Of Ethics, Trials, and Tribulations


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Experts representing different parts of the team involved in clinical trials came together on a call to discuss the current state of conducting clinical trials in PAH. Below is the account of the invigorating conversation moderated by guest editor Harrison Farber, MD, from Boston University, with Frederic Bodin, MD, VP, Head, Global Medical Science and Communication, Actelion; Scott Halpern, MD, PhD, MBE, University of Pennsylvania, and Rino Aldrighetti, President, Pulmonary Hypertension Association.

Dr Farber: I have about five or six topics I would like to cover. If we cover all of them, fine, but there are two or three that I think are essential. The first topic I wanted to talk about is very simple: In this day and age, are placebo-controlled clinical trials in pulmonary hypertension now obsolete? Are they still relevant? And if they're obsolete, how do we get the information that we need to find out about drugs?

Dr Halpern: I would start by drawing a distinction between placebo-controlled trials where the control group receives only placebo versus those in which placebo versus the active intervention are used as add-on therapy while allowing patients to remain on any other vasoactive medications that may be receiving at the time of enrollment.

Dr Farber: Let's go back and look at this issue more closely. Do we believe currently that given the state of pulmonary hypertension, true placebo-controlled trials in which the person is on no background therapy and receives either active drug or true placebo, are no longer doable? Are they obsolete? Are they relevant? And if so how do we get around all of this? Knowing in fact that if somebody is on background therapy the response difference between placebo and drug is probably going to be much less than in previous trials.

Dr Bodin: We face this question regularly as we conduct clinical trials to test new drugs. I think there are two aspects that are essential to us. The first aspect is the duration of the trial. If the duration of the trial is two or three months, it is unlikely that two or three months of delayed intervention will have a long-term effect, especially because stable patients are included in clinical trials. Another aspect, which is country specific, is also important to consider: in some countries, there is no PH therapy or only therapy such as calcium channel blockers and anticoagulants and so that would be the classical background therapy that we often find in those patients. In those countries, it is appropriate to run a placebo-controlled study. It is then possible with mixed populations also included in PAH clinical trials: on one side naïve patients and at the same time patients that receive background therapy.

Dr Halpern: I'll respond to both those points. First the point about there not being a high likelihood of clinical deterioration over a short duration of a trial in a true placebo-controlled study: I agree that that's a reasonable probability. Although presently we don't have the data available to show that there are no long-term deleterious effects of being without indicated therapy for two to three months. To the extent we could obtain those data I think that would inform the ethics substantially. Second, with regard to the appropriate background therapy being what is available in the local country in which a study is being conducted, I agree that the available standard in that country serves as a useful framework for thinking about what the control intervention ought to be. The only addition I'd make to that is that when doing a study in a country that doesn't presently have PH therapy available the sponsor of the study takes on an obligation to make that therapy available at affordable cost if in fact it proved effective in that population.

Dr Farber: Okay. We are going to get to this in much more depth I think as we go on. Rino, from the patient advocate standpoint what would you think?

Mr Aldrighetti: I agree with Scott. What we've observed—using the example of Mexico—was a country that was in evolution. Seven or eight years ago there was nothing and what the Center in Mexico City did kept patients alive by being involved in one clinical trial after another. Over time treatments became available in that country. The arrangement always was to keep the patients who were in the trials on the therapies if the drugs showed success. While not ideal, it seemed to me the model was the only option based on drug availability in the country. Fortunately, that situation was a bridge to more recent improvements. We work with PH associations in 50 countries that are at various levels of drug availability. While we certainly would like to see universal availability, that's not going to happen tomorrow. Therefore the issue for us is the creation of a pathway to therapy for people and knowledge about its availability.

Dr Farber: It sort of gets to this point that I think was alluded to by everybody is the fact that there are more and more clinical trials being conducted in—if you want to call them places in the world, third world countries—where a lot of these drugs are not available. If you want to call it outsourcing clinical trials, okay. So there are several questions about this. One of which has

been mentioned, that if you conduct trials in places where there are not pulmonary hypertension drugs available is it your obligation at the end of the trial to make sure that the people who at least were part of the trial have access to those drugs should it be successful? And then two is do the trials in other countries represent patients that are likely to be seen in countries where there is going to be larger penetration of the drug, if you will, just because of the financial aspects and things like that? And I'll throw that open to whoever wants to go first.

Dr Halpern: The view of most ethicists is that for a trial to be conducted in a resource-poor setting, that is only acceptable from a justice perspective if the explicit goal is to test the ability of a treatment to improve the health or wellbeing of people in that country. So to the extent that a drug, if proven successful, was not going to subsequently be readily accessible to all people in that country, not just those who participated in the trial, then it could not be ethical to conduct a study in that setting under any circumstances because then the less well off of the world would be bearing the risks and burdens of research where the benefits would go to the more well off of the world. And that simply couldn't be considered just.

Mr Aldrighetti: There is no question that that's true. This morning I had a conversation with a staff person whose mother is a late stage PAH patient in Florida. As I understand it, the hospital, unused to seeing PAH patients, made a series of errors in terms of clearing out her line that almost cost her life. What turned the situation around is that we had a staff person who was able to get in contact with a specialty pharmacy representative who began to manage the situation. I think that colors my answer today. It is certainly true that to do research without making the drug available to people post-study (assuming success) is not a moral thing to do. But that's only part of the problem. The other part is how you build up a structure where the medical treatment of patients in those countries can be delivered correctly. We're having a hard enough time in the US creating education to make sure that people are treated well and according to the latest knowledge. That's an important part of the issue as well. Even with drug availability, PAH remains a complex disease and physician and nurse education is a critical component to be able to treat patients appropriately.

Dr Bodin: I don't think that everything is black and white and it's difficult to talk about moral injustice. If you think about this and if you would adopt what has been said before, then there are some countries where you would never do clinical trials. Wherever you do a clinical trial, the first thing that should be considered is the quality of the data; ie, whether the center is trained to do clinical trials. I think this is very important that we first focus on the quality of the data that are being collected. Every patient at every site benefits from being in a trial. I think this is something that we have observed; the number of visits is higher than is normal. The patients benefit from the standard of care provided in that trial. I agree with what has been said that patients involved in a trial should be provided the drug afterwards. I think that this is the industry standard now. I have a little bit more of a problem to say if the drug will not be made available or cannot be made available in a given country we will not do a clinical trial for one simple reason. It's that I think we don't know. I can give you a clear example of some of our projects that we at a certain point in time because of those reasons we avoided some countries. Today, we have to recognize that the economical status of those countries has changed and that it has been possible to make the drug available in those countries. So I'm not sure it would be moral or justified not to do a trial in a given country just because we anticipate that the country would not evolve economically. I think it would deprive some very good investigational sites the benefit from being involved in a clinical trial. So I don't think there is such a black and white answer to your question, Hap.

Dr Farber: Just to make this a little more interesting, there is a statement that I'm going to read from the Declaration of Helsinki which says: "Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and the priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of this research."

Dr Halpern: Yes, I don't think there's any ethics body that would disagree with that statement at this point. In response to the other comment, I don't think the data are at all clear that there is a health benefit to participating in trials versus not. And that even if that were clear, there is a fundamental difference in the ethical underpinnings of care versus research; so at least in the United States, and I don't know the extent to which this is true elsewhere, but for sure in the United States by law, federal law, institutional review boards are precluded from considering the health benefits of participating in a research study relative to receiving treatment outside a study as a benefit or a moral justification for conducting that study. So I don't think that line of reasoning can be used to support conducting research in a disadvantaged nation.

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Dr Farber: Scott, do we have any idea whether this is true outside the US?

Dr Halpern: I do not know. But my understanding is that all countries—I mean almost every country in which research would be conducted—is a signatory of the Declaration that you just read from. So that fundamental statement about access and responsiveness to the needs of the country would stand regardless.

There are simply too many assumptions underlying the premise that a country might evolve sufficiently such that it could afford a drug that was tested much earlier. You know countries don't improve their financial situations and social climates and health care infrastructure at a nearly sufficiently rapid pace to argue that a study of a drug that would not presently be available could still be okay on the idea that that drug might some day be available.

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Dr Farber

Dr Farber: In the case of this disease we're talking about, no matter where you go a relatively small number of patients exist compared to a general population.

Dr Halpern: Yes, I think that's true. And I guess it relates to another question that you asked, Hap, that we didn't discuss as much, which is the extent to which the results of a study in a resource poor setting would generalize to the patient. . . .

Dr Farber: . . . in a setting that's not resource poor.

Dr Halpern: Now you know I don't know that I'm sufficiently expert to comment on that. That's really an epidemiologic question. But it strikes me that in many resource poor settings, perhaps not all, the primary cause of PH is schistosomiasis. And that's certainly not the case in most developed nations. I think it is at least an open question, if not a serious concern, that results among schistosomiasis-induced PH would not necessarily generalize to patients with connective tissue disease-associated PAH, with familiar PAH, with chronic thromboembolic disease, or the other entities that more commonly afflict patients in developed nations.

Dr Farber: I agree with you, Scott. I have no idea whether the response to any drug if you used it in people with schistosomiasis would be equivalent to connective tissue. I don't think we know that. And in fact in a lot of clinical trials for obvious reasons certain subgroups of PAH patients have been excluded. You know in most of the clinical trials people with liver disease have been excluded or people with HIV have been excluded and yet we extrapolate the results of a generalized trial to those patients without actually knowing whether they're actually correct.

Dr Bodin: I agree with the point regarding the etiology of PAH. I don't think we would mix different patients with different etiologies in a clinical trial. I don't think that has ever been done.

Dr Farber: No, because it's very hard because the subgroups would be exceedingly small. And it would take an incredible amount of resources and a particularly long period of time to recruit to fill those trials.

Dr Bodin: Yes.

Dr Farber: You know and you'd run into the problem, too, that even if you just took patients who have portopulmonary hypertension, liver disease associated pulmonary hypertension, the variability in liver function and the variability among those patients would make such a trial almost to be prohibitive. I can't imagine anybody would ever be able to do that.

Dr Halpern: In the schistosomiasis case, it's interesting in that tying it back to the placebo-controlled trial topic that we discussed earlier, I think one could very reasonably and ethically conduct a true placebo-controlled trial of a PAH medicine in schistosomiasis-associated PAH that could be done in any country in which the drug would ultimately be made available should it prove effective in that disease. There is no standard of care that I'm aware of in that specific etiology of PAH. For the same reasons that we wouldn't want to generalize results from schisto-associated PAH back to idiopathic PAH, we ought not generalize in the other direction either.

Dr Farber: So we could go to Brazil and do a placebo-controlled trial with just schistosomiasis.

Dr Halpern: Yes, as long as the agent that is being tested would be accessible to Brazilians if proven successful.

Dr Farber: Actually, Fredric, that's a good question because that is a huge population, a sub-population that has not been studied.

Dr Halpern: Yep. It really should be done.

Dr Farber: People estimate that there are somewhere between 200 and 600 million people in the world who are schisto-infected.

Dr Halpern: If I were running a pharmaceutical industry that made a PAH agent I would be very excited to do this study with one of my existing drugs. Understanding that I might have to reduce its cost to make it accessible in that nation, but even at a substan-

tially reduced cost it would seem that would still be a profitable undertaking or at least a high return on investment study to be done. The development costs are already behind you. So now you've got an agent and you're essentially looking to expand its indications. So I think that's a defensible study to do and probably one that should have a fair bit of buy-in among patients, clinicians, and pharmaceutical industry alike.

Dr Farber: So what do we think about that idea?

Dr Bodin: I think that it's difficult to make an economical, financial, or ethical consideration. As a sponsor you have to think about the return on your investment that satisfies all parties involved. And there are regulatory implications that you have to respect. We are trying to stay away from doing pulmonary arterial hypertension clinical trials in certain countries because the health authorities impose an enormous financial burden for the treatment of these patients. And I think that this is why it's difficult to generalize. Every country has to be considered one by one. And you are confronted with different situations. Country by country you have to consider the quality of the data that you get. And there are countries where you need to do a lot of training. And even with that training you don't get the quality of the data that you would like to get. Going from one country to another increases the standard deviation of any test enormously. And you never know how to power your trials. You need to do so many things at the same time that it's not simple.

Dr Farber: Well, I think that's probably true, because just speaking for myself, I'm this total optimist that thinks that everything can be done. But I have no concept of what it would take to get a clinical trial up and running outside of the United States, or what kind of financial burdens are imposed on companies, what kind of regulatory burdens are imposed on companies, etc. I mean we rightfully or unrightfully so, being based in the US, we're probably very shortsighted and all we know is what we face. But I'm sure it's different, as you pointed out, for every country in the world.

Dr Bodin: Just for example, do you know how much time it takes to set up a trial, to get ethical approval or health authority approval, for a trial in China?

Dr Farber: I have no idea.

Dr Bodin: It's 14 to 16 months. So it's huge and requires a lot of effort. All of the documents that need to be translated into Chinese and the discussions, costs, and resources that go into that are huge. It's not that easy.

Dr Farber: Well, in a way, it almost becomes prohibitive because if it takes say a year or a year-and-a-half to even set up a clinical trial; by the time you get the trial set up the drug you're interested in may not be relevant anymore.

Dr Bodin: That's right.

Dr Farber: There is an interesting book that was written called *When Experiments Travel: Clinical Trials and the Global Search for Human Subjects* by an anthropologist. The author's last name is Petryna. And it's a fascinating—I didn't read the whole thing yet but it's fascinating. She basically goes through the history of clinical trials and the—as she calls them—"the look," the search for human patients. It's really not about pulmonary hypertension, per se, but it's about clinical trials in general when you're looking to find enough patients to do a trial. If any of you have a chance, pick it up.

I do have another question that comes up: given the fact that there are innumerable clinical trials going on now for pulmonary hypertension, and no matter how you want to describe this there are a limited number of patients either available or to which we have access, do we think that this puts a particular burden or a particular stress on physicians to try to enroll patients who may or may not actually fit all the exclusion or inclusion criteria of the trial, or fudge them a little so that they can get the trials done? And if so, how does that affect our data?

Mr Aldrighetti: As the non-physician on this call, I am struck by what Dr Bodin says regarding individual nations' regulatory issues. Any interconnectedness to achieve the size of populations that researchers need seems lacking. There is a need for an international structure to govern some of this, to ethically support the structure and need for clinical trials. Whether in wealthy or poor nations, this is of interest globally for the development of solutions to diseases—particularly rare diseases—where populations are limited.

Dr Farber: What would be a framework for trying to get it done?

Mr Aldrighetti: In the past, we've looked at connecting with some of the UN structures that could facilitate this and we find them even more bureaucratic than our own government structures. I have concerns about how this could be achieved. I think these structures are often driven by small points rather than a large goal. Perhaps an alternative starting point would be conversations within and among the international medical associations. Other assets in making a case and addressing the problem could be

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the patient rare disease associations, NORD in the US and EURODIS in Europe and similar emerging voices in Asia, Africa, and Latin America. In any case, for this issue to become an international target I think that conversation needs to start with the physicians and researchers who could make the case and have credibility to carry it forward.

Dr Farber: So, Frederic, if we were able to set up—let's just live in the pie in the sky world for a minute—an international committee to oversee all this, would that make your people's lives easier?

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Mr Aldrighetti

Dr Bodin: I don't know. I think it would depend on the conditions laid down by this committee. As a sponsor we have so far a different attitude. I agree with Rino—if someone would work at this I would be delighted because that could help us to standardize the approach to clinical research worldwide. That would be a dream. Look at the centralized procedures like in Europe. For example, I remember the time where we had to go to France, to the UK, to Belgium, to Italy, to Spain. Back then we had different questions, different standards. And now we have those approvals that are dependent on the European community and it's much easier for us. So I tend to believe that this might help us if there would be a body of experts who would help us regulate the research worldwide. And that could also maybe resolve some of the ethical questions that were raised beforehand. In the meantime, we try to work country by country with what we can. Every time there is a new trial, it helps if you are interacting with the health authorities; it helps negotiating, it helps contacting the people. All this has been very useful in reducing the timelines and the duration of translations and negotiations. So this is the way we try to approach this problem.

The point I would like to come back to just for one second is about developing countries where the drug may not be available later on. And there could be several reasons as to why a drug may not be available later on. It could be for financial reasons, but it could also be because locally health authorities don't see the need. You know some countries have much higher priorities than dealing with pulmonary arterial hypertension and they have not expressed an interest in even looking at the trials that eventually could be made available to them. So that also needs to be considered. And I don't think that because of that we should deprive these very good centers—and I have several examples of excellent centers in mind that could provide excellent research. They have staff and they could do excellent work. And the patients would nevertheless benefit from the research and being involved in the clinical trials. I have been long enough in pharma that, although I agree with Scott that there is no formal proof, I still believe that the standard of care in the context of a clinical trial is always beneficial to the patients. I have many examples of looking at the placebo group and at the morbidity associated with a disease in the placebo group and the morbidity in the general population where you see that in the placebo group in a clinical trial it's much lower than in the general population. This is not only because of inclusion and exclusion criteria. I agree there has been no formal evaluation of that. But I think, nevertheless, that patients involved in clinical trials do benefit from interventional studies. So altogether I understand and I sympathize with the very strict ethical attitude of selecting the countries where you go on the basis of making the drug available to that country. I'm also sensitive to other aspects which are, I think, very important to consider, which is the benefit to the patients involved in a clinical trial, the benefit to the work that is being done with some sites that are excellent sites, and I think altogether it would be a loss to humankind to not involve those patients or sites.

Dr Farber: To expand on that a little, I agree with both of you actually, Frederic and Scott, that although there are no formal studies to show that taking part in a clinical trial is beneficial, most of us who have patients in clinical trials probably believe that they get better care just in the fact that they're seen more frequently and the fact that if things change it's probably picked up sooner. Now whether you can do something about it or not may be arguable and that's why there are no good data. But I think when we argue about comparing anything against historical controls or past studies, we always use the argument that, "well, the patients now have gotten better care"—just better background care which we assume is due to the fact that they're in a clinical trial. But you're right. A lot of what we do—let's face it—is totally anecdotal, never been studied, and just our feeling that we're doing something productive.

Dr Bodin: You know it's interesting what you just said because we have what we call post marketing registration studies like we follow cohorts of patients and we are following some PH patients with or without treatment in cohorts. And in parallel we are running clinical trials. So at the same time we have the morbidity and the mortality which we can observe in those cohorts and we also have placebo groups. And when we apply the inclusion and exclusion criteria and analyze the subgroups of the cohort placebo group, they always get better.

Dr Farber: It might be good to see these data. Yes,

another issue that I'd like to get into here is: I think most of us in pharma and physicians and from a patient care standpoint are less than happy with the end points or the designs of clinical trials or the designs of clinical trials that have been "forced upon us" by regulatory agents that are trying to find parameters that we think are relevant to patients' clinical outcome. How do we go about setting up better end points, convincing regulatory agencies that there are better end points, and doing clinical trials that probably would have more relevance to our patients' outcome?

Dr Bodin: This question is relevant for us. We have been involved in clinical trials in the past and we continue to be involved in clinical trials. We have seen a fantastic evolution over time. And you're right Hap, we started with the famous researchers and then we educated clinicians about time to clinical worsening. Then people questioned the definition of time to clinical worsening and then we ended up with what I would call an international definition, which was defined in Dana Point. And then we always are now on the next step. We see that we have to define the end points a little bit differently from what has been decided in Dana Point. So it's a permanent evolution. The only thing that is true is that I think progress is nice too, but I don't think we can satisfy ourselves with that. And on our side—and I'm talking here only for Actelion—we have decided that future trials will be only event-driven trials. So I should talk about morbidity and mortality trials. So we look at death and other important events, serious events that happen in the course of the disease and these are now the only primary parameters that we test.

Dr Halpern: I think it's a critical question and I agree with Frederic on that count. You know it's not clear at all what the right end points are right now. There's been a lot written about it. To the extent that we don't know the correspondence between the end points we're using and true patient-centered outcomes that casts some concerns about the utility of conducting these trials at all. And if we're not gaining meaningful information from them, then that has some concerning features with regard to whether we're meeting research participants' expectations when they sign on to take part in one of these things. Having said that, there's a tradeoff between using a surrogate end point, which potentially allows one to see a difference sooner and thereby conduct a shorter study, which has not only benefits for industry but potentially benefits for patients, particularly in the context of a placebo-controlled trial. So if we were to wait for mortality outcomes I think we'd all agree that we'd be talking about substantially longer studies that maybe have some unintended consequences for the participants. So it's a difficult pickle that we're in. I think there are some potential solutions related to using newer statistical methods to validate surrogate end points against true patient-centered outcomes, particularly using the long-term follow-up studies of many of the trials that have been conducted to date. The number of subjects needed for these analyses and the trials needed is not small. So it would require the individual proprietors of these data to come together and make the data available uniformly so that investigators could conduct the appropriate analyses, for example to validate change in six-minute walk distance as an end point in PAH. It's doable. The data are there. But they're not all there in one place.

Dr Bodin: I agree with what has been said here. And Scott, I cannot agree more with what you said about the need for the improved statistical method. It's very interesting actually. We are trying to work on this with well known statisticians. It's difficult and it requires long-term data. The death rate in clinical trials is lower because most stable populations are included; we tend not to have patients who are severely affected and evolve too quickly. They are typically excluded from clinical trials. For the rest of the population who are included in clinical trials, having longer term data in large cohorts and developing specific tools where you can try to identify whether a change in six-minute walk distance or a delta in PVR is a surrogate for mortality is difficult. But I think that with the development of new statistical tools we might achieve this. And I think that will be great. But we're not yet there.

Dr Halpern: The only thing I would disagree with is that the tools are there. They're very well established. What's not there is the data existing in one place. There are no tools that I'm aware of to validate end points within a single trial and single follow-up study. But there are multiple tools available for collapsing data across trials and across follow-up studies. And there are probably enough studies and follow-up studies that have been done to date such that if all the data were available in one place these could be done in a couple months' time. And we'd have answers.

Dr Farber: That would be great if we could actually do that. I think a lot of this gets to the point that, as has been pointed out by everybody, that we don't have a well-documented end point or end points to study. In addition we have a disease in which, unfortunately, the best way to study the disease involves invasive testing. So it makes it harder to develop very good data. You know if we

". . . there are some potential solutions related to using newer statistical methods to validate surrogate endpoints against true patient-centered outcomes . . ."

Dr Halpern

just had some magic noninvasive test that would answer all these questions, obviously part of these discussions would go away.

Why don't we give each person a minute or two to summarize what you think the current ethical issues are and how we get around them. Be concise. Whoever wants to start.

Dr Bodin: Thank you, Hap. Well I again would like to emphasize the fact that what should drive the choice of sites irrespective of the country should be quality first. Now I understand that ethical aspects may be involved; they should be considered. But this is not actually up to a single individual to judge. I think it is up to a group of experts or people specialized in humanities to decide about this. Again criterion number one should be quality. Regarding end points I think there is a need to evolve. I think what we do is always a compromise. I have worked in several fields and I think PH is not an exception. I think with morbidity/mortality long-term trials, long-term exposure, I think we have reached kind of the best we can do so far. And I think that the next step is probably to define surrogate end points and I hope that we will be able to do that soon for the benefit of the medical community, for the patients, and also for us as sponsors to be able to push and support the research forward. Thank you.

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Dr Farber

Dr Farber: Scott?

Dr Halpern: Maybe I'll conclude by raising an issue that you alluded to, Hap, but we didn't get to discuss. But I think is one of the core ethical dilemmas that face the PH community as it strives to improve the evidence base available to guide therapy for this devastating disease: that is the conflicts inherent in physician/investigators serving those dual roles simultaneously where the investigators designing and taking authorship on most of the trials are also those who are charged with recruiting patients. In an ideal world and in more prevalent diseases, the standard would be to have those two roles very separate. It's not particularly practical in the PH world because just as there aren't that many patients there aren't all that many clinicians expert in management of the disease. So we need to grapple with this by thinking through different ways to mitigate those conflicts, as they probably cannot be eliminated. And ways of mitigating would probably take the form of eliminating any residual financial incentives for clinicians to enroll patients in these trials. But also to be sure that we curtail the use of authorship or other professional advancement incentives based on recruitment. Trial authorship or study authorship should be determined prospectively and independent of how successful one is in enrolling his or her patients. And that would go a long way toward reducing the conflict a physician-investigator faces in deciding whether a particular patient is or is not appropriate for a clinical trial.

Mr Aldrighetti: The Pulmonary Hypertension Association is a successful nonprofit that has been built upon the engagement of all elements of our community to achieve a simple purpose—a cure for this terrible disease—and, until we have it, better treatments for patients and a better life for patients and their caregivers. We do this based on the belief that any person whose life is touched by PAH has the right to fight back as much or as little as their health and interest allow. Our job at PHA is to make that possible.

This approach gives people hope and ownership of all we do. It also allows us to exceed what others might think of our numbers of 20,000 to 30,000 diagnosed patients in the US (compared to diabetes 24,000,000) would enable us to do.

In recent years our struggle to do the right thing on behalf of patients has been made more difficult, particularly in regard to our relationships with the pharmaceutical industry. We carefully built those relationships upon clearly defined ethical ground. We recognize our common and divergent interests and the support we will and will not seek or accept. Over time we have experienced unfortunate obstacles as a result of actions by regulatory agencies and political leaders.

We understand that regulators are charged with protecting the public by providing reasonable and important regulatory oversight. But what we are experiencing in today's rapidly evolving climate may best be described as "unintended consequences" that result in providing fewer, not more, safeguards for pulmonary hypertension patients.

Sometimes I fear we are moving closer and closer to the reality described in Kurt Vonnegut's great short story, *Harrison Bergeron.* And that would be a shame.

Dr Farber: Unfortunately, I think we've reached the end of our time allotment, although I think we could go for another hour without any problem. Frederic, Rino, and Scott, I really do appreciate this. I thought this was an outstanding discussion.

Speakers: Thanks so much. Thanks for coordinating, Hap, it was great.