly think the investigators might feel as though their autonomy and judgment would be restricted in some way if such a system were to be implemented.

Dr McGoon: In an ideal world, that would be helpful. There's been discussion about a consortium to try to orchestrate studies, but it's difficult to imagine how this would be structured or get widespread buy-in. There are so many competing interests.

Dr Badesch: That said, I do believe that clinical research has been relatively successful in the field of PAH, and it may not be necessary to make large changes to the approach that has been utilized to date.

Dr Park: Among the researchers in the field of PAH, I think a basic understanding of priority does exist, which is to gather data to allow us to practice evidence-based medicine. However, as mentioned, there is a very small number of patients who fit the enrollment criteria. So we have the critical questions that we need answers to and a very limited number of patients who can help us answer them. Given these constraints, how do we best proceed to maximize our goals of obtaining meaningful results?

Dr Halpern: Do you perceive any additional barriers in terms of difficulties in obtaining consent for patients who actually are identified and eligible for studies? Or has that not been a big problem?

Dr McGoon: Sometimes consent may be too easy to get. Patients want to be part of the next potential increment in efficacy. Our discussions with them need to provide balance. We have to explain

the potential downside of participating in a trial, such as the follow-up schedule and the implications of randomization and placebo-control. People understandably want to be in the group with the active drug. But we have to remind ourselves and them of examples like the CAST trial in which it seemed, for all the right reasons, that an anti-arrhythmic drug was supposed to help patients and it wound up reducing survival compared to placebo.

Dr Park: It certainly sounded good on paper and made a biologically sound hypothesis.

Dr Badesch: As more therapies are approved, patients learn about and want the commercially available therapy. It is important, however, to understand that "add-on" therapy needs to be based on evidence demonstrating both safety and incremental efficacy. There appears to be rather common usage of combination therapy in the relative absence of good quality evidence supporting this approach. While we have good evidence pointing to benefit from the addition of sildenafil to background epoprostenol therapy, this is not true for a number of the other combinations.

Dr Park: I've run across similar situations. We explain the concept and rationale behind RCTs and how important it is for all parties to adhere to the protocol. Even then, when they enter a clinical trial, patients do so thinking that they will have the choice of receiving individualized care as occurs in clinical practice. Having to adhere to a clinical protocol, which can place some restrictions, may be difficult for patients to understand.

Dr Halpern: So are you as a clinician able to explain the protocol and parameters of clinical trials in a way that enables you to get truly "informed consent"?

Dr Park: We try to have family members present at the time we discuss possible enrollment and we go over in diagrammatic format what the trial design is. They can then choose to have a discussion outside the clinic setting to talk it over further. At the end of the discussion, there are times when the patient does not sign due to certain specific factors but giving the patient this opportunity to discuss with others makes them better informed and a more willing participant.

Dr McGoon: I do a lot of selection even before I raise the idea of participation in a clinical trial with a patient. I may need to bypass the concept if the patient doesn't grasp the idea or if they have progressed rapidly in their disease and this is initial treatment or if the current therapy is okay. Under those circumstances it may not be appropriate to take a chance on an investigational drug vs an already approved medication.

Dr Park: Pre-screening is absolutely necessary and I think we do this among our patients to varying degrees. As mentioned, we are seeing a more elderly patient population who usually have a greater number of co-morbidities so careful pre-screening becomes even more crucial.



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Dr McGoon: On the other hand, it could be argued that pre-screening may be an imperious role. If a patient meets enrollment criteria, how much latitude should we have in deciding whether the idea of a study should be presented to the patient?

Dr Halpern: Do you think the act of presenting the option to a patient of being in a trial as both the patient's physician and as one of the investigators in the study has a persuasive role? And does it create conflicts?

Dr Badesch: I don't think so. I try to present a balance between commercially available options and the therapies being tested in clinical trials to our patients. Who else can step in and present those options adequately? I do try to openly disclose any relationships that I might have with the sponsor of a study, and these relationships are also delineated in the consent form.

Dr McGoon: Most of us in the PAH medical community know each other, and from what I've seen and heard in discussions about study design and conduct, I think I can say we are conscientious in providing information clearly and appropriately. Nevertheless, subtle biases are also at play here. If a physician is on a steering committee, even if there is no objective gain for that physician, he or she might somehow be perceived to have an interest in a study having a positive outcome, even if it's only to be included on a publication that gets more attention than a negative outcome would. I'd certainly like the drugs to succeed, though I think that I frame this as a desire to have more effective therapeutic options.

Dr Badesch: The design of a trial may be set to optimize the likelihood of detecting a treatment effect. The inclusion and exclusion criteria are often rather strict, identifying a study population that might be most likely to respond to the treatment under study.

Dr Halpern: Is choice of endpoints also a factor?

Dr Park: Working with the limited number of patients and the short duration of the trials, trying to assign the best endpoint that will give us biologically plausible and clinically meaningful outcome measure is challenging.

Dr Halpern: What is the optimal outcome measure for a randomized clinical trial in PAH in 2009?

Dr Park: I think that is a question we all are asking. Should there be standardized criteria to be used uniformly in every study? For instance, what factors best determine "clinical worsening" during a trial? Looking at the completed trials, its definition has not been consistent. Some of the endpoints considered are objective while others are subjective. Should they be considered equally or in a predetermined weighted scheme?

Dr McGoon: We need some measure that incorporates a holistic understanding of well-being—some combination of a quality-of-life instrument and survival. Maybe a kind of "area under the curve" accounting for duration and degree of improved quality of

life by whatever criterion is felt to be most appropriate.

Dr Badesch: Quality of life has been under-assessed. It deserves more disease-specific emphasis. That said, quality-of-life instruments take time to complete. The resources and time to implement these instruments is lacking.

Dr Halpern: Do you think it's possible for patients in 2009 to enroll in an RCT with a true placebo control in the absence of background therapy? And the follow-up question is, if they would enroll, do you think it's appropriate for them to do so?

Dr Park: That is probably one of the most difficult questions to answer. We have seen from prior trials that patients who were randomized to placebo arm do not seem to "catch up" during the open-label treatment—their long-term outcome seems worse. So ethically speaking, can we continue to pursue trials with a placebo arm?



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—Dr McGoon

Dr McGoon: The answer depends on the context. Placebo control in a treatment-naïve patient is difficult to justify though it is appropriate in patients who are on appropriately indicated baseline therapy in an add-on study. Even in treatment-naïve patients who fall outside previous study criteria there may be a role for placebo studies, for example, in asymptomatic patients with evidence of mild or purely exercise-induced PAH where the endpoint is progression to some level of

increased severity of disease. Since there is no approved therapy and there is equipoise about whether any treatment delays progression in that situation, use of placebo seems ethically defensible.

Another example would be in an area of the world where there is no alternative option. That presents a whole other question about the health care environment and access to medical care. Is it unethical to conduct trials in that population? Is it appropriate to start someone on a medication with the implied incentive that they would get a drug that wouldn't be available to them otherwise?

Dr Park: Even in the US, if you inform a patient that they will be provided with the drug as part of participation in the trial, how much does that affect the decision-making process? Also as more placebo-controlled trials are being conducted outside of the US, can we apply the data from those trials in making clinical decisions in the same manner that we would with studies performed here?

Dr Halpern: Among patients who are successfully enrolled, what are the primary reasons for their saying "yes" to participation?

Dr Badesch: In many patients, it is an altruistic decision. They want to contribute to gaining new knowledge that might lead to better therapies in the future. That's a major reason to participate.

Dr Park: I think that patients who enter a clinical trial with that motive really do the best. They are committed to the study and are interested in the science and wish to see it completed. They are

conscientious about follow up, adhering to directions, etc. These are the patients who participate knowing that it is because of other patients who were willing subjects like themselves that we have come this far. Since they have received the benefit of others before them, they want to be part of the process and contribute themselves. It's not always so clear for other reasons—trying to please the physician, financial gains, or others.

Dr Halpern: You had raised the possibility earlier that perhaps there is a subset of patients who are enthusiastic about early access to the latest and greatest. Do you think that might be what drives enrollment for some people?

Dr McGoon: Altruism is part of it, but the element of personal gain also exists. People can feel good about participating and I don't think there's anything wrong with that. It's hard to deny that the "carrot at the end of the stick" is that after participating in a randomized portion of the trial, they often will have open-label access to the drug. And often it's free. I'm not sure there is anything wrong with that, but it gets to the issue of incentive and motivation.

Dr Badesch: I have a colleague who actually counsels against open label-extension studies, arguing that they are of very limited scientific value. Because there is no control arm, no one knows if the therapy is of benefit during that extension period. Safety data may also be difficult to interpret. It may therefore be inappropriate to offer participation in an extension study as a carrot.

Dr Park: One could argue that in a disease such as COPD or hypertension, where you have tens of thousands of patients to choose from, it's a different story. When the number of patients involved is as small as in our field, trying to get clinical relevance of a drug beyond the timeframe allotted for the trial with the placebo arm does have utility.

Dr McGoon: The concern of Dr Badesch's colleague strikes me as almost too moralistic. The counterargument is that it would be preferable to have an extended study to understand long-term effects. A Phase IV, if you will. I'd much rather have a trial where the patients are required to come for follow up and formal assessment, instead of trying to tease out adverse events in a post-marketing setting. We need to know what the long-term safety of the drug is. It's not perfect; but an extension study is better than nothing.

Dr Halpern: Let's switch gears to another touchy subject. What are appropriate incentives for physician investigators to participate in these trials? What are appropriate incentives and what are necessary incentives? And just to be clear, when I say incentives, I don't mean specific financial remuneration.

All: There should be no incentives to enroll patients.

Dr Park: I think that should also include any academic incentive, such as recognition based on enrollment. Authorship should be based on the strength of contribution—the designing of the study, administration during the trial, and those critical in bringing the trial to successful completion.

Dr Halpern: There must be some incentives, though, right? Researchers can't just volunteer their time. What are the real-world incentives? Is money received for covering costs of patients—their tests, travel, time?

Dr McGoon: It's variable. It seems reasonable that the costs of performing a study should be borne by the entity with a financial stake in the drug. That includes tests, investigator and study assistant time, patient travel—anything beyond the costs of otherwise clinically-indicated processes. The research is part of the investigator's job—it's not volunteering, but neither is it to be gainful. Nor should it be a loss to the investigator or the institution, which on occasion it has been.

Dr Halpern: Let's go back to authorship. How are things like authorship currently being determined?

Dr Badesch: Those who are involved in design of the study, analysis of the data, and writing of the manuscript, are usually listed as authors. The principal investigators from several of the highest enrolling sites are often also included in the author list. Is that an incentive to enroll? Perhaps.

Dr Park: I suppose the ethical question remains—how does that influence the investigator? And if I can play the devil's advocate:

Is that terribly wrong?

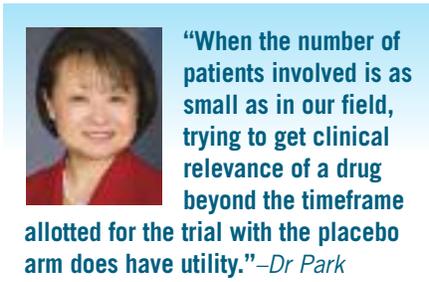
Dr Badesch: That's effort-proportionate recognition, rather than incentive to enroll.

Dr McGoon: If Dr Park enrolls 100 patients, was recognition her incentive to enroll patients? What's wrong with enrolling patients? But if it encourages being loose with applying entry criteria, that's a big problem. My experience being on some clinical endpoint committees where you can see the history of patients once an endpoint comes up is that you sometimes wonder in retrospect just how did this patient get involved in the trial?

Dr Halpern: There has been some media attention recently about the problem of ghost authorship where people who appear as authors were either not involved in the design of the studies or were not involved in the writing of the manuscript. Do you perceive that to be at all prevalent in pulmonary hypertension?

Dr Badesch: I've never seen a problem with direct oversight by authors in the manuscript editing process. Perhaps that's somewhat unique to our field, but the investigators and steering committee members seem to be genuinely engaged, and truly invested in seeing an accurate, fair, and balanced presentation of the results of a trial. Authors will accept help from writers and statisticians, but I've not seen a lack of involvement. I consider ghost writing to occur when someone else writes the paper and you simply put your name on it. On the contrary, most pulmonary hypertension investigators are engaged, outspoken, and very much involved in the preparation of the final product.

Dr McGoon: I agree. The only time I had a draft to review from another writer the paper was directed at a lay audience. It was so bad, I had to rewrite it. It's harder to rewrite than start from



scratch. There are some registries where drafts of abstracts may come from other than the investigator such as from the statistician who has been contracted with the registry. They are involved with the study; they have been in the study design, and they're objective. They are not the sponsor. I don't have as much problem with that, especially knowing that PH papers will be gone over by every one of the coauthors with a fine tooth comb to a fault.

Dr Badesch: PH researchers are people who revise their own revisions, seeking the best possible manuscript in the end.

Dr Halpern: Is there sufficient direct access to the data by authors? Or is it a case of authors' interpreting the numbers that are provided to them?

Dr McGoon: That's a good point. I've always been a little troubled by the relationships among study sponsors. You develop relationships with individuals sponsoring the study; you develop a trust, rightly or wrongly. There would be room for lobbying the system for the data repository to be one of the academic institutions participating in the study and analysis. The commercial entity can contract with an academic institution just as easily as a company whose relationship we aren't privy to.

Dr Park: An important factor is having access to the raw data. One of the things that has to be understood with the members of the steering committee and the sponsors is when the members need to see specific information, they would have to be provided. There's always concern about the time, the cost, and other factors that come with such a request, but how can you not have such provisions if you're going to put your name on the analysis and the results of the study?

Dr Badesch: It is often required by top-tier journals.

Dr McGoon: One of the nice things about the REVEAL registry, as an example, is that each institution has access to its own data.

Dr Halpern: To all the data?

Dr McGoon: At this point, no. The data reside in an independent repository.

Dr Halpern: Are there other tensions in conducting randomized trials in the current environment?

Dr McGoon: There is a bad side to every good intention. Recognizing that there are biases and opportunities for unethical treatment of patients has evolved into a gigantic morass of regulations, and the paperwork is challenging. Just the idea of getting a study approved is daunting to an individual institution. That might be considered as a well-intentioned but definite impediment to conducting research. If you look back to the '60s, they accomplished things one after another just like that. That's because they just thought of something one night, and did it the next day. Obviously, though, we wouldn't have regulations now if there hadn't been abuses in the past.

Dr Park: In the current era, there is a vast difference in the level of difficulty of getting a study approved from a centralized IRB vs an institutional IRB, as an example.



“Given the scarcity of patients for trials, how do we as researchers prioritize enrollment in the several different trials for which they might be eligible?” – Dr Halpern

Dr Badesch: I think that's a great point. Centralized monitors can provide a broader overview of study conduct and progress. Individual IRBs create significant duplication. It's the aggregate data from all of the sites that really make sense. There are some researchers who are strongly advocating for centralization of monitoring. I'd generally agree with that approach.

Dr Park: We are limited by personnel issues and availability of nursing time. These are tough challenges for us to prioritize between working with our coordinators to keep on top of all the regulatory demands, provide proper care to the patients, and participate in clinical trials that are worth conducting with the questions that need to be answered.

Dr McGoon: I'm thinking it would be very interesting to present these same questions to lay people, to patients. It would be interesting to hear their concerns and priorities. We should all have the same concerns.

Dr Halpern: Indeed, this seems like a useful area for future research. And with that future direction in mind, we'll bring this dialogue to a close. I'd like to thank you all for your insightful and candid comments on these issues that lie at the core of our ability to move the field forward in a clinically relevant and ethical manner. ■