

Adrian Hernandez:

Hey, this is Adrian Hernandez and welcome to the NIH Collaboratory Grand Rounds podcast. We're here to give you some extra time with our speaker and ask some of the tough and interesting questions you want to hear most. If you haven't already, we hope you'll watch the full Grand Rounds webinar recording to learn more. All of our Grand Rounds content can be found at rethinkingclinicaltrials.org. Thanks for joining.

Lesley:

Today, we're here with Harlan Krumholz and several members of the Yale team who will be continuing the discussion from the Grand Rounds session of a few weeks ago, "Digital, Decentralized and Democratized: Lessons From The Yale PaxLC Trial." Harlan, welcome to this podcast, great to have you with me and really excited to have the Yale team here to field some of the great questions that came forward.

Harlan Krumholz:

Oh, thanks so much, Lesley. We're really happy to be here.

Lesley:

Let's start with the big question, right? Can you give your perspective on how generalizable the experience of the PaxLC Trial is? Is this just relevant for Long COVID trials? Do you see it as being generalizable beyond?

Harlan Krumholz:

Yeah, that's a great question and it's one I hear a lot. Let me just say that when we started on this journey, when we thought we could pioneer a transformative way to do clinical trials, we weren't just thinking, "How do we do something that could only be configured to Long COVID?" But rather we thought, "Could we put into place something that could serve as an investigational new drug trial, in this case, a phase two trial, that would be generalizable to the wide range of things that you might do in outpatient medicine?"

So in this case, you have a condition, could you qualify people, be able to review their medical records and determine whether they've really met inclusion criteria, confirm it with them, and then have them go for qualifying labs, for example, at Quest, be able to collect biospecimens from their home, be able to ship drugs to them? In our mind from the beginning was this idea that we wanted to create a platform that could be used for a wide range of things, but of course, we had some things that were specific to this particular issue and we were committed to generating knowledge that would help people with Long COVID. But in our minds we're thinking, "If we are successful here, other people will be able to pick up on this and so will we, and be able to do this in a wide range of areas."

Lesley:

That's terrific. And actually, that leads naturally to my next question, which is about scalability, right? You did this, you tested this, you developed this in one context, and then the question becomes how do you scale it beyond that, right? So maybe the first question there is around all of the work that you did to sort out regulations at the state level, which was, I'm sure, a very complicated task, right? Did you keep track of that? Does that scale to the next trial?

Harlan Krumholz:

Well, the great thing about this project is just the enormous number of people on our team who are just so talented and were so committed, and also so detail-oriented. So, we've collected and archived everything that we've done. Let me hand this over to Julie Holub who really has had oversight at the Yale Center for Clinical Investigation over this study, over this trial, and I think we'll give Julie a chance to reflect a little bit on what she thinks about scalability and some of these things we've learned and how we've documented them.

Julie Holub:

Thanks, Harlan. When we first started thinking about implementing this study, and one of the most important ways that we made it scalable, hopefully, we've set up a system that could work in other institutions, academic medical centers, et cetera, is to really partner with our HRPP, so our Human Research Protection Program, which the IRB falls under, partnering with them early and having more of a conversation. Traditionally in a study, we would put together all the pieces, make the protocol final, and we would submit it to them in its final state.

And we actually worked with them a lot earlier than I think a lot of the studies that we generally do. That's not the approach we take. We went to them with this idea with the concept really early on, and we partnered with them to think about how to finalize the protocol in a way that could work with both the HRPP regulations, IRB considerations, and operationally to meet our goals.

Lesley:

Great. That's excellent. And you really tackled such an important aspect of this, the IRB approach, which scaling that is something to be sure.

Harlan Krumholz:

Of course, the issue was single IRB in this study, so we just had to manage our own IRB, but as we think about creating policies and ways of thinking that could then generalize to other studies, I think that was in our mind. And I know Erica Rocco who led all of our IRB efforts is amazing. And, Erica, do you want to talk a little bit about what were some of the challenges we encountered and how is that going to relate to future studies, do you think, as this scales out?

Erica Rocco:

Hi, this is Erica. I'm the regulatory project manager for this study facilitating IRB communications and the IRB submission. And I think what Julie said, that part of the key here was having very clear, consistent, open communication with our local IRB was key. And our IRB was maybe a bit sensitive to the seemingly different or seemingly higher level of risk for a decentralized trial. So we did work closely with them to make sure we were submitting and conducting a protocol minimizing risk as much as possible. When the IRB had questions, ask for confirmation on a lot of things because they don't see very many decentralized studies, we've been able to successfully work with them to address everything.

I think that as decentralized trials become more common, there may be an opportunity for local IRBs to consider having a board specific to DCTs. If the volume is truly high enough, maybe there'll be commercial IRBs that see more decentralized trials more often and have application materials, review processes that also better accommodate review of these types of studies as they increase in our research world.

Harlan Krumholz:

We have a terrific IRB, but this was still new ground for them, and we had to continually recalibrate them. Things would come back from the IRB and they would talk about sites and we'd say, "No, no. We want to remind you, we don't have sites." There were issues that would come up that they were getting better and better about thinking about over time, it was just sort of a new thing. But honestly, they were willing to dig in and be with us. But I don't think I even realized how it was a frame shift for them in terms of thinking about these things.

Lesley:

That's a great point, that sort of ongoing dialogue and bi-directional education almost that's required when you're doing innovative things and bringing innovative approaches to the IRB and others. That's a great example. One of the questions that came up during the Grand Rounds was around guidance, right? There's some guidance. The FDA's issued guidance around decentralized trials, but probably more guidance would be useful. I'd love to hear your thoughts about what kind of guidance might help to actually facilitate the uptake of decentralized trials and maybe de-risk them for all parties involved.

Harlan Krumholz:

Yeah, this is a really great issue. And Amy Hummel who leads our regulatory efforts. Amy, you mentioned something about this in the Grand Rounds. You said that you sort of wished the FDA would be able to provide more, but you weren't sure that they could. And then someone from FDA actually posed this question, "What would you like to see if you could?" So, Amy, what do you think?

Amy Hummel:

Sure, thanks for that question. My comment had actually more been dealing with the different state level laws and regulations that we're trying to balance with the telehealth and the prescribing and the shipping, and that's definitely stuff that's not really FDA's purview. That might be a better place for an organization like CTTI or SOCRA or something to provide resources for academic medical centers because we shouldn't be reinventing that a thousand times over each time, and we're probably not best equipped to do that researching. But as far as what we could get from the FDA, there's two ways that sponsors can get guidance. One is through formal meetings, and even when you do this, "How do we do this, FDA?" That's not really the kind of question they usually answer for you, and that's how we feel a lot of times with this. But then you frame it, "We propose to do X in this way, does the agency concur?"

And if they don't have a problem with what you're saying, they'll say, "Sure, yes, we concur," but if they might've also been fine with a little less or a lot less, they may or may not offer that to you. So then you're kind of setting a higher bar than might've been necessary. The other way is through, as you said, guidances and FDA did put up that guidance on DCTs back in May, but I think there's a lot in there that maybe they could expand on or clarify. So if any FDA people are listening, this is my plea to be timely in coming out with that final guidance that incorporates some of the feedback that came through on that guidance. I can give you two very specific examples. One is on the 1572 form, clarifying where that threshold is for who needs to be listed as a sub-investigator versus who is just a local healthcare provider who can go on a delegation log or task log. And maybe that's actually something that would be an update to the FAQs they have on filling out the 1572.

Another area, and this is something that we've talked a lot about in our study, is around adverse event collection. The FDA draft guidance says you need to ensure that adverse events are appropriately captured and adequately addressed, but that's true for every study, that's not unique to DCTs, and we want to make sure that there's not an expectation of a higher bar that winds up coming out of that

compared to a traditional trial. What qualifies as appropriate and adequate is kind of where we need that help. Many trials use diaries that participants fill out at home and bring in at visits to the study site weekly, monthly, quarterly, and everybody does that. That's very typical. In our study, they're filling it out online and it gets uploaded right away. And we actually said that it's going to be reviewed pretty much almost in real-time, like the next day. And if they don't fill it out for two days or they report something that might be indicating an adverse event, we will call them right away. Is that really necessary?

Did we have to do that or did we feel because the data's available to us, we should be acting on it, we're obligated to do it? I don't think that should define best practices for every future decentralized trial. I don't think that there's the manpower to do it in a huge study. Our flow is kind of slow enough that it's manageable, but if you have 100 or 200 subjects on drug at the same time, that's multiple people needing to only do that all day every day. And another thing is how is this real-time collection impacting adverse event reporting itself? That's something I think we're all kind of interested to see in our study.

Lesley:

That's an excellent point. When we begin to collect something a different way, we're no longer comparing apples to apples with trials that have done it different ways with that. That's a great point. I'd love to maybe shift gears now and talk a little bit about the data. As I understand it, you are getting EHR data through FHIR, using FHIR to get EHR data from these different organizations. Can you talk through how the data flowed for this trial, and whether and how that applies to the next trial that you would do in a similar way?

Harlan Krumholz:

Yeah, and I think this is an important point. We talked about this just a little bit in the presentation. So we are using Hugo Health, and a disclosure that I'm a co-founder of Hugo Health, and my involvement's overseen by the COI Committee of Yale, all disclosed and there's oversight of it. But what's happening is that people who are showing interest in the study are connecting to their medical records via the public-facing API that's required out of 21st Century Cures Act. We always say that the data's going from B to C to B. It's going from the health system to the individuals' secure cloud-based account where they now have agency over their data and then they're giving permission for that data that's now under their control, their data, to be shared with the study. And it could be done with wearables, it could be done with payers, it could be done with pharmacies. In this case, we're doing health systems only.

So they filled out a questionnaire that says they are ostensibly eligible for the study. They're connecting to their medical records so that their records can come to them and they can share it into the study for us to make a determination about whether or not they, according to their medical records, meet eligibility criteria. And then we can use that data flow for secondary outcomes, self utilization outcomes during the study. But I want to just give maybe Andreas Coppi and Mitsu Sawano a chance. Andreas is the one who's doing work, also, by the way, with Rohan Khera, overseeing this. Andreas is the one sort of engineering this movement and into a format that Mitsu then reviews. So, Andreas, do you want to just talk about how this is going from your perspective, the data flows in from their account through Hugo?

Andreas Coppi:

Sure. Thanks, Harlan. This is Andreas. Basically, Hugo's harvesting the EHR data on behalf of the subjects that we're following in the trial, and they basically are grabbing updates, let's just say, weekly. So what we do is we watch a file server that they've made accessible to us, and any of the new files that show

up, we'll pull down. These are typically FHIR-formatted files. Occasionally, there are some other different formats and Hugo gives the subjects the availability of uploading some manual records, which has been very handy too because they're able to share any of the medical records that they want to that we think is relevant to the trial. But with most of the connections, we're getting these FHIR-formatted files. We'll go through those and extract a certain set of elements that are of interest to the clinicians, and they're basic things like the recent labs, recent vitals, active medication list. There's some exclusion criteria.

I should back up first and just say that the initial use for all the EHR data is for screening, or I guess we call it pre-screening. So Mitsu and the other clinicians get as much EHR data as we can provide to them, and then through other forms and interviews, then they decide who's eligible and who's not eligible for the trial. But the data that we get before I pass it on to Mitsu, we'll extract these elements that I was talking about and we'll put it into a simple readable PDF file. We actually had an outside consultant do a validation procedure on this early on, so we're trying to limit a little bit of any sort of exotic data mapping that we're doing. We're just trying to extract elements and then put them in a readable way in a PDF file that's easy for them to store and open up for reference whenever they need to.

One of the biggest assets of the data that we're getting in is that we're, except for some health systems where there are a couple of defects going on, we're getting the full text of the clinical notes. So that's a pretty rich source of information for Mitsu and his team to be able to go through. I will say, just in terms of scalability, we've had most of these things automated. You're dealing with a couple of major challenges. One is that there are a few different EHR vendors. Obviously, Epic's the big one, Cerner's the second. Neither of those are, still, they're not completely perfect. There are some smaller ones as well. And then there's actually each instance of, let's say Epic for example, is a little bit different from one hospital system to another. They store things differently, they code things a little bit differently. So you see a little bit of a challenge in that variability as well. So we haven't solved it by any means, but I think we've seen enough at this point that if we were to move on to another study, we'd be up and running very quickly with the same framework.

Mitsu Sawano:

Hi, this is Mitsu, a physician scientist at Yale CORE. Harlan and Andreas has pretty much explained everything about the process over here, but maybe just going over the workflow that we have. So once a potential participant signs up for the PaxLC study, they go through the pre-screening questions and then once they qualify through that set of questions, they come through to the Hugo team and then the team, which do fantastic work on having the participants connect their EHR data and allowing us to review their medical records. And once that happens, the Hugo team sends us that FHIR data and Andreas does his magic. There are two types of PDF files that I receive.

So the one contains basic demographic information, lab results, vital signs, medication lists, and previous medical histories. Now, all this is extracted from basically ICD codes or some kind of computerized phenotypes. The other type of PDF file that I read are the clinical notes that also Andreas already have mentioned. And this allows a rich, full text of information that you would actually be able to see in usual medical records. Now, this combination allows multiple ways in order to cross-validate whether or not that information is correct and certainly helps determining eligibility in a very efficient way.

Lesley:

That's terrific and so helpful to understand the process and the workflow. I really appreciate you walking through that. Decentralized trials involve a lot of logistics. Non-decentralized trials involve a lot of

logistics, but there's some different logistics required that need to be addressed in these trials. One of the questions that came up during the webinar was around just shipping of samples, and I wonder if you'd like to talk a little bit about that and other kind of logistical issues that you had to work through.

Harlan Krumholz:

That's another great one. Let me just hand this over to Bornali Bhattacharjee, who is really running this out of the Iwasaki Lab and is a terrific scientist and has also been put in a position of trying to make all these arrangements. Bornali, what do you think?

Bornali Bhattacharjee:

Thank you, Harlan. I think we began conservatively with some experience and we have come a long way and we have learned a lot. I believe we tried to begin conservatively by keeping the Yale Clinic option open for local participants, and at the same time, we partnered with a Quest diagnostics company called ExamOne. We had prior experience working with them on an observational study and we wanted to use them for this study as well, but we added variables. So the first step was to organize a kit where you had everything organized by catalog numbers and temperature conditions. For different experiments, we require different conditions in which the samples come in and that we did rigorously. And they built us a kit, which they usually deliver to the participants. We also wanted to know from participants their general health condition at the time of collection, so we also organized a requisition form in which each phlebotomist is trained to ask a few questions and get answers.

So we received that requisition form. That was the second part. The third variable that was added because of the trial is that for any kind of metabolomics, including pharmacokinetic analysis, you need to process the sample in order to get plasma within two hours of collection, which is tough for a decentralized study. The ExamOne team organized their phlebotomist and each phlebotomist was trained so that they could process at least one tube and process the plasma and send us samples in dry ice. So the plasma comes in dry ice for our 14-day collections, and this is how we tried to organize it. We did run into trouble and we learned our lesson. First thing was dry ice. And because it's a research lab, we had organized a calendar where we would receive samples on Tuesdays and Wednesdays and collections would happen on Mondays and Tuesdays. And the team was organized in such a manner that we could do that. But soon, we learned that dry ice couldn't reach the phlebotomist on Mondays, so we had to curtail collections for 14-day collections like on Mondays.

So that's when we had to reorient ourselves, reorganize ourselves and then prepare a separate calendar. This has been one of the challenges that we have faced. And the other thing, for any researcher who is into a decentralized study means a lot of effort also has to be given in logistics and coordination. I think that's another challenge that we have to tackle before we say, "Okay, we have the samples, we have the data, we are ready to wear the immunologist hat and start analyzing the data." So I think those are the things that we have learned from. So what is the one lesson that we have learned? Maybe going forward, we'd like to have multiple vendors so that we can organize collections and we know where they have more phlebotomists for certain states. That would be helpful, that we have realized coming a long way. But I think we've learned a lot of lessons and I think we are prepared to tackle and finish this study, for sure.

Lesley:

Excellent. Thank you. Harlan and the entire team, this has just been terrific. I wanted to end, actually, with maybe picking up on Bornali's response there, and that is what are the big lessons that you've

learned, one or two lessons that you've learned in this that you will carry with you to the next decentralized trial?

Harlan Krumholz:

I'd say the biggest lesson I've learned is it's possible. You actually can get this done. And that all of these challenges that you see, everything from something small about expectations, about the consent process, or what it means to be able to ensure that we could do a trial that met or exceeded the standards of the traditional trials. That we were going to be able to collect adverse events, that we were going to be able to respond to patients. That they didn't have to see someone face-to-face in our site in order to be part of our study. That we could address the issues with these clinical trial deserts. That just because there's so much to talk about and we're at the end of this podcast, I want to say how proud I am of this team. It's remarkable.

But everyone was committed. And I think in the end, now that we've shown it's been done, I hope that everyone will see that, for the right question and for the right situation, these might be more highly efficient and more equitable in the sense of being more convenient for people, not causing people to have to take off work, find parking, drive. We heard from people who just said, even a 20-minute drive, that's gas to them. Everything is one bit of friction when you have to go to the site. So I'm just going to end with that high-level comment that what I'm most proud of is that we've shown that this can work, it can work well, and it can work at a very high level with rigor and high standards, and we hope that'll be the beginning of much more.

Lesley:

Thank you again, Harlan. This has been terrific. Really appreciated the opportunity to learn more from you and your team. And I invite everyone to please join us for our next podcast where we'll continue to highlight really exciting changes that are going on in the research world.

Adrian Hernandez:

Thanks for joining today's NIH Collaboratory Grand Rounds podcast. Let us know what you think by rating this interview on our website. And we hope to see you again on our next Grand Rounds, Fridays at 1:00 PM, Eastern Time.