Jill Harrison:

Hi, this is Jill Harrison, Executive Director of the National Institute on Aging IMPACT Collaboratory at Brown University. Welcome to the IMPACT Collaboratory Grand Rounds Podcast. We're here to give you some extra time with our speakers and ask them the interesting questions that 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 the companion Grand Rounds content can be found at impactcollaboratory.org. Thanks for joining.

Susan Mitchell:

All right. Well, welcome everyone. Today we have the great pleasure of talking with the three PIs of the NIH Health Care Systems Collaboratory, which for over 10 years has advanced the nation's capacity to conduct ePCTs or embedded pragmatic trials in various healthcare settings and targeting quite a wide spectrum of health conditions. I want to welcome doctors Leslie Curtis, Adrian Hernandez and Kevin Weinfurt. Welcome.

Leslie Curtis:

Hi. Good to be here.

Kevin Weinfert:

Thank you.

Susan Mitchell:

Great. Well, today's an opportunity to extend our discussion from the IMPACT Grand Rounds that doctors Weinfert, Curtis, and Hernandez presented a few weeks ago, really thinking back on the experience of the Health Care Systems Collaboratory and where we are and where we're going. I'm going to start with a pretty big question. Two of the main reasons, sort of the stumbling blocks of traditional RCTs is that they're expensive and they're often underpowered. In fact, these couple considerations were, in part, some of the impetus for ePCTs trying to do more for less. Acknowledging, I think we've learned that there's a lot of learning yet to be done in conducting pragmatic trials, and for all the challenges that the IMPACT and Health Care Systems Collaboratory experienced to date, some suggesting that even ePCTs are maybe equally difficult trial design in different ways, introducing a whole new set of shortcomings. The big question is, what would you say are the markers that further investment in pragmatic trials by funding agencies are either warranted or not warranted? Maybe Kevin, I'll start with you. Or, maybe not.

Kevin Weinfert:

The softball questions. Wow. The markers that... Say the last part again.

Susan Mitchell:

Well, I'm just sort of wondering... At some point we're going to have to take stock and decide whether investment in this type of trial design or ongoing investment, is it something we want to continue doing or something maybe we don't, or need to pivot or something like that. Acknowledging why ePCTs were promoted over a decade ago now to try to get over the shortcomings of traditional RCTs, but now we have a new set of challenges. So, I'm just wondering... put your hat on as the head of the NIH. What's the markers for continuation or saying maybe this isn't a trial design that's worth pursuing?

Kevin Weinfert:

Yeah. I'll start out. I know Leslie and Adrian will be able to fill it in a bit better, but one thing that strikes me is that when the Collaboratory began, I think this comparison between a more traditional trial and a PCT was made with the idea in mind that maybe similar research questions were being answered. I feel like now, 10 years later, with the rise of implementation science and hybrid designs, I think there's more sensitivity that there are different types of questions for which the PCT design and typical settings that we see in the Collaboratory are best suited. And so, it's not the case that for some of these questions, you could do either a traditional trial or a PCT. I think we have a better understanding that there are some questions for which this is just the right design regardless of what it's going to cost or not. But, there are those other questions, say A/B comparisons between existing treatments, that maybe there's the option of doing one or the other, but I guess that's one big thing that has changed. I don't know what Leslie or Adrian would have to say to that or add to it.

Adrian Hernandez:

The way I would think about it is that healthcare is about a three trillion dollar industry overall, and if you were just to say like, "Hey, take 1% of that 30 billion that we should be doing as minimal R&D on how healthcare decisions are made that are different from what the usual NIH portfolio has been." Absolutely. As you get closer to the daily decisions that happen in healthcare, that's one of the things that the Collaboratory is trying to do, is embedding R&D, if you will, within healthcare. For any industry, 1% actually would be teeny tiny in terms of what one should be doing to continue to invent the future.

Leslie Curtis:

Picking up actually on, on something that both of them alluded to. There's a real question about what is the future of embedded pragmatic trials. From my perspective, there isn't a question of whether there is a future for all the reasons that both Kevin and Adrian said. I think the future, thinking about how we design even better for implementation since that's really one of the compelling reasons to do an embedded pragmatic trial, because at the end of the day, we want that evidence to be able to be implemented directly into practice, right where the evidence was generated.

Susan Mitchell:

That's a good segue into my next question. I think you maybe answered it in some ways, but being part of the Health Care Systems Collaboratory for a project several years ago, I know that some of the earliest effort to advance the methodology at the Health Care Systems Collaboratory was really a lot focused on design, statistics. There was a great effort put into regulation and ethics, and, I think, really advanced a lot of the methodology in those areas. I think now with the learning we've done, the question is, what really now is the ongoing focus to further hone down and provide a foundation for conducting these trials rigorously? I know everyone so far has mentioned implementation, and I'm wondering if we had to pick a few areas to focus on in the next few years in terms of improving how we do these trials, what's the focus of the Health Care Systems Collaboratory now, or priorities in the next few years?

Leslie Curtis:

As you said, I think implementation and designing with implementation in mind is a growing priority and something that we're already working on. Thinking about how we capture and categorize the types of interventions that are being done and how well those actually are being, the fidelity of those interventions in the trials. Another piece though that I think is also likely to be a major topic for us is,

what's the right randomization design? Early on, there was a lot of interest in things like cluster randomized designs and stepped wedge designs, and many of our trials have learned the hard way that what seemed like the straightforward way to go wasn't quite so straightforward. So, really thinking carefully about when individual randomization might actually make more sense than some of the other approaches.

Adrian Hernandez:

I think a related thing that, while it's a topic area that's of high interest to everyone, which is how to close health inequities, it's also the research on how to do so, especially within doing embedded clinical trials where it's really important to have the communities engaged and bring them along, or co-create these for the communities here. And so, I think those are going to be special efforts here, and they'll have different potential issues that will be encountered as people are trying to get closer to addressing those types of questions.

Kevin Weinfert:

Maybe I'll just add a last thing, and that is really a consideration more for investigators who would be coming into the Collaboratory with a trial than it is for us working with trials that are already accepted. And, that is trying to figure out when it's the right time to test interventions of a given complexity. I think the experience to date is that there were some interventions that people were very hopeful about that didn't really pan out. The question is, was it too light touch? Was it based on too many assumptions for which we didn't really have proof of concept about? And so, I think there'll probably be more reflection now among people proposing trials about the right situation for testing and intervention and what's that intervention that ought to be tested. For our part, from the Collaboratory side, we'll continue to try to document things like intervention complexity, and to look across trials to see what lessons can be learned about the degree to which interventions demonstrate effectiveness as a function of their complexity and other environmental characteristics.

Susan Mitchell:

Yeah. I think that there is this balance between too light a touch and too complex so that it can't be implemented, and too light a touch so it doesn't do anything. I think we still haven't figured out what works, although different things might work for different circumstances. The other thing we've struggled with a little bit at IMPACT, and I'm just wondering what your take is, especially for dementia, we've noticed that a lot of our pilot studies are coming in and want to either adapt an intervention that's been used in non-dementia to the dementia population or maybe a dementia intervention, but adapt it for a Latinx community. We're struggling a little bit with how much adaptation is too much adaptation where you've changed the intervention, you've got to go back in what we refer to a lot as the NIH stage model. But again, you don't want to take 15 years to do something. Adaptation is something we've been thinking a lot about at IMPACT. Any thoughts?

Kevin Weinfert:

It's a really big question. It seems like people are going to need to be more mindful about all the different ingredients of a given intervention and the rationale for why it's supposed to work and a very careful analysis of how they're adapting it, and to what extent are they just changing window dressings versus making real structural changes, maybe inadvertently. And also, we and NIH have spent time trying to figure out what types of tests need to be done in that first year to assess feasibility and things like that. If people are adapting interventions, what are some of the hypotheses that need to be tested

then prior to going into actually conducting the trial that reassures us that the intervention is still working the way we assumed it was, and so we don't need to go to an earlier stage of evidence generation. It's going to be pretty tricky to do.

Leslie Curtis:

Susan, to a point that you made, there's a real balance, a fine line between studying the adaptation of the intervention for 15 years, until that adapted intervention is no longer relevant, but we know perfectly well exactly what it would look like if it were. I like what Kevin proposed, probably just off the top of his head, but just being much clearer and more articulate exactly what those assumptions are, test them, discuss them, and then make plans to formally test them during that first year of the study before you go forward.

Adrian Hernandez:

It's an example where it's easier often to discuss and put it on PowerPoint slides than actually do it in the real world. And so, I think one of the things that will happen as we go forward is that, as these types of programs are increasingly more embedded or increasingly seen as necessary for improving health, then that fosters an environment where adaptation will be highly relevant. The other thing, to Kevin's point, there is going to be certain situations where there's going to need to be a decision making to really understand, do the interventions work as planned, or how they need to be modified along the way, or the external environment actually causes them to be modified by necessity because we're doing this inside of everyday life.

Susan Mitchell:

Let's give a few more minutes to the issue health equity and ePCTs. We've put a lot of thought in it and realized each of the PRECIS domains has health equity considerations different from a regular traditional randomized trial. I'm interested in how your Collaboratory is going to be taking some practical steps to advancing integration between health equity and embedded pragmatic trials.

Leslie Curtis:

As you know, Susan, the Pragmatic Trials Collaboratory, we learn by virtue of the demonstration projects that are funded by NIH Institutes and Centers. This next tranche or set of demonstration projects will be focused on interventions, we'll be testing interventions to reduce health inequities. The answer to your question about what we will do, I almost reframe it in my mind as, "And how will we learn about what to do and how to really use embedded trials to reduce health inequity?" So, we have a great colleague who will be leading some of the community and health equity focused work in a new core in the Collaboratory, which is exciting. We will also be looking to the demonstration projects to help all of us in the community learn about how to do these best and what we can generalize from their experience to the broader community.

Susan Mitchell:

Yeah. I'll give a personal shout out to the best practice sheets that we've worked on that just came out recently that we hope everyone can leverage pretty high level, but very practical.

Adrian Hernandez:

Similar to what we've done for other Collaboratory programs, is these cores and a core dedicated to this area will help people understand their blind spots, what they may not have realized before as they

launch studies that are directly trying to address health inequities in some way. The second thing is that there is an underlying premise that if you have these programs that are closer to the health of all that it will naturally help improve health inequities. That's a hypothesis. And so, we actually have to see if that actually bears out or when does it not, or what situations does it not. And, there's also some interesting and important ethical considerations, especially for these embedded programs that often rely on a waiver of consent because they're essentially testing out different strategies of care that exists in usual care, but vary, especially with the history in certain communities with research that crossed ethical boundaries, or mistrust in science or mistrust in healthcare. And so, how we do that together and address those uncertainties are important.

Kevin Weinfert:

I'll add two other things related to training and developing new scholars. I think that we have an interest in trying to diversify the research workforce in pragmatic trials. And so, we're exploring an approach whereby we would get fellows who could participate with the Collaboratory Coordinating Center and learn about doing pragmatic research, but fellows who are from underrepresented minority populations. And then, the other thing that we are doing very intentionally is looking at the training activities that we do as, I know IMPACT does, and looking at those agendas and slide sets and trying to figure out the best way to incorporate the perspectives of diversity, equity, and inclusion in the curriculum there, and not make it just a side token topic, but how is it meaningfully integrated into teaching people about pragmatic trials? So, those are a couple other things that we're working on.

Susan Mitchell:

Yeah, we have a little bit of a similar program called our Faculty Scholars Program, where we have junior people come and join our cores, and we found it's also a really good venue for bringing in a more diverse group of young investigators. Well, that's exciting that you're going to have a core and I look forward to learning from it. Last question, just getting a little bit away from the science, as you know, I'm an MPI with Vince Mor and we've quite the partnership at IMPACT, and it's become clear that he has his buckets and I have my buckets, and I'm just wondering about the experience of having three PIs and how you guys divvy things up and work together to make such a great Health Care Systems Collaboratory work.

Kevin Weinfert:

Adrian and I just do what Leslie tells us to and it all works well.

Susan Mitchell:

That's what I figured. Yeah.

Kevin Weinfert:

No. I will say, seriously, that when Rob Califf called us up and said, "I'd like you three to do this", we all said yes. And, we had worked with one another. Actually, Adrian and Leslie worked together for years and years, very closely. I was surprised at just how completely effortless the multiple PI workings went. I'm not exactly sure why that is, but it just did. And so, we each have some different foci. We each have slightly different cognitive styles, and it just somehow works in a quite magical way. I can't really compare it to any other situation I've had like this.

Adrian Hernandez:

I'd say it's just a lot of fun. People have collaborative and complimentary areas of interests here, and there's also a trust on each other. As things go along, people all get busy, and so someone else will pick up the ball and move things forward. So, it's very natural and it's just, I'll say, pure fun.

Leslie Curtis:

I think that's it. The reason why it works so well is because we actually have a lot of fun.

Susan Mitchell:

Well, I can give my opinion why it works so well, is because Tammy Reece really takes care of all you guys. She's in control of you.

Leslie Curtis:

That's right. We all do what Tammy says. That's the right answer. Tammy doesn't forget anything either. She makes us look infinitely more talented than we really are.

Susan Mitchell:

Well, this has been fun, and I just want to thank you all again for your leadership and your collegiality. I just thank you.

Kevin Weinfert:

Great. Thanks for the opportunity, Susan.

Leslie Curtis:

Thank you, Susan. Take care. Bye-bye.

Susan Mitchell:

Bye.

Jill Harrison:

Thank you for listening to today's IMPACT Collaboratory Grand Rounds Podcast. Please be on the lookout for our next Grand Rounds and Podcast next month.