Pulmonary Hypertension Clinical Trials and COVID-19: A Discussion With John Ryan and Roham Zamanian

In this special discussion for the Pulmonary Hypertension Association, Guest Editor John J. Ryan, MD, MB, BCh, BAO, of the Division of Cardiovascular Medicine at the University of Utah in Salt Lake City, Utah, spoke with Roham Zamanian, MD, Associate Professor of Medicine and Director, Adult Pulmonary Hypertension Program at Stanford University in Stanford, California, on the impact that COVID-19 has had on clinical trials for pulmonary hypertension.

Dr Ryan: My goodness, it's an incredible time we're in. What we want to touch on is the impact of the COVID-19 pandemic on pulmonary hypertension (PH) research. Based on your expertise in the field and the relationships you've built over the years, we felt that your perspective and experience would be representative of what a lot of people are dealing with. Can you talk to us about the impact of COVID-19 on your research program?

Dr Zamanian: That's a really broad question, but I think I would be remiss not to point out that I don't think anyone expected not to be impacted from a research perspective by an astronomical event like this. I think what you may hear, at least from our single center experience, are things that are, both in a good way and a bad way, impacting research in general but especially for a rare respiratory disorder.

Our perspective is as a center where we conduct basic, translational, and clinical research; and on the clinical side, we do our own academic studies, some National Institutes of Health (NIH) funded and some sponsor initiated. Across the board, this pandemic has strained and stressed our resources. I'm not the expert in the basic studies, but I can tell you that, from what I hear from my collaborators, the conduct of basic research has been impacted by the footprint of the laboratory bench environment, in other words, the limitations of having a number of postdoctoral and other research colleagues in a small laboratory environment.

When the pandemic initially hit, there were tremendous limitations, and as we moved on through more of a progressive easing of those limitations, the conversation very quickly became about how many postdocs per square meter would be allowed to be in an enclosed indoor laboratory bench environment. That's what I hear the most about from our bench researchers, and the limitations on mobilizing and activating postdoctoral researchers and research scientists back into the laboratory with or without COVID testing has been really, really interesting.

On the clinical translational side, same thing. What we saw initially was a rapid closure of exposure, meaning there were institutional mandates on interactions at the university medical center between our clinical research subjects and the clinical research team. I think one of the things that we learned early on was how important communication is at the Department of Medicine and at the university level. I don't think anyone was prepared to have these kinds of organized conversations about what would happen to clinical research.

We were stuck in a situation in which we felt that the experimental therapies being offered to these patients with a rare disease was, in a way, lifesaving; at least we felt that it was crucial that these were subjects who really needed to still experience the clinical research conduct. Initially, it was a fog-of-war situation where communication was difficult; we didn't know who to get permissions from, but eventually, the Department of Medicine set up a system where we proposed and got authorization for conduct of clinical studies that we felt were urgent.

To do this in a more organized way, the bottlenecks were the ability of patients to come on campus on the medical side to conduct their clinical research activities, the protocols by which our clinical research staff could come to the medical center to evaluate these patients, and what the proper environment was for those interactions to take place. Did the clinical research team need to get COVID tested? What about the subjects? Did they need to be tested every time they came in?

Within that tangle of issues was the idea that respiratory function test, pulmonary function testing, ventilation/perfusion testing, 6-minute walk testing—in the very early days, at least with the 6-minute walk—there were barriers to us conducting those indoors by American Thoracic Society (ATS) standards because of the belief that submaximal exceptional study would generate particles that could be dangerous to both the performing candidate and the respiratory therapist or research coordinator. Eventually, we devised protocols with masking, and if you wonder what masking would do for those exercise tolerance tests, we spun out protocols from that. It wasn't very quick for us to get back to pulmonary function testing. We had a whole lot of exceptions and requests to both sponsors and the NIH for exceptions of pulmonary function tests if we needed to perform them. For example, with the ventilation/perfusion tests, we could do with just the perfusion.

Dr Ryan: Thank you, Roham. As you look at this now and as you look toward the future, do you feel that there are particular groups in your research environments, either interventional procedures, drug investigation, basic science, that have been disproportionally affected, or is there a patient population in your study that has been disproportionately affected?

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Dr Zamanian: I think the things that the institution views as less justifiable are things that are viewed as lower priority, for example, the Pulmonary Hypertension Association (PHA) registry, very relevant to our conversation here today. The institution did its best, but there was a lot of hesitation, also for the patients who felt that they were stable enough and just wanted to have a telehealth medicine visit instead of coming in, and the tidal wave of follow ups and new enrollments that we have missed thus far probably bears the largest footprint of the impact of the pandemic.

I can tell you that biological sample collecting for our own biobank has been deeply affected because of both the hesitation of patients and conducting blood testing and sample handling in an era of a respiratory-transmitted disease. Now, for us, blood banking is less of an issue, but we have a program here for collecting exhaled breath condensate in patients with PH, and certainly that's not at all justifiable or dangerous depending on your perspective. A lot of these projects, certainly the ones that are more on the academic side or NIH funded, already have very lean budgets. Also, NIH trials that depend on 6-minute walking tests being collected at a certain point in time, those patients are now no longer allowed to come in for just a simple research visit. We lose those measurements as well.

But I think the pandemic isn't all a negative thing. The positives are, how do we conduct clinical research in a real-world environment? Can we take 6-minute walk testing to the patient's home, and can we collect registry information using telehealth approaches? I think it's a challenge, but it's rising up to that challenge and overcoming some of the limitations that's exciting, the opportunities that we can create for the future of research.

Dr Ryan: I agree. It does seem that, particularly with the PHA registry, with having to shift the inability to at least enroll people for a period of time, as well as with your inhalational work with biosamples, these do have the potential for long-term consequences, in terms of our general needs, because the PHA registry is, by definition, a longitudinal study. If we have missed 6 months, that has the potential to extrapolate long term into our understanding, so I do think the missing data could have a long-term impact and will take us some time to catch up on.

I think, at the same time that, if we can build this, if we can adapt it and draw upon the ways we've adapted, then potentially in catching up, we can do things better and actually use a lot of the tools that we've had to use over the last 9 months. What are the changes you've seen that even long term are now going to become standard for you? What positive changes have you seen that might make you say, "I never thought of doing clinical research this way before. Now, I can't imagine ever doing this another way"?

Dr Zamanian: I wish it was going to be as simple as that, but you're correct that there are going to be tools, that all this hard work we've all undertaken is actually going to pay off in the future. I think one of the positives that I see is this consideration from the institutional review boards to recognize, not only now in difficult times, but maybe going forward, what the telehealth or virtual world means in terms of patient-related research.

It was very, very unusual—unheard of—for us to be able to conduct consent electronically, and now we have a project that we call Dynamite TH, which is a telemedicine or telehealth mobile device platform that we can send electronically, and patients initiate their screening procedures from home before they come to the clinic. That's a really nice example of what is happening. Another thing is that the capacity of my research team on the clinical side to operate virtually, obviously learning how to work around Zoom and how to get things done, even things as simple as signatures. These are the skills in technology that have enabled us to do these virtual contacts and consenting for patients and operationalizing clinical trials.

The other thing that we've been successful in doing is getting our industry-sponsored colleagues and other sponsors to accept virtual site initiation visits. I don't know about you, John, but our institution would not permit medical monitors and still does not permit medical monitors to come in to monitor our site or even do a site initiation visit. What we've been stuck with is either they send the medical monitor into 14 days of quarantine, or 5 days before getting COVID tested, before they come on campus, or we just do this virtually.

I don't know what your experience has been, but those have been clear positives that are going to impact the access of patients to clinical trials in general. If a patient who wants to do a clinical trial lives 6 or 7 hours away from us, then we can think about how we would operationalize at least parts of the procedure from afar. What's been your experience?

Dr Ryan: Our interventional trials pose a particular challenge because of the things that you brought up; they require so many moving parts. The patient needs to come in. They need to stay in a bed. They need to go into a procedure. The device or monitor person from the interventional company traditionally was always there at the bedside or involved during the hospitalization or at randomization and so on. That, when we were restricting access to people such as you described, was a big challenge to figure out.

I do think, however, that if we can enroll people virtually—or remotely rather than virtually—if we can do that and then better prepare the people who have PH so that, if they live 6 or 7 hours away from us, they've already met the clinical trial person over the phone, over a video, when they come down. Hopefully, they feel like they already know me. Everyone's now expecting you because there's been a requirement to do this testing, with a lot fewer surprises. I'm hopeful that this will make the experience better and will enable us to reach more people. I do have a concern, however, that we have introduced a barrier in technology; technology is still not readily available to everyone. If you're not able to immediately access reliable Internet or a smartphone or computer to do consents or review documentation, then this is a barrier introduced to both your clinical and potentially your re-

search care. I do have a concern that the people whom we will now be able to enroll into registries and trials might shift away from those who are socioeconomically disadvantaged. This is something that, within our registries and studies, we have to pay close attention to.

Dr Zamanian: That's a really important point. I completely agree with you. It's probably going to exacerbate that problem of access to care, requiring technology that you and I and others may take for granted.

Dr Ryan: Another thing I wanted to touch on is the issue of dissemination of research, how COVID-19 has affected that and will continue to affect us in 2021 and beyond.

The first issue is conferences, and it's the biggest one that I'm concerned about. That was how I met Brad Moran, and as you know, we've had incredibly strong collaborations and work very closely together. That's how I met Vinicio de Jesus Perez. That's how I met Anjali Vaidya. The people whom I work most closely with in my own research career, outside of my institution, I've met them at conferences, and I've learned about their research at conferences.

I can't see you and me going to a conference. I don't know when we're going to be at a conference together again physically. How do you feel that dissemination of research has been impacted positively or negatively? How do you see conferences and the role they play going forward?

Dr Zamanian: I feel very much like you. My own career development and my own experiences are highlighted by those personal interactions at conferences. The first poster that I presented at ATS, the first person who really gave me strong feedback was Paul Hassoun. I will forever remember that and learn from that. I do think I am also a very big proponent of those personal interactions because I feel conferences are a really exhilarating discussion environment. There is nothing as good as being in an audience asking questions, engaging with speakers, and speakers engaging back with the audience.

That's a big impact. I have not been able to understand or participate in any meaningful way with any conferences since the beginning of the pandemic. I haven't been able to do anything at ATS now, primarily because it's a big world now. It's divided, and on multiple days, it's all virtual. I don't know about you, but I have Zoom fatigue, or whatever platform you use. Then dealing with time zones as well, being able to balance personal and professional life while already strained in our professions with this pandemic, it's all become much, much worse.

The only positive I can think of is thinking about one of the missions of the Pulmonary Vascular Research Institute in terms of global dissemination of these kinds of interactions. I hope that we would turn back to in-person conferences, but it makes me feel that maybe some of this is positive for people in marginalized countries who are interested in rare diseases. For physicians in those countries who can't make it to a conference in person, now, if they have access to Wi-Fi or the Internet, being able to interact in that kind of environment may be a positive.

I am hopeful that, in the future, we can really go back to a conference environment much like what it was before, although I don't know when that would happen. If I had to guess, I'd say maybe in some combination of both, but I miss it, too, and I think it's a big detriment. Already in the rare disease field, we have our collaborations, as you said, but we're siloed by those collaborations.

The whole point of conferences is to meet people from outside the areas of your own expertise, and I feel like, since the pandemic, I've been—it's great to meet up with my existing collaborators. I love them, but I haven't had, probably because of all the barriers identified, haven't had a chance to make unique conversations with colleagues that I would otherwise have met just out of the blue.

Dr Ryan: I don't know the answer to this. Knowledge dissemination, conferences, you're right that the networking and social aspects, getting to know people, are key. Do you think that dissemination of knowledge has been affected by COVID-19? Is that a long-term issue? Do you feel that there's less dissemination or that it's more difficult? The way I think about it is that knowledge dissemination has become much more bite sized because, at least in the communities that you and I work in, and really every community, to be honest, I think people are able to take in less information.

Everyone is so busy. Children are being schooled at home. Work is bleeding from day into night. I think people can only take bite-sized information in, which has resulted in some disinformation as knowledge is being disseminated. There have been some positives; namely, it is quite easy now to see a social media post with a graphic illustration and capture the essence of a paper by looking at a centered illustration or something along those lines. What are your thoughts on the impact of COVID-19 on the dissemination of pulmonary vascular research?

Dr Zamanian: I think, first and foremost, the focus. This is not a criticism, but the focus of both respiratory and medical journals on publishing everything about COVID has put a strain on, and as you've alluded to, some of it is not very high-quality work. This pandemic is important, I understand, but that's been at the cost of the great work that hasn't been published quickly enough. We had a manuscript we submitted in February, and now it's in its first revision with a journal, a really well-respected journal. It took 6 months for us to get our reviews back. I think that's an impact. As to the dissemination of information otherwise, I'm proud to highlight my work. I love highlighting your work or Vinicio's work through Twitter or whatever social media, but I also feel, like you, that I don't see a broad enough attempt in an unbiased way to highlight work in pulmonary vascular disease through social media. Sometimes I don't know who is behind the Twitter accounts that post different things about the latest great thing about research in PH. They can put a PH in the name of their account, but it doesn't mean I know who that is. I hope there

are some future initiatives that attempt to work on what you just said, a fair and rapid dissemination of important publications. Like you said, we all depend on those activities.

We have a PH grand rounds at Stanford that we do. We have begun to invite other colleagues to present at our grand rounds. At least that's a marginal way to allow some of that dissemination. I totally agree with you about the level of misinformation to where it impacts patients and the patient's beliefs. While I think this is the next best thing in PH, I think Dr Google was always there, but now it's become, as you said, bite sized, very quick, easy to consume, easier to misconstrue findings in our field. I think that's a difficult situation.

I don't know if I have the right answers here, but I do believe that, generally in science today, we need to have a platform that enables trust from the community of patients we serve. With how political things like mask wearing have become, what is going to keep someone or some entity from broadly disseminating disinformation in an unscientific way? I hope I'm just being paranoid about this, but this is something that we as a community, and certainly the advocacy programs such as PHA, need to keep in mind about these platforms, that they can disseminate information that is unbiased and truthful in the way that it is summarized.

Dr Ryan: I agree. I think I see two obligations for those in leadership, people like you and me and others we've talked about. One is to be advocates and harbingers of truth, to keep pushing forward with a good message, to keep our own presence felt because I think there is good that we can offer there.

The other aspect is that I do feel that, for the next generation of people coming behind us—the Roham Zamanians and John Ryans of 20 years ago—I suspect it is very hard for them to get their voices heard. I think we need to advocate and recognize our responsibility in terms of bringing the next generation through. I'm hopeful and optimistic that collaborations, obviously with PHA, who are very invested in future generations, and with other groups will be integral enough.

Dr Zamanian: You took the words right out of my mouth. I think that anyone who's lucky enough to have Dr Ryan as his or her mentor, these are the mentors that we need to be for our junior faculty. We're ready to excite people about coming into this field. It's more crucial than ever that we're selfless and promoting for our junior faculty. As a group, I think that's the trauma of COVID for them in an environment where a lot of them are already competing for incredibly difficult funding that I suspect is getting more difficult. We all need to advocate for their development.

Dr Ryan: Advocacy and more funding are something very near and dear to our hearts and those who will be reading this. Thank you so much, Roham, for joining me today.

Dr Zamanian: Thank you for giving me the opportunity and leading this. This is a really important topic.