



Good Clinical Practice: Considerations for Trials with Pragmatic or Decentralized Features

September 13, 2023 from 7:30-9:30 am ET

00:00 Welcome and Overview: Lea Ann Browning-McNee

Lea Ann Browning-McNee: Hello. Welcome to our meeting this morning. Good morning to those of you who are in the US, and good afternoon or good evening to those who are joining us from other parts of the world. We're really glad that you can be here today as we discuss the good clinical practice considerations for trials with pragmatic or decentralized features. It's a popular topic. [00:00:30] We've had a few thousand folks register for today's event, and because of that, we're going to ask you to keep your microphones and your cameras off during today's discussion.

I'm Lea Ann Browning-McNee. I am with the Reagan-Udall Foundation for the FDA. We are a nonprofit, non-government organization that was created by the US Congress to support FDA in its mission.

I'll go to the next slide. We'll run through a few housekeeping notes before we dig into [00:01:00] our conversations today. Because the meeting is large, as I mentioned, please keep your mic and your video turned off. The meeting is being recorded. Sometimes because of internet connections or browser preferences or other technical issues that we can't always control, we have posted the slides for today's meeting on the foundation website. You can find those at www.reaganudall.org. So feel free to take a look there if you're finding that your video [00:01:30] may be a little fuzzy when we're looking at slides during today's presentations.

You can also submit questions throughout today's event by using the Q&A feature in Zoom. Many of you submitted questions in advance, and we really appreciate that. We'll be working as many of your questions and the themes from those questions into our conversations today.

As you likely already know, but we have to remind you to be official, speakers will not [00:02:00] be discussing any specific regulatory actions or decisions during today's event. Then I mentioned slides earlier. I'll also note that yesterday's slides are up. This is day two of a two-day meeting. Yesterday's slides are already posted, if you want to take a look at those. We'll also be

posting the recording of both days, as well as the transcripts from each day as soon as we can following the meeting.

To take a quick look at our agenda, in just a [00:02:30] few minutes, I'm going to turn things over to Dr. Khair ElZarrad of FDA, who will provide some opening remarks and a recap of what we discussed yesterday. Then we've got three very distinguished presenters, Dr. Otavio Berwanger, Dr. Noelle Cocoros, and Dr. Adrian Hernandez, who are going to really walk us through their experiences and insights with utilizing pragmatic or decentralized clinical trial features.

So a [00:03:00] quick look on this next slide about why we're here today. We've mentioned it in the title of the webinar a few times, but we really did want to bring together experts who have practical experience in the conduct of clinical trials with pragmatic or decentralized features. We think it's really important that we're able to hear these different perspectives, hear from this practical experience to inform the development of responsive policies and guidelines that can encourage [00:03:30] innovation, but also equally important, protect participants and safeguard the reliability of trial results.

So to get us started, it's now my pleasure to introduce Dr. Khair ElZarrad. He serves as the director of the Office of Medical Policy in the Center for Drug Evaluation and Research at the US Food and Drug Administration. Dr. ElZarrad?

04:00 Introduction: Dr. Khair ElZarrad

Dr. Khair ElZarrad: Thank you so much, Lea Ann. Do you hear me?

Lea Ann Browning-McNee: Yes, we do.

Dr. Khair ElZarrad: All right. Thank you so much. So I will [00:04:00] just start by a few remarks. First of all, I just want to thank our speakers, again, some of the busiest experts in the field, and they took the time to join us today. We're very grateful for that. I want to also thank my FDA colleagues and the Reagan-Udall Foundation team for really making this meeting happen. Thanks also to all of you who are joining us today and those of you specifically who submitted questions.

So as a part of FDA's overall effort to modernize clinical trial ecosystems and to advance innovations and efficiency in the design and conduct [00:04:30] of clinical trials, we want to continue to engage and hear from all stakeholders. This meeting is part of that. We intend to hear from academics with experiences in conducting trials with decentralized and pragmatic features.

As FDA and other partner regulatory organizations around the world are continuing to develop guidances on policies on clinical trial design and conduct, we really must incorporate the learning and experiences that we hear from the ground, from those who are conducting those trials. This will help make our policies [00:05:00] more responsive, appropriate, and agile to protect trial

participants and the reliability of trial results while at the same time encourage and facilitate innovation.

So a little bit on the terminology here. Trials with decentralized features are generally understood to be trials where some or all of the trial-related activities occur at locations other than traditional clinical trial sites, typically away from the investigator. We also note that pragmatic features are generally described [00:05:30] to include broad eligibility requirements, more flexible inclusion criteria, if you would, a simplified protocol, and streamlined data collection. This typically incorporates existing healthcare infrastructure, including the data from routine healthcare, sometimes referred to as real-world data.

These are just some of the features here. Those trials typically have the potential of being more inclusive and more efficient, in part because they can be embedded in healthcare [00:06:00] settings. I've heard them at times being called point of care trials as well.

I personally view decentralization, or decentralized and pragmatic features, as elements that can be incorporated into a trial as appropriate to streamline the trial process, to make the trial less burdensome, and to incorporate available infrastructure, data sources, available tools for us to make the trial a little bit more agile. Ultimately, the goal is to produce reliable and generalizable results in the most efficient fashion.

[00:06:30] Lea Ann mentioned the questions we received, and this meeting is designed really to hear from three esteemed experts. We heard from three yesterday. We're hearing from three esteemed experts from today as well, and the idea is to have a dialogue and to hear additional elaboration and input, specifically during the panel.

So what we did, and thanks again for submitting the questions and comments during the registration, we received hundreds of comments and questions, [00:07:00] and we are very careful in how we try to analyze those and put them together into themes. But clearly, we can't address all of those comments and questions during the meeting itself. But the consolidated themes is what we will hope to take to the panel discussion today.

As Lea Ann mentioned, we will also have Q&A chat box open with colleagues monitoring it, and if time allows, we will try to incorporate some of those questions into the discussion. We were able to successfully do that yesterday. However, rest [00:07:30] assured that if your comment or question is not mentioned specifically that none of this is wasted. We intend to look and see if there are themes that can be addressed as we continue to engage with our stakeholders and ultimately to see if there are themes that can also inform our policy development. So again, thank you for that very much.

Just a little bit about yesterday. Yesterday, we had a very informative three talks, and I highly encourage you all to see the videos. I'll [00:08:00] never be able to do justice in a few remarks here. But we started with Dr. Eric Lindsey. He's a professor and Head of Psychiatry at Washington University. From the start, he challenged us that trials with centralized setting, and he called them fully remote trials, they can improve, actually, the speed and quality simultaneously of how we produce evidence. He highlighted certain challenges for us, for example, how to get to precise measurements [00:08:30] of certain endpoints, and he highlighted the solutions for us. So his talk was really balancing both the challenges and the solutions.

He mentioned actual example in trials evaluating antidepressants to trials during COVID and post-COVID as well and showing us how the decentralization can really add to the agility of the trial and make trial happen, really, in a manner that's efficient and in a manner that's patient-friendly as well.

[00:09:00] Then followed with Dr. Lindsey, Craig Lipset spoke to us. He's an advisor and a founder for Clinical Innovation Partners and a co-chair in the Decentralized Trials and Research Alliance, DTRA. So he provided also a very interesting discussion on the jargon and how we describe those trials and highlighting sometimes that the jargon is not very helpful. For example, the model in decentralized clinical trials is decentralized from a process perspective, decentralized for the site, per se. But he highlighted how this model [00:09:30] is actually centralized around the participants, around the patients, and how the terminology and the way we describe those trials are so important and how we portray the benefits.

Then after that, he walked us into reasons why decentralization can be really helpful. We typically think of the benefit to patients, for example, bringing the trial closer to patient, making the trial less burdensome to participate in. But also, he made the case in addition to the patient factors and the business continuity aspect and how decentralization [00:10:00] will allow us to have more agile clinical trials, more robust clinical trials that can be done while also being efficient from a business perspective as well. He brought in also that the third aspect here is sustainability, how the decentralization model, so it's helpful from a sustainability perspective, and he elaborated on that. He also highlighted to us examples of how COVID actually was an accelerator of [00:10:30] those tools and how we were going to move forward beyond the pandemic. So again, another good talk.

We finished with Dr. Kenichi Nakamura from the National Cancer Center Hospital in Japan. He actually described one of the first fully decentralized clinical trials in oncology, an area that I had the misperception, actually, initially that oncology may not lend itself always to decentralization. He showed us how, actually, that can [00:11:00] be done, utilizing multiple tools, all the way from utilizing e-consent to utilizing healthcare providers. He brought in certain aspects that I think are very pertinent from a policy perspective as well, for example, the role of training when training is required, when you have this

sporadic decentralization and utilizing healthcare providers, and I think his example really linked what we think of as pragmatism with decentralization as well.

[00:11:30] He brought in certain challenges and opportunities from an international, global perspective. For example, they collaborated with Thailand on some of their work and highlighted how the variation in medical licenses, for example, was an obstacle that they were able to successfully address. Nonetheless, it shows the logistical aspects of this trial.

So I'll end by saying that from yesterday, it was really highlighted to us that trials with decentralized and pragmatic features are very useful tools, something [00:12:00] I think we all could agree on. Those trials could make the process, could make the study more efficient and more user-friendly. In fact, these trials can provide a more comprehensive understanding at times of how participants are interacting with an intervention.

One of the questions during the panel that was addressed to them was about the safety aspects. How do you ensure the safety and privacy of the participants in those trials? I recall the answer. When decentralization's [00:12:30] done right, this actually could provide even more comprehensive aspects of how the patients are reacting to the intervention. This doesn't, of course, alleviate the need for us to understand, because of the remoteness potentially the distance between the participants and the investigator, are there other safety parameters that should be addressed?

Overall, we heard great examples of how you're able to conduct those trials in a robust fashion, [00:13:00] in a meaningful way to produce generalizable evidence, and we've heard about certain areas that I think from a policy perspective ... I'm a policy guy, not an expert like our speakers. I think from a policy perspective, we have an opportunity to address, for example, the shipment of the investigational products and the logistics around it, aspects on data privacy, aspects on data quality, and the overall ecosystem for the safety chain. How do we make sure that the participants are safe across all those logistical [00:13:30] areas?

This is not an assumption that those trials provide us with additional risks, necessarily, but they may ask us to really be more customizing, if you would, of our approaches to make sure that the variety of the logistics are addressed from risk perspective as well.

With that said, I think you heard enough of me. I want to turn it to our real experts on the call here today. I'm going to go ahead and go to our first speaker, and I believe that's [00:14:00] Otavio, correct? Lea Ann, maybe go back to you. Sorry. Go ahead.

14:00 **Presentation 1: Dr. Otavio Berwanger**

Lea Ann Brownin...: No problem. Thank you so much, Dr. ElZarrad. Yes, let's dive in and hear from our experts on the conduct of trials. So first up, we have Otavio Berwanger. He is the executive director of the George Institute for Global Health, and he also serves as the chair in clinical trials at Imperial College London. He's going to share his insights, including his perspectives [00:14:30] on the opportunities and the challenges that are presented with decentralized and pragmatic features in clinical trials. Professor Berwanger, I'll turn the mic to you.

Otavio Berwanger: Thank you very much, Lea Ann. Thank you very much, Khair. It's a pleasure to be here. I'd like to thank you for the invitation and congratulate you for putting together such an important event. I'm a big believer in pragmatic and decentralized trials, and I think both concepts actually go together. It's, I would say, a [00:15:00] marriage made in heaven, if I may say that. I'll try to discuss both concepts together during my presentation, and I would like to start by just why I'm presenting this exposition of Gertrude Stein and Pablo Picasso and what this has to do with the talk today, is that I'm on vacations in Paris with the family, but I wouldn't miss this event under the circumstances. [00:15:30] Today this exposition just opened at the Musee de Luxembourg here in Paris. I'm staying exactly in front of the Musee de Luxembourg, and I went there during this morning here in Paris for the exposition.

It reminded me of actually two or three important aspects which are similar to our discussions today. First of all, both Pablo Picasso and Gertrude Stein, and they came from different backgrounds, literature and of course [00:16:00] painting, but they had a profound understanding what came before them. But also, they were innovators. They wanted to push and to move the needle and to move the field forward.

But the second thing is that their interdisciplinary collaboration between them were very strong. So it was all about friendship and collaboration. So I think the innovative aspect [00:16:30] and the collaborative aspects are also very important for what we're trying to achieve here. Of course, decentralization comes together with innovation. We need to be aware of the hype, but collaboration is essential. When I say collaboration, it means collaboration between the regulators, academics, sponsors, and most importantly participants. Next slide, please.

The George Institute is a global research organization. We have offices [00:17:00] in different countries. We do projects in 55 countries. It's part of our strategy, transforming the way we deliver trials, the way we design them. Next slide, please.

Why is that? What are the problems we need to solve? That's why I think this meeting today is so important. First of all, there is an issue of external validity and applicability. It varies from area [00:17:30] to area, but we can say that roughly just 5% of eligible patients participate in clinical research. If you look at this funnel, most patients with certain conditions are not included in trials, and

we have little or no evidence to guide our decisions in clinical practice and also to guide regulatory decisions.

So we ended up, next, please, with a lot of off-label indications. So external applicability is a big problem that we need to solve [00:18:00] in traditional trials. The other problem relates to diversity. I think the COVID-19 vaccine trials, the initial ones are a good example where initially we didn't have enough evidence on children, on elderly, on pregnant women. There's a big issue in terms of diversity related to race and ethnicity, sex and gender variances, and we need to address that if we need to provide reliable answers and to really inform decisions.

[00:18:30] Of course, I think sometimes there is a confusion between quality, good clinical practice, and complexity. There is a concept, and once again, I'm very biased towards pragmatic models of trials and must say that, must disclose that. But usually patients with varying severity of disease are excluded from trials, and sometimes we understand it's in order to maximize [00:19:00] the number of events in a trial, for example, with my area, cardiovascular disease. But patients with comorbid conditions are excluded from trials. Patients with certain treatments are excluded from trials. But in reality, we need decisions and we need evidence for these populations as well. Next slide.

So the other two important problems we need to solve, it's comfort and convenience for participants. The most important [00:19:30] stakeholder in a trial is not the chair of the executive committee or the executive committee members or the investigators or even the healthcare authorities and regulators. The most important stakeholders are the participants. Usually what happens is participants need to adapt to the trial procedures. I'll make the case that actually it's the other way round. The trials need to adapt to the participant needs. This is an informal [00:20:00] survey in the US, usually in the United States, and of course it's also a problem in big countries and even a bigger problem in low- and middle-income countries where clinical trial participants in the US, for example, travel 67 miles on average to study sites. If it is someone with disability or if it is an elderly patient, usually the son or the daughter or a relative needs to be together with them. So it creates lots of problems [00:20:30] from a social perspective.

The other important problem we need to solve and we need to be mindful of are the carbon footprint of traditional trials and the environmental impact of clinical trials. Decentralized models can theoretically solve some of these problems. Next slide, please.

I pretty much agree with Khair, and thank you very much, Khair, for the great summary [00:21:00] of the session yesterday. When names come out like decentralized trials, sometimes these names mean different things to different people, and that's fine. There's a bit of hype related to those names, but probably you've seen this graph or other versions of it before. But yes, initially, people just described decentralized trials as trials which were siteless. You

actually [00:21:30] don't rely anymore on an intermediary, which is a research site and the team and a location to include patients and to capture data.

So it's more of a black and white word, but actually is not exactly like that. What we have, and this is an important lesson learned, is that we have hybrid models, and there's no one size fits all that will apply to all situations. Next slide, please.

[00:22:00] I think while COVID changed society forever, here we are in a virtual meeting with several of you, and maybe 10 years ago, no one really believed in virtual meetings like this. But other business segments and sectors have changed in the past two, three decades. Let's take, for example, one that deals with very large datasets, very complex data, [00:22:30] deals with international variations, different regulations across regions, and also uses personal and sensitive data, which is banking and finances. Now I think it is impossible to have a bank account without having the bank app. Probably 80 to 90% of, let's say, the procedures that you do related to your account, [00:23:00] the procedures are done virtually.

We're still more risk-averse than the financial sector, and the question is are we right, or are they right? Of course, there are risks, but it has changed the efficiency of financial operations, no question. The next slide, please.

Yeah, and I really like this graph here, the sources on the left bottom of the slide, [00:23:30] and as we can see, it's not a black and white word, as I mentioned. Actually, what we have is more a scale from white to black with some shapes of gray.

So currently what we have, most of the examples, at least in my area, which is cardiovascular medicine and cardiometabolic trials, are hybrid models. We have some decentralized components, but some procedures are still hybrid [00:24:00] and require in person visits. Once again, I think the lesson here is that there's not a single solution for every situation, even within one specific therapeutic area.

But the concept, and I think in the title of the slide, is decentralized trials need to meet participants where they are. That's, I think, the most important lesson to be learned. If we want to do [00:24:30] a successful decentralized trial, we need to engage participants. It is vital to engage participants even in the steering committee of the trial or as part of the trial team or at least to have some participant advisors. I think that's an important aspect because otherwise we may think that by using technology, we are providing more convenience and comfort to patients, but it may not be the case for all study procedures. [00:25:00] So I think that's an important concept, is the participant engagement is more important than the technology. Technology is just a way to achieve that. The next slide, please.

So I think that's one important lesson learned, and this is a nice model. Some of you probably have seen a similar slide before, and I will go ongoing to all procedures that can be done in a decentralized trial. But [00:25:30] as you can see, the key thing here once again is the participant is at the center of the trial as the most important stakeholder, and everything else adapts to the participant. Obviously, when I say everything else adapts to the participant, obviously respecting the trial methodology, respecting the regulations, respecting the study procedure, but taking to account, of course, the participant's voice and the participant's view. [00:26:00] I think that's something really important. So next slide, please.

So a couple of lessons learned from some concrete examples that I was involved with. This is a short or a brief summary of the previous slide. But there are things that we can do related to trial management, participant enrollment, and also the trial conduct and what are the benefits related to that. Next slide, please.

So in [00:26:30] terms of the participant enrollment, as I mentioned, we have two fundamental problems, which are external validity and applicability and diversity. I also would say there is a problem that needs to be solved related to efficiency. More than 50% of trials don't reach their target sample size or their target number of events, which is a problem. So by using different approaches to identifying patients, [00:27:00] for example, taking the most of real routinely collected data, digital channels, and technology, we may speed up recruitment and improve diversity on these trials because digital recruitment, for example, can lead to multilingual prescreening in different regions, can reach online communities, and so and so.

The other important thing in terms of participant protection and safety and information and transparency, which [00:27:30] once again is vital, I think with technology now, there are multiple approach to ensure understanding through electronic consent process, including video consulting, quizzes, gamification, and other tools that can actually inform patients better in terms of their options. I don't think in a traditional trial, honestly, giving a 50- to 60-page constant form to a participant is truly informing them reliably on the benefits [00:28:00] and risks of participation. I think we can use tools to improve that. Next slide, please.

The other thing I think is a challenge and a concern is participant adherence to the investigational product, participant in hybrid study site adherence to study procedures, and of course participant retention. But once again here I think we may have some solution. [00:28:30] When we measure adherence in a traditional trial using sites which are more pragmatic and we measure adherence through [inaudible 00:28:39] counts and self-reporting. They are reliable methods, but they have some drawbacks, and maybe technology can help us here. There's a couple of examples, and I won't mention the names of companies, et cetera. But there's a couple of examples here where we

[00:29:00] can augment delivery of the investigational product using reminders, photos, smart packing, smart pills, of course still restricted to some situations.

This was done during COVID, and it worked quite well. Of course, by shifting some of the procedure, all the procedures in some cases to the participant's home, we can improve retention and of course improve convenience for [00:29:30] participants. The next slide, please.

Finally, I think there is a misconception that when you do a decentralized trial or a hybrid trial, participants are on their own. You just include them, send them the investigational product, send them some blood kits for home collection, and that's it. They are on their own, and good luck for them. It's not like this, really. What [00:30:00] we have now are new roles in terms of trial coordination.

Otavio Berwanger:

What we have now are new roles in terms of trial coordination and central vertical coordination of trials, which can still provide enough support and engagement for participants in a more convenient manner. Of course, I don't have time to discuss everything related to using routinely collected data when we embed these trials in existing systems, but there's also ways to achieve that. Next slide, [00:30:30] please.

Another interesting concept, actually it's not necessarily new. This was used in trials in the past. For example, the classic MRC hypertension trials in the UK in the early '80s and late '70s used that, actually. If we want to meet patients where they are and we need some procedures that require more complex measurements and assessments, we can also use mobile clinical trial units that could complement some [00:31:00] of the decentralized features. Next slide, please.

And just to finalize, just two quick examples. This is a trial I'm involved in in the executive committee and in the leadership team together with some colleagues, like [inaudible 00:31:18], Chris Cannon and Mark [inaudible 00:31:19], and Stefan James, among others. And we're testing, the clinical question is not relevant here, but it's as a trial in patients with myocardial infarction, or STEM or STEMI, [00:31:30] they're randomly assigned to evolocumab, the PCSK9 inhibitor, or routine clinical care, in order, during the acute phase of acute coronary syndrome, to assess the impact of this intervention on major cardiovascular events. The primary endpoint is, won't go into details here, but it's a combined cardiovascular endpoint. Based on total events, so it's not timed to first events, but total events. This is a hybrid trial conducted in three completely different settings. And besides the importance of the question, I think [00:32:00] the most important aspect here is that we have good examples of decentralized trials but conducted within a single region.

We have very large wounds but conducted in the US, the UK, and Scandinavia, but we need to expand that and that's part of our work now at the George [inaudible 00:32:17] Imperial College, expanding that to different regions. So this trial has been conducted in three completely different settings, which are

Brazil, where both of the patients are coming from, United States and Sweden. Very [00:32:30] different settings in all aspects. Patients, it's a hybrid trial, as I mentioned. Patients are randomized in hospital, but then they receive the drug at their home and we ascertain endpoints by interrogating routinely collected data in networks in these countries or in registries in Sweden. And just a couple of thoughts and this trial is ongoing, is recruiting extremely well with very minimal or no loss to follow up at [00:33:00] this stage and good or to excellent adherence to therapy to investigational product therapy.

Next slide please. A couple of thoughts. First of all, I wouldn't call it exactly innovations, but it borrows from, uses pragmatic features, minimal inclusion and [inaudible 00:33:20] criteria. Minimal procedures and ability to screen so you can identify the patient and randomize them, randomize the patient almost immediately. And of course [00:33:30] the procedures are streamlined. Next slide please. And it uses a hybrid approach, as I mentioned. Next slide please. Yeah, so there's hybrid data collection and there is a lot of, in terms of the operational aspects, it facilitates the trial delivery. Next slide please. And this is some of the informal [00:34:00] feedback we're getting from sites.

Number one, from all the members of the executive committee is the fastest recruitment rates everyone's seen in the regions for trials in myocardial infarction. And it's a hybrid trial and we opened a site and most of them are able to enroll a patient within a day of activation. And these are some of the investigator's feedback from different regions, screening and enrolling were smooth and it was nice to be able to randomize within [00:34:30] a single EDC. So it's a single system, so it doesn't require multiple systems. And most importantly, the participants are interest, almost everyone qualifies and the data entry is not burdensome. So it's really embedded in clinical practice and hopefully we'll provide a reliable answer. And just to finalize, next slide please.

This is part of what we're trying to do at the George in terms of the elements that we see [00:35:00] as important in a decentralized trial. As I mentioned in the beginning, the pragmatic and decentralized components, we think it goes together. So streamlined eligibility criteria, streamlined procedures, at least in the cardiometabolic care are vital for the success of a decentralized trial. Let's not forget the importance of high quality in terms of concealed allocation, blinding, ITT analysis. There's also, [00:35:30] that was used in COVID, we can use innovative designs, we can use innovative statistical models. So it's not just about the technology, but it's about the methodology, the quality by design approach. We discussed innovative approach and the importance of participant engagement. So I think in terms of a guidance, I would consider these different elements. Next slide please.

And I'll finish with [00:36:00] this slide here. There's actually two more slides, but we'd like to very quickly just mention some initiatives. So one thing we're trying to do is really to conduct this on an international basis. And currently we're working with some partners in different regions, UK, US, Scandinavia, Netherlands, Brazil, to conduct such trials that there are two big trials being

planted and we invite regulators [00:36:30] and other groups to help us with that. If you want to use our trials as a model to reform the guidance and to test [inaudible 00:36:40] procedures of the guidance, we'll be very open to that. In terms of hybrid trial, we are a hundred percent towards collaboration. So there is a consortium of ARLs and also we're working with some foundations like the Wellcome Trust in the UK in terms of improving diversity in the trials. And that's called [00:37:00] the Message Program. Next slide please.

Well, the way we set up this collaborations in each country is also being developed. And next slide please, and next slide please. I would like to finish here. And also we would like to make the most of collaborations. And I also would like to thank Martin [inaudible 00:37:26] for sharing and his group for sharing this slide with me. I think there are some [00:37:30] modern initiatives out there and we need to join forces, I think the good clinical trials collaborative, which is a very comprehensive guidance, but also pretty much towards the pragmatic and efficient model could also be useful to inform some of the decisions. And we see that once again, like Gertrude Stein and Picasso, it's all about collaboration in order to move the needle. I'll stop here and thank you very much for your attention.

38:00 Presentation 2: Dr. Noelle Cocoros

Lea Ann Browning-McNee: [00:38:00] Thank you Professor. We really appreciate your insight. And I will note that one slide that you didn't get to but is on our website if folks get a chance to look at it is your takeaway summary. I just think that is a super helpful slide in underscoring what we most need to understand in this arena. So thank you very much. So now let's turn to Dr. Noelle Cocoros. She is the principal research scientist [00:38:30] at Harvard Pilgrim Healthcare Institute as well as the principal associate in population medicine at Harvard Medical School. Dr. Cocoros, we are excited to hear from you.

Noelle Cocoros: Good morning. Hello. Thanks very much for having me. My name is Noelle Cocoros and I'm very happy to be here. If you go to the next slide, so much of what I'll talk about today is actually covered in the paper that's referenced here. This just came out somewhat recently in clinical trials, so I'm going to try to touch on quite a bit that's in there as well as some other [00:39:00] papers that I'll mention in a moment. And the types of studies that I'll be talking about actually are a bit different from what the other speakers yesterday and today have been discussing. So hopefully that's of interest to some of you. And I'll try to cover both really big picture issues as well as some more detailed ones. It kind of covers the range of the level that I work in, which is both the high level as well as in the details.

So in terms of objectives, I'll tell you a little bit about pragmatic clinical trials embedded in US health plans, also known as insurance [00:39:30] companies, highlighting a little bit of how they vary in comparison to one's embedded in clinical practices. I'll talk about the key advantages and benefits for embedding these kinds of trials and leveraging existing healthcare data and infrastructure.

And then of course talk about many of the challenges that I've encountered in my work and the projects that I've worked on as well as highlighting lessons learned so that it's not all just challenges. If you go to the next slide, so this one I'm going to try to do a little bit of baseline [00:40:00] setting. I know that this is an international audience and I want to make sure everyone has the key underlying concepts.

So as I mentioned, I'll be talking about primarily randomized pragmatic trials that were embedded in US health plans, insurance companies, and these trials used billing claims data, which were the data available from health plans to identify the subjects of interest to facilitate patient and provider contact and to conduct the analysis. And so a couple of things [00:40:30] on what that all means. So administrative claims data from these kinds of health plans or insurance companies has everything that is billed to and paid for by the insurer. So covers all encounters, meaning ambulatory, outpatient and inpatient diagnoses, received procedures as well as medications that have actually been given to the patient as well as detail on hospitalizations, although the granularity of that detail is a little bit more limited and that's an important issue to understand.

[00:41:00] And importantly, I want to mention the US FDA Sentinel initiative because some of what I'll be talking about really stems from that. So the Sentinel Initiative for some of you, you probably are well aware of this, but there is an aspect of Sentinel that is an active medical product safety surveillance system that has claims data from a large number of health plans across the United States. And there are claims that have been transformed into a common data model and that enables us to work in a distributed network approach, [00:41:30] which is a pretty efficient way of conducting public health surveillance and research. The data are heavily quality checked and routinely updated. The department I work in is actually the Operations Center for Sentinel and I'm the lead epidemiologist for the operations center. The reason why that's important to understand is that the NIH Collaboratory Distributed Research Network, which is where some of the work that I'll be talking about has been conducted, is comprised of a subset of the Sentinel data partners or health plans.

And it enables researchers [00:42:00] to conduct pragmatic trials in the network taking advantage of the data and the infrastructure that's actually been curated for FDA. And so that's an important resource to be aware of and a little bit of context for my comments today. So just briefly on the three trials that are mentioned here, these are ones that I've personally been involved in. The first is IMPACT-AFib. This is a clinical randomized, pragmatic trial that is completed. It was FDA funded as a proof of concept basically to demonstrate [00:42:30] that it is possible to do a large randomized pragmatic trial in this kind of setting. It involved an educational mailing that was targeted to both patients and their providers and it was patients with atrial fibrillation who appeared to be at high risk of stroke and not have recent use of an oral anticoagulant.

So that's what we identified in the claims data. Five health plans participated. We randomized over 190,000 people to give you a sense of the scale. And the primary outcome was initiation of an oral anticoagulant. [00:43:00] And again, here we use the claims data to identify the individuals of interest to facilitate the contact with the patient and provider and to conduct the analysis. D-PRESCRIBE-AD is an ongoing trial. It's quite similar in terms of design and implementation to IMPACT-AFib. This one though is NIH funded. It's also an educational mailing. It's targeted to adults who have dementia. So the educational mailing goes to the patients and their caregivers as well as providers. And these patients appear to be on [00:43:30] a potentially inappropriate drug from what we can see in their claims data such as an anti-psychotic or a sedative hypnotic. For this, we had two health plans.

We randomized about 14,000 people in the first trial. And the claims data are being used in the same way. And the last I'll mention, this is still in the planning phase. There's been NIH funding received for this first planning year. This will be a cluster randomized trial aimed at improving evidence-based statin initiation in patients with atherosclerotic cardiovascular disease. [00:44:00] The idea here is you identify the patients and providers using the claims data, but there'll be a pharmacist who contacts the clinicians to get approval for contacting the patients. And the intent is to increase high intensity statins and there'll be an interaction between the pharmacist and the patient as well. So if you go to the next slide, this is to say that there are many lessons that we have learned from even just from IMPACT-AFib, but from all of the trials that I just mentioned. So much that we actually [00:44:30] published a trilogy of papers.

So these are a couple of the prior ones and the results from IMPACT-AFib are reported separately in JAMA Network Open. If you go to the next slide, for those of you who may be interested, I won't talk about this in any detail, but there were ethical considerations raised during the planning of IMPACT-AFib, and this paper addresses some of those in case you're interested. So we go to the next slide. This is a little bit of a high level overview of the advantages, probably much of which I don't need to explain [00:45:00] to this audience. But for trials that are embedded in either health plans or clinical practices, much of it applies to both of these kinds of settings where you can leverage the data for various stages of the trial, whether it's identification of potential subjects to facilitate contact and to conduct the analysis with supplementary data being possible due to data linkage.

So you can use the claims data for certain aspects of the analysis and then supplement it with, for example, patient reported information [00:45:30] when you need large numbers or if you're concerned with generalizability in that you don't want to only look in one site, that's when the multi-site pragmatic trials come into play. They of course come with more considerations and a lot more careful planning, but they also come with other efficiencies. So if you need large numbers and there's a reason to do a multi-site using something like the NIH Collaboratory Network enables you to also use a distributed approach which limits the cross-site variation in terms of certain aspects [00:46:00] of

implementation of the trial. And then in terms of generalizability, you can think of this on a few different levels in terms of the patient populations, the interpretation of the results, and then the likelihood of the intervention being able to be readily adopted.

And so that's what I'll say in terms of the big picture advantages and then the next few slides if you go to the next one. So this is where I'll talk about some of the lessons learned. Again, really big picture as well as getting into some of the real details [00:46:30] to be aware of. So these first two slides will be on, you can think of it as a little bit of the planning phase. And again, these apply from my experience from working in trials embedded in health plans, but much of it also applies to those embedded in clinical practices. So as Octavio said, strong collaboration is really key. And from the perspective here, what I'm talking about in particular is deep engagement of the sites where you're conducting these kinds of trials. So [00:47:00] these sites, let's talk about health plans specifically, but again applies to clinical practices.

There are experts at these sites, not just in terms of their organizations but also their data, their patients or members and essentially how to work within their organizations. And so really early on, we've included in the, really since the inception of the studies that I've mentioned, the inclusion of representatives from leadership in these different health plans. And [00:47:30] that's been incredibly important. They've been involved from the beginning, have maintained their engagement and really served as internal champions. They can provide obviously not just the oversight and required participation of the sites, but really help you understand the inner workings of their organizations, help you become aware of programs that are going on in these settings already that may impact your study, which is really important. They'll help you understand the timelines for review and clearance and all of the logistics of implementing this [00:48:00] kind of study. And that's a really important thing to have early on.

And then in terms of IRB, so for multi-site studies, a single centralized IRB is really important. In the US a commercial IRB is going to be most efficient. They just simply meet more often. And in terms of IMPACT-AFib, this may not apply to many of the trials that some people in the audience are thinking about, but for IMPACT-AFib and D-PRESCRIBE, these were interventions that were so [00:48:30] similar to the work that the health plans already do in terms of quality improvement activities that we were able to obtain a waiver of informed consent. Again, it may not be applicable for many of the trials that you all are thinking about, but it's important to be aware that that might be possible. Let's see, in terms of study populations, so the take home is that restrictions may apply from a US perspective, if you are thinking about including patients who are covered under a Medicare commercial plan, [00:49:00] it's important to be aware of that and plan from the very beginning.

For IMPACT-AFib, we actually obtained a letter of support from the Centers for Medicare and Medicaid services and that facilitated plan participation. So it's

important to be aware that you may run into some concerns there. In terms of the identifying, oh, and I guess one other thing to say on that restrictions, if you're interested in Medicaid members of health plans to participate, I don't personally have experience with that, but I'll [00:49:30] just say it comes with a lot more considerations and might be really, really difficult to implement. As I understand it, there's state by state approval of participation. And then this last part on this slide is where we get into some of the details. And I thought it might be worth mentioning that identifying clinical providers if that's important to your trial, using claims data as the resource can really be tricky. It's not impossible to work with.

We've done it multiple times, but it does require deep understanding [00:50:00] of the data and careful planning. So for example, an individual clinical provider can have multiple IDs in the system and then each ID in the system may not represent a person but instead represent a facility due to how care is billed for in the United States. And so understanding those nuances and intending to work with them is important. The other thing to mention is that identifying clinical practice groups is really hard in claims data. And so depending on what your intention is, for example, [00:50:30] if you're trying to avoid cross-contamination of having similar, of having the same provider care for patients in multiple arms of your study, you may need to use geographic restriction or cluster randomization by geography to avoid that cross-contamination. So that's another sort of, in the details, aspect of this kind of work to keep in mind.

If you go to the next slide, so this is a little bit more on the planning phase, so I'd highly recommend that you include a patient representative from the beginning. [00:51:00] For IMPACT-AFib, we had someone who is heavily involved in the AFib patient community. Involved from the beginning and she really helped make important decisions about the trial. For D-PRESCRIBE-AD. We had focus groups that engaged caregivers for patients with dementia as well as providers. And that informed a lot of the work as well. If you're conducting trials, particularly in a health plan, if that's where you're embedding your work, understanding loss to follow up and the rate of turnover within a health plan is really [00:51:30] important. It obviously varies by not just health plan, but primarily by age group. And I'm speaking again to the United States perspective, and that needs to be taken into account, not just in terms of the logistics of when the trial has started and when the intervention begins, avoiding very end of year because of the turnover in the calendar year, but also for long-term trials that are going to have a long follow-up.

You're going to want to take into account the rate of loss to follow-up just by simple turnover [00:52:00] within membership. And that's an important thing to be aware of. Data, there's a lot to say here. I obviously will keep it brief and there's a lot to say both in terms of claims data and electronic health record data if you were to be working with clinical practice groups. A major thing is taking into account data quality. If you're using something like data that's been created for the Sentinel System for example, obviously there's a lot already embedded in that system in terms of the infrastructure [00:52:30] and how the

data are checked and maintained. And even with that, you're going to have points in the trial where you're deviating from that source data. And that really still requires very careful review and checks and planning for that. When you're working with claims or EHR data, and also to note, you obviously can conduct feasibility analysis and that can be really, really helpful.

But you should also, if you're using these kinds of real world data sources, use whenever possible validated algorithms to identify your subjects of interest or at least to [00:53:00] do that initial identification. And then also for your analysis, whenever possible, use strong algorithms. And there's other ways of addressing this as well. You'll have to make decisions obviously about the conduct. Again, this is a little bit more in the details of if you're using something like a distributed network, how are you going to do that? So if it's a multi-site trial, how homogenous or heterogeneous will you allow some of the steps in the trial to be? And again, I'm [00:53:30] talking somewhat from the data perspective of identifying the patients of interest and conducting the analysis. You can do it so that you have a single program that's run at all sites so that there's really little variation or you can have something more like a common protocol that's implemented at each site with the intention of them being the same, but expecting some variation.

And then in terms of fresh data, I'll keep this brief, but for those of you who have worked with claims data in the United States before, in general research for these kinds [00:54:00] of data, we often are waiting until the data are settled and near complete. That obviously won't cut it for this kind of work. And so you have to anticipate getting fresher data so that you can ensure that the patients are still truly eligible essentially at the moment of study start. And that's a really important thing to plan for and requires a fair amount of deep understanding of the data and planning. And then I'll say, you're using real world [00:54:30] data, it's not created for us. And so you have to essentially protect yourself and protect your trial against that or your studies. And so save data along the way, you're not going to be able to really go back and recreate the data.

So know that and anticipate it going in. If you go to the next slide, so this is a little bit more thinking about how the trial will actually be implemented. And so patient and provider engagement, this is true for clinical practices as well of course, but from [00:55:00] the health plan perspective, this kind of engagement is intensely scrutinized. And so understand that, anticipate it and work with the site experts to make sure that concerns are addressed and you have enough time built into your study timeline to enable that. Basically what we've found is that you won't be able to do outreach to patients without also letting their providers know what you're doing. That's maybe the high level take home here. There's obviously a range of modes of contact available [00:55:30] for both patients and providers, and we all know that people respond or respond differently or respond at a very low rate differently depending on the mode of contact that we're talking about, whether it's a phone call or text message or letters to obviously take that into account.

We had a pretty variable rate of undeliverable mail in the IMPACT-AFib trial in terms of provider mail coming back to us, and that was somewhat surprising with as high as 11% [00:56:00] on deliverable mail for one of the sites. And also, maybe this isn't a surprise, but in that trial we created a study website targeted to the patients and it had incredibly low traffic to that site. So we've learned the lesson that it's probably not worth doing that. In terms of your analysis, there's an enormous amount that I could say here, but I'll just mention that if you're using claims data for part of your analysis, then you need to understand the lags that are involved and the time that it gets, that it takes [00:56:30] to get to near complete data. It takes longer for hospital-based care to essentially get into the claims data. And so plan for that and understand it.

And then there's a lot that happens between randomization of patients and when the work actually starts, at least in the kinds of trials that I've worked on. This can be weeks if not longer, and patients may be becoming ineligible during that time. And so you have to understand that. And one thing to keep in mind is you might have to do something like a modified intent to treat analysis, which is what [00:57:00] we did for IMPACT-AFib, which is described in some of our manuscripts. So that's another important consideration. And then if you go to the next slide, this is a bit of a summary of some of the major advantages and challenges to keep in mind. I mean, I think the big picture is that there is a lot that can be leveraged from existing infrastructure such as those infrastructure and data that exist for US health plans that can be used for pragmatic trials, particularly large ones.

[00:57:30] There are a lot of challenges that come with them too. And so it's really this balance of does the setting, does the data, does the infrastructure meet the needs of the study? Is it basically fit for purpose? And if so, and you need that kind of sample size, for example, and the setting makes good sense and the intervention makes good sense. Then I think with really thoughtful planning and care, you can really overcome many of the logistical [00:58:00] considerations that arise essentially at every single step of the trial. So I think again, it comes down to, as Octavio said, a really strong collaborative approach. In this case, I think a really strong coordinating center who works very closely with the sites who understand their data best and using those sites on an ongoing basis. So thanks very much for your attention. The last slide, feel free to reach out with any questions you have or if you have interest in the NIH Collaboratory [00:58:30] Distributor Research Network.

58:30 Presentation 3: Dr. Adrian Hernandez

Lea Ann Browning-McNee: Great. Thank you Dr. Cocoros. You really kept your promise of sharing both the big picture and those important details that are going to help us think about the strategies and the challenges that lie ahead. So thank you very much. Our last presenter is going to focus on having the trial meet the patient. Dr. Adrian Hernandez is a cardiologist and also Vice Dean and [00:59:00] executive director of Duke Clinical Research at Duke University School of Medicine. I'm happy to add that we're also proud to say he's a board member here at the Reagan-Udall Foundation for the FDA. Dr. Hernandez, we'll turn to you.

Adrian Hernandez: All right, well thanks for having me on here. And I'll look to wrap this up so we can get to the discussion and answer all the questions and particularly the hard ones that you all pose in terms of this area. So if you go to the next slide, [00:59:30] I just want to outline a few things that I'll go through. I want to kind of provide a high level view of what's the problem we're aiming to solve, what's a practical approach, and I also want to give some case examples and some lessons learned just so we can make sure that we know that there's still more work to do. And everyone in this so-called zoom room has something to do to help the evidence generation system improve and take advantage of decentralization of clinical trials. And then also want to leave with [01:00:00] a few questions that we want to make sure we all ask ourselves to ensure...

Adrian Hernandez: A few questions that we want to make sure we all ask ourselves to ensure success. If you go to the next slide. So what can we all do? Well, I'll just say that we've all contributed to the Gordian Knot of clinical trials, whether it's an investigator, a sponsor, a regulatory agency, a health system, an IRB, we've all added things and contributed to this kind of tangled knot of what we do for clinical trials. Now's the time really to untangle that. We saw during the [01:00:30] COVID era, the pandemic that we're able to do things that hadn't been done before, in part because everyone was working together to untangle this Gordian Knot.

And now we're hearing that there's actually a roadmap where we can actually further this along outside of COVID-19. And I think it's on all of us, all our different perspectives and what we do to actually hold to that commitment to make clinical trials better. Because as you heard at the beginning of this, [01:01:00] regulatory agencies such as the FDA are actually putting forth different guidances that will help us out, but it'll be up to us, whether it's a sponsor or an investigator, a health system to actually follow through in terms of implementation of policies into practice.

If you go to the next slide. And so with that, just leave this as trying to make this very personal in that, have you or someone you love participating [01:01:30] in research? I have, and I'll share my experience here shortly. And if you go to the next slide, did you enjoy it? And so people may not think about it that way, but I think it's really important to think about it from a person or patient perspective. Would you actually recommend it for others? And so if you think about that way, I think there's a lot of things that we can do to change this and there are a lot of reasons why we have to do that to be more person-centered.

If you get to the next slide. And [01:02:00] I'll share my experience. So I signed up for a COVID-19 vaccine study, actually got approached by a number of different investigators and teams and was able to sign up with one of the studies. And at the very beginning of it was quite convenient, because almost everything was without traffic. It was a lot at home. Then as the trial progressed then there's follow-up that I need to have, I was really committed as a participant to follow through [01:02:30] to be a good participant. What did I encounter? I encountered traffic again. I went into sterile waiting rooms, and

then I saw someone entering data on a computer that had actually already been collected at least a couple other times. And so you can see that it's pretty easy to fall back to the so-called status quo pre-pandemic. And so it's up to us to think about how it would feel to be in a trial and what we can do with hybrid approaches to meet [01:03:00] the person or the patient where they are, where they work or where they live.

Go to the next slide. And there is important reasons for doing that. So just like we have healthcare deserts in the US and around the world, so too we have clinical trial deserts, and so I'll just offer that why we have healthcare deserts where there are people who have lower access to healthcare. It's even worse for access to high quality clinical trials. And so we [01:03:30] got a bridge to divide here.

Go to the next slide. Now one could say, well, what is something convenient within a few miles of every person? There's been models that have been tested out during the pandemic and there's been some hard lessons learned. And an example is that we found that there was great utility, for example, for retail pharmacies and vaccine studies, but if you try to extend it to other areas, it may be more difficult, because [01:04:00] engagement matters. And so an example is, well, the same concept could exist for convenience stores. They're quite convenient, hence the name. And so they're often a few miles from every person. But would you go to a convenience store to participate in a clinical trial? And I think one of the issues around clinical trials, it's different compared to other digital models or convenience models, is that actually it's a human health experiment. And so that engagement [01:04:30] on the human side is really important and it's a social network that has to be considered.

Go to the next slide. And so the world is open to many possibilities. This is work done by the city group clinical trials transformation initiative and FDA public partnership that highlighted that in the past we were very site centered. We made people come into the site to do everything. Now [01:05:00] with new technologies and new approaches and being able to think differently, we can be very person centered. Now there's certain things that we'll definitely have to take advantage of what is available at a site or a system, but there are other things that can be done at home. And then also through data linkage, be able to incorporate data that hasn't been done before and especially with disparate data that may not have thought of as possible in terms of understanding the total picture of someone's human health.

Go [01:05:30] to the next slide. And so I'm going to share an example with regulatory enabling studies. So it's really important that we think about evidence generation that meets different stakeholders needs not only creating clinical evidence that may go in guidelines, but also meeting the needs for regulators so they can make a decision on the benefits to risk. So Activ-6 is one example where it was actually evaluating whether someone can feel better or [01:06:00] not with acute COVID. If you go to the next slide. And so it's really

fundamentally asking two questions, how to help people feel better faster and how to prevent hospitalizations or death in a platform trial.

So if you go to next slide. And the way it was designed is really a click and mortar approach. We knew that in some cases and people are going to engage the healthcare systems and that's our trusted partner, and in other cases they preferred to do things at home. And so having [01:06:30] both available allowed us to be able to engage people where they have the most trust and most convenience. We're able to identify people through these systems and at home and enroll them and then understand their preferences for different arms for the study, collect data remotely and then do randomization to one of several arms. And if you go to the next slide, then be able to do follow- [01:07:00] up. And one thing that's really critical is being able to have different mechanisms of follow-up because not everyone is savvy with the internet. Not everyone actually has a smartphone that can actually use what is needed for data collection. And then also some people don't necessarily trust some of these mechanisms because of other issues that have affected privacy and data breaches. And so having a multi-pronged approach for [01:07:30] complete data was important.

If you go to the next slide. And so what's the bottom line here? That through this platform we were able to enroll across all 50 states, which is not typical. We were able to follow the pandemic where the pandemic was going because one of the key issues was there are hotspots that are going to pop up anywhere, and so how can you be convenient to where the hotspots are? Overall 26,000 people engaged in the portal. [01:08:00] There are 93 sites that were part of the click and mortar, so every state was covered. And then we had 13,000 out of 23,000 that began the consent process and then ultimately almost 10,000 consented to lease one arm and then further eligibility criteria established for over 7,700.

And so it's also important to understand the whole funnel here, to understand where people get engaged and what it takes there. And we [01:08:30] were able to use a number of different experiments using from radio ads and traditional media to social media ads, to local engagements as well as leveraging health systems to get to this final number of 7,700. We're still actually randomizing and at the peak of different times we've had 400 plus and randomized per week. And then even during other times where other studies were slowing or shutting down, we [01:09:00] were consistently randomizing 60 a week across the study. We recently just launched another arm for Metformin and we'll see how things change as the pandemic may have receded in people's eyes, but COVID cases are going back up and understand whether this model can be useful for other areas like this.

If you go to the next slide. I'm going to share an example of what I call research on research, which some of you may know the [01:09:30] adaptable study, which was really the first large scale pragmatic trial leveraging electronic health records across 40 sites and ultimately randomized 15,000 people to over the

counter aspirin 81 versus 325. Just to highlight what it takes to get that kind of engagement. Over 650,000 people were identified as being eligible, 450,000 people were approached through low touch methods, and then are most successful with some [01:10:00] combination of engagement through a healthcare system. We're able to have the highest rate of enrollment because that was a trusted channel it seems like. The ultimately 31,000 joined the portal and then 15,000 did e-consent and then we had 49,000 virtual visits. So operationally this was quite successful. I'll just say that I thought we would have success if we were able to get 5,000 and so getting 15,000 [01:10:30] and our goal was highly successful. But we also learned some lessons, and so let me share some of those.

If you go to the next slide, engagement really matters. And so while you can have technology that enables people to eat more easily, join a study that is perhaps necessary but insufficient. And so we are very proud that we have people with a lived experience, the group in the middle that you see here for those who have [01:11:00] cardiovascular disease and joined us from end to end, from designing the concepts. In fact, actually even picking the question here to the consent process to how it looked, what was the stories to help describe that? So it was actually engaged consent as opposed to informed consent, to the ultimate end were the dissemination across tens of thousands of people through Dr. Gibson's social media site. And as [01:11:30] he noted, it was the first time that they had a participant in a trial present the background for why the study was done and the primary results. So end to end, having the engagement with a team of people who had lived experiences was really critical.

If you go to the next slide. And I'll provide some data on why that may matter is that... Well, it wasn't engaging and so we had the opportunity of testing different ways of reaching out to people. We were happy to partner with several health plans [01:12:00] and while they have the data to identify people, the health plan outreach wasn't as engaging, so over 185,000 people or contacted and only 0.8% actually touched the portal. And so you can see here the funnel gets really... Has to be really big to get to high level of participation and that may not necessarily [01:12:30] work out for the best. Now certainly there are other ways to improve engagement, but again, I think it gets to this idea of how you go through trusted channels that people are used to seeing for joining studies. And so hybrid approaches seem to be something that will be helpful as we go forward.

Go to the next slide. So I'll just finish up here is that I hope everyone thinks about decentralization of clinical trials. I think all of us, whether [01:13:00] it's a sponsor, an investigator, a study team, a regulatory perspective is really thinking... Or fit for purpose. What's the trial characteristic? What can we do that would be better decentralization that can fall into the easy column? I'm not saying everything is going to be easy because there's going to be certain things that we just have to do in a way to ensure something is done the best way until we have a better way.

But there are many things in this set of domains such as engagement, [01:13:30] establishing initial eligibility criteria, trying to get a representative cohort and engage consent, data collection, quality assurance, safety and endpoints that we can take advantage of decentralized methods. One word of caution though I'll say is that just because you have a technology that can so-called reach everyone, and so a smartphone as an example, our example from adaptable is that we had to do something very different to get a more diverse and inclusive population. [01:14:00] And actually it wasn't through just a so-called smartphone. And so I think that is an important lesson as well.

Go to the next slide. And so just in summary here, I think everyone probably agrees that the speed of science is from the last two days is really incredible and there are many more questions and answers. I hope I've convinced you that people matter. So engagement matters, experience, and also [01:14:30] how we do things differently to ensure we have equity or access to trials and engagement, that is important. We do need to meet the real world as opposed to kind of creating this artificial world. And so we have to think about being convenient, but actually be smart. Just because it's a convenience store doesn't necessarily mean that's where you go for healthcare or clinical trials.

And so thinking about what's a person that's going to walk through those doors and what they will say when they so-called join or want to join a study or be approached. We got to be trusted [01:15:00] and we're in an era where trust really matters. It did before, but it seems like it even matters more now. And so being trusted is really important. And ultimately we all have to contribute to this, to untie the Gordian Knot and to hopefully bend the curve to gain lives and lose less and have more value. So with that, I look forward to our discussion. So thank you.

1:15:30

Moderated Discussion

Khair ElZarrad:

Thank you so much Adrian, [01:15:30] Noelle and Otavio, really appreciate your talks. If you don't mind turning on your cameras so we can move to our panel discussion. I'm smiling because since you said Adrian, the Gordian Knot of clinical trials and then real world versus artificial world, just really I think overall the discussion today from all of you, I feel like it's moving us a little bit away from the terminology of what's pragmatic, what's decentralized, the real world data used [01:16:00] into more fit for [inaudible 01:16:02] approach and hopefully seeing all of this as simple tools that can be utilized in any clinical trial to make the trial more efficient, more patient friendly, frankly more patient centric in a true sense. So hopefully we can see this movement. I feel like sometimes it gets stuck in terminologies and definitions rather than really applying those practical tools to move clinical trials ahead.

And then hearing you all today, I feel like you're really all nudging us [01:16:30] into that direction. So thanks for that. I so appreciated the point about the logistics and the difficulties for patients. I recall one of my colleagues mentioning that a CDC study found that there is a 15% decline in participation

for every 10 mile travel. So this are real when it comes to patients and patient situations. I think we should really take all of that in a very careful consideration. So thanks again [01:17:00] for helping us focus on that.

With no further delay, let me jump into a couple of points that we've been hearing, questions both during registrations and frankly during the chat about, and I'll start with you Otavio, but then others please comment here as well. And this is specific to when we have trials utilizing healthcare providers. So you have healthcare providers as part of the trial, which is a feature of pragmatism, but I think it's increasingly, again, we should see [01:17:30] that the healthcare infrastructure and healthcare data are just available for us to be utilized across the board.

But for utilizing healthcare providers, we receive many questions typically on differentiating between healthcare providers that are expected to provide routine care versus those engaging in research. What are the barriers for that? What are the lines even? Are there specific data integrity and safety consideration while healthcare providers are involved? And in practice, what are the challenges and barriers for conducting those trials involving [01:18:00] healthcare providers, involving healthcare data as well? I know this is more of an encompassing question and hopefully you can touch on a little bit. So I'll start with you Otavio, and then go to the rest of the group.

Otavio Berwanger:

Yeah, thank you. Thank you very much, Khair. I think one point that Adrian made very clear, and I completely agree, is that we're nearly... This is all very nice, but we're nearly scratching the surface here. So I think first of all, it's a work in progress and things are really, really not sometimes straightforward. I think to your point, [01:18:30] I think this is one of the pain points that we need to solve. Well, I think pragmatism can help. I think if the number one thing I would do, and this is exactly what we're trying to do, it's understanding different contexts. For example, in the UK, a lot of the care is provided through the GPs and in other countries is different.

So understanding your point of view and your context, [01:19:00] it's important. Whenever possible I think using a streamlined approach for trials, if it's a hybrid trial for example, that rely on healthcare providers, maybe the trial procedures will need to resemble more closely clinical practice. And the reason for this is that I understand a regulatory perspective, but you also want the intervention to be applied in clinical practice. So in clinical practice it will be applied [01:19:30] anyway in the real world. So I think whenever possible, bringing the trial procedures closer to clinical practice may help. I think you cannot put a lot of burden on other healthcare providers outside research. I think that's not... So I think their help should be in terms of engaging participant, identifying participants and once again, maybe some of them helping the trial when the [01:20:00] procedures resemble clinical practice.

I think the hybrid approach, and I also agree with Adrian, that there's no one size and I also made this point. There's the multi-pronged approach, so you

need to be flexible. So you have a patient portal, you have a virtual coordinating center, a regional coordinating center who can both compliment the gathering of data, which are vital and a little bit different from clinical [01:20:30] practice. And in terms of the routinely collected data, I think we need more and more what we call [inaudible 01:20:40], which are research within research. So maybe something that could be useful if you're using routinely collected data, maybe we can or we should understand, for example, conducting initially before using it for a trial, conducting retrospective analysis, understanding those baseline characteristics [01:21:00] match... Does the endpoint, the [inaudible 01:21:02] rates are similar to what a traditional trial will do.

So there's a lot of empirical and methodological research that can be conducted or pilot studies before embarking on a big trial. So I think it's a mix of these elements, pragmatism resembling clinical practice, having a multi-pronged approach with a global and virtual regional coordinating center and a patient portal. I think that's the way I would approach [01:21:30] it. I think you're on mute, Khair. Sorry.

Khair ElZarrad: Thank you. No, I was saying before you go, in your last slide you had that collaboration slide showing multiple countries working together. I'm wondering if you can just before moving on, if you can touch a little bit on how the differences in healthcare standards, for example, or healthcare approaches can potentially be addressed or taken into consideration in those trials.

Otavio Berwanger: Yeah, so [01:22:00] I think this is definitely a work in progress, early stages, but what we're learning is... And once again there's no one size fits all approach. So you cannot use, I didn't have time to show a slide regarding the UK, but that won't be applicable to the US, won't be applicable to Brazil, will be applicable to Scandinavia. So you need to understand the context. In the end of course, you need a common data link, a common data management [01:22:30] charter. You need a common SAP, but you need to understand the context. So the key thing is efficiency and pragmatism, and you'll need to adapt a bit to the different models in each countries.

And at this stage, what we're doing, exactly understanding how it works in each country, what will be the best model and you won't [01:23:00] be... So we won't design one single table of trial procedures and you just follow that. So in terms of the trial conduct and efficiency, we want of course is the same protocol, the same data, the same analytical approach, but the way to get there logistically may vary between context to context. And the other thing I would add is also the patient perspective, the participant perspective. Sorry, it is also vital here.

Khair ElZarrad: Thank you very much. Thanks Otavio. [01:23:30] Adrian or Noelle, would you like to chime in?

Adrian Hernandez: Yeah, so just two things. One, I think anything that we can do to make it easier on the burden for clinicians and study teams will go a long way because right now in healthcare around the world, people are burnt out and so you really

need to change that. And so I think there are principles around simplification that we certainly [01:24:00] can do, but also let's make sure we are engaging those teams at the right times at the right moment. I do think it is really important that clinicians stay in the game. I'll just say my mother, when she signed up for a study that even [inaudible 01:24:16] was coordinating, she didn't trust me. She actually called her cardiologist, the good John Alexander, because she's like I need to talk to Dr. Alexander to see if I should sign up for this. So I think having clinicians engaged is really important [01:24:30] and we got a lessen the burden. And study teams, we can't forget that, the study teams are critical.

Khair ElZarrad: I think that's really a critical point. I think we think of burden... I tend to think of burden a lot of time from the point of view of participants and minimizing that. And when we start talking about those large scale trials involving all those healthcare providers, I think thinking about it as the team, the burden on the team, the burden on those providers who are still expected to do their day-to-day work, to take care of the patients and [01:25:00] then become part of the trial, that's something to think about. Not to be too FDA centric. We think quite a bit of that, at least from the point of view of decentralization, for example, and how we approach healthcare providers to minimize any especially unnecessary documentation and workload that may not be useful in that sense. So thanks for that. Noelle, would you like to touch on any of this?

Noelle Cocoros: Yeah, I'll just say quickly, I think that the question around [01:25:30] provider engagement and what it can look like, and again, looking at the trials that I've been involved in and thinking about are somewhat different than what the other presenters have. For IMPACT-AFib, for example, the intention was to test the system, to test the infrastructure, to test the ability to do this kind of work. And so intentionally the intervention was a very low touch one with minimal contact both to the patients and the providers. I'll give away the highlight, which is that we didn't see an effect [01:26:00] from the trial, and I think there's a lot of different explanations for that, but one may be that it was too low touch. And so recognizing that, that's why in the next round of work that we've been thinking about requires or is including more explicit contact with the provider and more engagement still relatively low. I think we'll see how it goes and whether it's enough to help change practice and change the kind of care that the patient's receiving.

Khair ElZarrad: Yeah, thank you for that. Actually, [01:26:30] one of the questions we keep receiving and I was planning on bringing it up is that not to always assume the preferences of the participants in a trial. Some of them may not necessarily favor digital tools to capture data. They may want to have that touch base and maybe a mixture and a balance in that in different trials. Thank you so much for bringing that up. So Noelle, you actually brought data quality in your presentation as well as Adrian and Otavio as well, and there is so much to touch on here. One thing, [inaudible 01:27:00] [01:27:00] that we try to avoid is that just because you're utilizing different data sources or utilizing different

technology doesn't mean that the risks are increased necessarily. Maybe there are different considerations around that that you have to consider.

So I was wondering if you can elaborate on your view from your studies, what does data quality mean to you? What kind of areas that I think a researcher should focus on when it comes to data quality from your context? And I'm going to go to of course, Adrian and Otavio to chime in this area from [01:27:30] their own perspective. I understand this is a large scope and a large area. We're discussing different data sources. You might have different data quality perspectives. So please chime in even the general concepts if you don't mind.

Noelle Cocoros: So I think obviously having worked with the Sentinel data for a long time, there's a really robust and routine set of checks, hundreds of checks that we do on the data to make sure that every time it's refreshed at each partner that it looks as expected and that there are no problems. [01:28:00] So there's this sort of technical aspect of how do you do that? There's also the understanding of where the data truly come from, and not just understanding it sort of on a high level, but being able to talk to the people that actually own and work with and really know the data. And that I think just can't be overstated.

And then on top of that, there's lots of ways that you can get a little bit deeper and really see [01:28:30] how it works. So an example is, again, I think going from the big picture to really how does it actually happen when you're implementing it is we were quite confident in our definition of atrial fibrillation when we were designing the IMPACT-AFib study, but it was really big and we were going to be contacting a lot of people. And so we decided let's actually look at some individual level data that we had in-house that we were able to look at and see, well, when we look at the claims' data, even just that, [01:29:00] does this really look like someone with Afib? So you can be checking yourself along the way. So that's a little bit more about the algorithm, but it still gets an understanding your data and ensuring confidence at every step. So hopefully that helps a little bit.

Khair ElZarrad: That's very helpful, thank you. Adrian. I don't know if you want to chime in when it comes to data quality and then I'll go to Otavio.

Adrian Hernandez: Yeah, no. So I think fit for purpose is really important for when you think about data quality. And so I think [01:29:30] one of the things that comes up is that often in these pragmatic trials or decentralization trials, people will think only about the primary objectives or the primary secondary endpoints, but as you know, your colleagues at FDA, they have to weigh the benefits versus risk. And so there are issues around pharmacovigilance. They just are not conveniently... And electronic health data in a way that can be useful. So you still have to have some mechanisms to understand [01:30:00] both the benefits and risk in ensuring complete data.

Adrian Hernandez: Both the benefits and risk and ensuring complete data. And so I think I'll use Activ-6. We worked with folks at the FDA to just make sure we understood that

if there was a regulatory decision, what we would need to have for our establishing what's the benefits and also understand what's a profile of risk there and taking hybrid approaches to doing both.

Khair ElZarrad: Thank you. And [01:30:30] thank you for highlighting the discussion with the FDA and I think discussion early with regulatory agencies in general. I think we need to remember that we also as regulators are learning as well. So thanks for highlighting that. Otavio, do you want to chime in?

Otavio Berwanger: Yeah. I do agree with Noelle and Adrian and I think understanding, first of all the data sources, and as I mentioned, understanding different contexts in different settings because I think one of the big challenges moving beyond just one country, which [01:31:00] is exactly what we need to do. But that's of course comes with lots of challenges.

I think the other thing is this, once again, conducting some methodological research, pilot studies, prospective analysis, making sure to understand what type of data can we use for baseline characteristics or endpoints, for safety events and what needs to be complimented by patient reported [01:31:30] outcomes or virtual interactions with patients or a patient portal. So I think there's no perfect solution. You will need to be context specific and trial specific.

But I think the hybrid approach at this moment would be the way to go. Maybe we won't be able to get everything we need in terms of vital data from one single source and the sources will be different in different regions. But I think a hybrid approach [01:32:00] at this stage can help. The other thing I think we need to understand, there are some good examples out there, but there are initial, once again, we're just scratching the surface, much more to be learned. There's a lot of hype around it too, but it's AI applications in terms of for example, endpoint adjudications and things like that. I think there's some potential there. There's a lot of hype, but there's some real potential to really develop [01:32:30] the way we ascertain events trials quite efficiently.

Adrian Hernandez: Kara, another thing that you triggered was I think we should also be taking advantage of definitions and competent phenotypes have been created over time. So just highlight a few examples. I mean the Sentinel Initiative over time has really created a nice library of definitions of different outcomes, both on a benefit outcome assessment side, essentially [01:33:00] on primarily around safety. And so I think we all need to make sure we're contributing to so-called the library to learn together and also get to that common ground. So the story about everyone agrees to common definitions is almost like the so-called saying of toothbrushes. Everyone agrees that you should brush your teeth and have a toothbrush, so you wouldn't necessarily agree with using the same toothbrush. And so getting people to think differently is important.

Khair ElZarrad: Yeah, [01:33:30] I know it's a little bit of, not necessarily separate link, but separate issue too. The idea of jargons and definitions that's used here and the difference understanding came up also yesterday. And I do agree. I think we

need to have at minimum consistent understanding of what we mean by those elements. Again, the hope is really that we see this as pieces of the Legos that fits the characteristic of the study, and like Otavio mentioned, [01:34:00] what's the hybrid trial that can be composed of those different elements to really answer the question. That fit for purpose aspect, I think it's critical. Thank you for highlighting that. Go ahead. Yeah, yeah.

Otavio Berwanger: Sorry to interrupt. And if I just add, but I think, and once again I'm biased towards the pragmatic model, so pardon me for that. But these definitions will need to accept some level of flexibility there. It's inevitable. [01:34:30] As much as possible. Of course, I know that for some circumstances it's a bit tricky, but some flexibility is needed and it needs to be streamlined because if we simply convert very complex procedures to the virtual mode, virtual, we won't be able to solve the problems that we're trying to solve. That's my view. But of course, all of us [01:35:00] need to work together, academia, sponsors, regulators, what are acceptable definitions, but that can be pragmatic, applicable and clinically relevant. I think that's the way to go. I'm not saying it's easy, but as a general principle, I think that's the way to go.

Khair ElZarrad: Yeah, I think that's a really good point. Again, like I said in the beginning, I feel like sometimes we get stuck in trying to define things rather than taking the concepts and applying them. And I think your presentations, all [01:35:30] of you today, really highlighted the hybrid concept, that we should get away from the one fits all kind of approach or all the elements have to be together. I think it's more of more that Lego approach where you take the elements that really works well for your trial and make sure it's their fit for purpose. Thank you for that.

One area that I hesitated to bring up, but I think I've seen multiple comments on it, so I think it's worth highlighting. I think Noelle, you touched a little bit on, you [01:36:00] mentioned validated algorithms in your representation. And thinking of both hype and reality, I think AI is really prime example of that. We see a lot of promising approaches that could be under the umbrella of AI, but also a lot of excitement and potentially hype in that area too. So I was going to ask if you don't mind elaborating a little bit, when you talk about algorithms for example, neutral, how you approach that, what does it really mean to you, the validation of the algorithm? I know [01:36:30] this is very much the article, so just in general if we can touch on that and maybe others would like to add as well.

Noelle Cocoros: Yeah. So I guess the way I think about it and the way I talk about it and have written about it before is around how are you identifying concepts of interest in either EHR data or claims data? And generally we're talking about claims data, but it would apply to both. And so developing an algorithm that defines some condition and then how likely are you that you've actually [01:37:00] identified those people of interest? And depending on often we're trying to get it so that we have an algorithm that we've identified people that we want, maybe we've not identified everyone and that's okay. So I think there's sort of two major concepts to keep separate in my mind, depending on how you're using the

algorithm. And I wrote with a group of people around this, what we call the certainty framework around essentially how sure do you have [01:37:30] to be that the algorithm you're using is identifying who you want.

And I think it really depends on what you're using it for. So like I said, for IMPACT-AFib, we were getting ready to send out many thousands of letters. We wanted to be really sure. And that's different than other kinds of research questions where the consequences, the stakes are lower. And so there's [01:38:00] good reason that in some settings you'll want to use an algorithm that you know works well in the exact data source that you are working with in an ideal way or in an ideal world. That's not always possible for a variety of reasons. And so sometimes you have to look for an algorithm that has been validated and has good performance in a comparable data source or something similar.

And then there are circumstances where you're kind of stuck or maybe the situation is such that it's okay to [01:38:30] use the best that's out there with the acknowledgement of the limitations because this is the only thing you have and the question is so important. Maybe the patient population is very underserved and it's okay. And so I think it really depends on what you're doing. That's how I've thought about it and that's generally how I've approached it in my work and my work with many others too, that use the best you can and understand your limitations. And then analytically, there are ways of addressing it. But I think with pragmatic trials and if you're doing outreach [01:39:00] based on identifying people using algorithms, the stakes are really high and you have to have a different level of confidence.

Khair ElZarrad: Thank you so much for that. Adrian, Otavio, would like to add anything?

Adrian Hernandez: Yeah, I think there is this answer, it depends, which everyone hates, which is I think in some settings where there's this gift of randomization and blinding. If you have a randomization, you're blinded, then there's [01:39:30] at least in a trial is large enough, then there are other things that you have to worry more about. I think in a setting where either there's not blinding, then there could be more problems for bias to get into a study. And so I think you have to consider what's the study design for the issues there? So I think just people hate the depends answer, but I think we [01:40:00] can be much more broader in terms of populations we include and also the outcome assessments if we're in a randomized blinded trial versus something that's open label where then we have to be a little more attentive to any kind of bias that may come in either reporting events or how populations are characterized.

Khair ElZarrad: Thank you. I'm glad to see that it depends is not just something we use as [01:40:30] regulators. I think it's very true in a lot of settings. I think you have to understand the context really to be able to approach it reliably. Otavio, sorry, you want to add something, right?

Otavio Berwanger: Yeah. So related to endpoints, I think once again, I think it depends on the type of endpoint. So all cause mortality and some fatal events are easier to ascertain than some more subjective outcomes like symptoms or a scale or things like that. And the other thing is like [01:41:00] any statistical method, the way to ascertain events, whether it's based on a routine collective data, whether it's based on a innovative soft touch adjudication, whether it's AI based adjudication, I think maybe the statistical analysis plan can pre-specify some sensitivity analysis.

And if you have consistent results using different approaches, I think you will increase your confidence on the reliability of the [01:41:30] data. And then of course, the results are clearly different. It's a problem and that needs to be understood and solved. But also I think the same thing we do with statistical methodologies. Sometimes you have the time to first event as a primary endpoint, but you have total events, you have mid ratio, have patient analysis, sensitivity analysis. And if they all point in the same direction, it would increase my confidence for the results. [01:42:00] So I'll definitely do that. Since we're still learning the best way to ascertain endpoints by [inaudible 01:42:05] routinely collect the data, I would pre-specify different ways of looking at the data, like when you have a final data set.

Khair ElZarrad: Yeah, thank you so much for that. I think all of you really highlighted the dilemma sometimes for us, as we work with the global regulatory community on GCB guideline for example, this is why we use sometimes if appropriate because we understand that the context matters and there are such a variety of [01:42:30] aspects to consider. Like you're saying, Otavio, based on what you're looking for, you might want to look at the statistical analysis plan, you want to look at the different ways of clarifying your approach. So hopefully we need to walk that fine line from a regulatory perspective. And I know many of my colleagues on the call today are regulators, so hopefully we'll take that message and try to apply. Thanks so much, Otavio, and the team. A couple more questions left. I know we're hitting the last 10 minutes of our call, but just a couple of questions that take us back a little bit to the patient here.

We've heard [01:43:00] quite a bit about decentralization and pragmatism bringing us closer to the patient, accessing more of a patient data. So that ecosystem's a little bit different the more compared to the very much traditional clinical trial where everything is very much boxed and concise in a certain way, at least. One of the key comments we've been receiving is if you can comment on the patient population specific consideration, and challenges when it comes to the use of digital technology and trials in general. One [01:43:30] thing that's put it for me into context is that decentralization sometimes contribute to the diversity or at times create roadblocks, which I did not think about it as creating roadblocks, but highlighted to us in some of the comments. For example, addressing the digital divide, favoring enrollment and engagement for those with access to technology. This is one example of that. I know that ecosystem is much larger. So maybe if you don't mind commenting on that Otavio, and then I will go to Noelle and Adrian as well.

Otavio Berwanger: Yes. You [01:44:00] raise a very important point and for us for example at [inaudible 01:44:04], low middle income countries are particularly important as well. So where the challenges may be even bigger. But also Adrian showed that clinical trials certain in the US, but I can assure that low middle income countries is this is even a bigger problem.

I think once again, you cannot have just one approach for all regions in a trial. [01:44:30] It's back to the fit for purpose or avoiding the one size fits all approach. You would need to be hybrid. So you would need to offer the trial participants multiple or different ways to participate, to enroll into participating in a trial. Increased costs to create some complexity. We are trying to avoid cost complexity, but that's something I think it's a good investment.

And [01:45:00] I think once again, engaging participants on the steering committee or as part of the trial team or as an advisors, it's important to hear their perspectives as well. And if you're doing that in different regions, you need different perspectives from different regions. So theoretically, but we don't have enough data to say that, but in theory, I think decentralization can lead to [01:45:30] improving diversity. One thing I can tell you for sure, the way we're doing trials traditionally is not helping in terms of diversity. That, I have no doubt about. As you know, over 70% of participants included in current trials, and I'm taking into account different areas, are Caucasian male. And that's a fact. And multiple surveys show exactly the same results. So we're failing to do that by using the traditional model. That's a fact. [01:46:00] Whether using a decentralized approach, will improve that, well, theoretically yes. But I think once again, using a hybrid approach and having participant engagement is the way forward. It won't be easy, but it's the way forward.

Khair ElZarrad: Thanks so much. Adrian or Noelle, would like to chime in?

Adrian Hernandez: Yeah, so I guess a couple things I'll note here. So we have seen some success in different areas, so I [01:46:30] have a slightly different take than Otavio. There are some example trials for regulatory approval in renal disease where we actually achieved a very diverse inclusive population. So I think one of the things that was done differently though was much more engagement for frontline clinicians for doing this. And also, I'll just say going where people are in terms of sites that are serve more diverse populations. But there's [01:47:00] still a lot more to do there in terms of what we can break our traditions here. But on the bigger questions you're raising for digital is that we've learned some hard lessons, I'll just say. And so you can see the slides in the past that people will show is like, well, there's a smartphone for everyone, or two, actually. One and a half is I think in some countries the average because people have more than one.

But in certain populations, either they don't trust it fully for a digital trial [01:47:30] or they actually share it. And so we learned the hard way of that happening. And so I do think that technology is enabling, but you also have to figure out which communities it can best serve and then what do you need to

do differently to further outreach? And so an example study that we have is a study of older adults to ask the question, do statins prevent cardiovascular outcomes [01:48:00] on dementia? Some people can use digital tools. Some people we have to call them directly through a call center or have site engagement there for collecting their responses and outcomes. And so we have a hybrid approach for that. And that's why for a 14-year old, it may be different. My son's actually participating in a sleep study. And so he's highly engaged with this Fitbit [01:48:30] and all this other jazz, but he's a little more digitally in tune than my mother. [inaudible 01:48:39] good for purpose.

Khair ElZarrad: That's fascinating because yesterday we've asked similar question too, and we were told that sometimes the age divide is more important than even the digital divide and the familiarity with the tool is really a critical aspect.

Adrian Hernandez: I think it's two by two almost, age. And then also communities [01:49:00] and terms of how they use it, because I think Otavio noted, low-income countries and low-income counties have similar issues in terms of either access or trust with those systems.

Noelle Cocoros: One thing I thought just follow on to what Adrian was just saying a moment ago about participation and the patient population being diverse in trials, is that understanding that particularly if you're thinking about racial and ethnic diversity, [01:49:30] claims data in particular are not great at capturing race or ethnicity. And so in the trial that's being planned right now, ACHIEVE, there's an intention to have at least 50% of the study population be black. And we simply can't rely on the data that's in claims right now to do that.

So the current thinking is that we'll essentially over sample or target census areas in the US that have a more diverse population. And [01:50:00] during patient provider outreach, actually, we would be capturing information on the race or ethnicity of the patients that we're calling about. So that would be some of the primary data collection. So if you're using some of these real world data sources, depending on the kind of diversity you're talking about, whether that's captured and if it's not, are there ways of working around it so that you're starting your patient identification with that in mind and understanding the challenges you may have.

So [01:50:30] wanted to mention that.

Khair ElZarrad: What a great point. Noelle, in this situation, I know you may not be able to speak directly to it, but hypothetically what ways you will go around that? Let's say one dataset doesn't give you the adequate diversity. Would you want to link to other data sets? How would you approach this?

Noelle Cocoros: I think at least in the ones that I've worked on and the ones I've thought about where you're starting with claims and then maybe you're going to do some primary data collection is you'd have to actually collect it at that point of

interaction. And so the [01:51:00] thinking right now is that we would collect it from the provider. And actually, in electronic health record data in the US, it's really quite complete. Whether it is accurate and valid and should maybe be updated or changed is a separate conversation. But at least the data elements themselves are very, very well populated in electronic health records.

So if you're starting there, it's a different story than if you're in billing data. And so I think the ways around this are different. But the other [01:51:30] thing to note, and this is just actually somewhat peripherally to just mention, is that we created an app for FDA, called the FDA MyStudies app, that is complimentary to these kinds of trials and enables linkage to claims data that was created for Sentinel. So that's a side note.

But I think it's really in this case, needing to get the information, ideally, it'll actually come from the patient. When the patient contact is actually made by the pharmacist, they'll collect the information. But [01:52:00] in the meantime, as we're creating the study participant cohort, it'll be collected. If it's in the claims data, we'll use it. If the provider has it from the EHR, we'll collect that. And then I think we'll probably collect it from the patient directly. That's the rough planning right now.

Khair ElZarrad: Thank you so much. That's very helpful and it's a great way to consider. Before I turn it back to Leanne, I want to just have a moment of an open microphone for all of you, in a way. Can you summarize your perspectives and the most important [01:52:30] advantages and key challenges for the type of trials we're talking about? Frankly for the type of tools and innovation designs we're talking about here. And then shy away because this is something we're planning on taking home with us to really try to figure out how to make our policies, how to inform our policies, make them more responsive to the need of communities, especially those of you who are doing the work on the ground. So Noelle, since your last week, I'm going to start with you actually, if that's okay. And then I'll go to Otavio, then Adrian.

Noelle Cocoros: Sure. I guess I'll say for the kinds of projects that I've worked [01:53:00] in, the devil is really in the detail. So I always like to say that the trials I've thought about or worked in are so easy to describe in a sentence and they sound so simple and it is so much more complex at every step of the way. So there are, and even in my presentation today, despite trying not to highlight all the lessons learned, trying to not dwell too much on the challenges, but there are ways of working through all of them. A lot of it is around awareness of what can come up. [01:53:30] And I think that if there's enough time and enough resources, I think this is where I don't know that any of us touched on this funding. If there's adequate funding for the work and you have the right staff and from all the different places that you may need them from in terms of the project team, including patient representatives for example, I think you can overcome these challenges. But it really requires careful planning.

Khair ElZarrad: Thank you very much, Otavio, do you want to go next?

Otavio Berwanger: Yeah, [01:54:00] sure. Well, I agree with Noelle. We cannot underestimate a challenge. It's a big challenge, but it's a good fight, I would say. But I'll go back to Gertrude Stein and Picasso. I think we need to learn from the past, but move the needle. I think we need to be open-minded. It will require collaboration across disciplines. It'll require collaboration between the different stakeholders like regulators, [01:54:30] like the FDA, academia, sponsors and patient and participants, representatives as part of the trial team. I think understanding the different contexts are important. And finally, I think we highlighted this through all the morning here or the afternoon for me here, is there's no one size fits all. It's a hybrid approach, it's a fit for purpose [01:55:00] approach is the way to go.

Khair ElZarrad: Thank you so much, Otavio. Adrian?

Adrian Hernandez: All right. Well, I actually it took a slide out here to outline some of the issues I see going forward, but let me just summarize real quickly. I'm an optimist here. I think we can do it. Well I kind of noted at the beginning of the Gordian knot. I think all of us can be committed to untying that. But I think to get to that, we do need to get to a [01:55:30] common administrative model. We've talked about a common data model. But how do we get things to be really common across the system? And that may not necessarily be in the FDA's purview, but if you see all that we have to do for contracts or IRBs or actually having investigators be approved, we do it over and over the same way, but not commonly.

I think another question [01:56:00] is how do we engage people? Right now, multiple systems have cold call policies as an example, or physician gatekeeping. How do we do things that let people opt in? How do we actually deliver something that will be helpful for them? How do we cross borders? It's not just state borders in the US but borders around the world, for decentralized product delivery in this kind of model. What's a proper oversight [01:56:30] inside our system? So for adaptable, the leading and enroller at Vanderbilt, they enrolled 2,000 people. Were they really the site PI for all those people? Well, they were the system PI, but others were actually caring for those patients. How do we ensure diversity, inclusion? Convenience may not always mean inclusion, so the engagement matters.

And then lastly, how do we reliably, ethically link data to ensure data quality? [01:57:00] So the technology's evolving for sure. Trust matters. So with permission and protecting privacy is critical and data quality is really critical. We're in an era where there's AI for anything. I showed a picture of the Gordian knot using AI DALL·E. I acknowledge that. And we are in an era where we're creating data mountains, data piles, and data lakes. And so how do we ensure data quality is critical for these studies? So just a few things, but I'm optimistic.

Khair ElZarrad: [01:57:30] Thank you so much, all of you. This is excellent. And I can tell you this is more motivation for us to work, to be active partners in advancing clinical trials. And I'm speaking not just for FDA. My colleagues in the ICH community are also listening to you today, and we intend to work on those areas and provide as much clarity as possible to advance the field. So thank you again for

informing us and for working with us. And I'll turn it back to Leanne. Really appreciate your time everybody. Leanne.

Lea Ann Browning-McNee: Thanks. And I'll echo your [01:58:00] appreciation to all of our speakers for sharing with us today. And an additional thanks to you, Dr. ElZarrad and the rest of the FDA team that worked with us to plan this convening. And thanks to all of you for joining us and for submitting your questions to the speakers. You helped make this discussion rich, and we appreciate that. A quick reminder that materials from both days will be posted soon, at reaganudall.org. And we hope you enjoy the rest of your day, in whatever time zone you happen to be in.