



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

September 12, 2023, from 7:30-9:30 am ET

### 00:00 Welcome and Overview: Amar Bhat

Amar Bhat: Hello and welcome. Good morning, good evening, wherever you are. Thank you for joining us. My name is Amar Bhat, and I have the privilege of serving as the Chief Operating Officer of the Reagan-Udall Foundation for the FDA. The FDA Foundation is pleased to host this important discussion about clinical trials with innovative design features to help inform the development of responsive policies and guidelines [00:00:30] that encourage innovation while protecting participants and safeguarding the reliability of trial results.

Before we begin, we have some light housekeeping. First, we have over 2,800 people registered for our two-day workshop, and we're so pleased you're able to join us. For those who submitted questions as part of the registration process, we have those, and we'll be raising as many of those as possible during the moderated discussion [00:01:00] portion of the webinar. As many of you know, but we must remind you, speakers will not be discussing any specific regulatory actions or decisions in today's discussion. Speaking of discussion, we welcome your active engagement. Please submit your questions through the Zoom Q&A. The recording from our two-day meeting and the slides will be posted on the Foundation's website as soon as possible after the meeting.

[00:01:30] Now, I'd like to provide a brief overview of the agenda. In just a moment, Dr. Khair ElZarrad will be providing some opening remarks. He'll be followed by Dr. Eric Lenze, Craig Lipset, and then Dr. Kenichi Nakamura, who will present an overview of trials that utilize decentralized or pragmatic features. Finally, Dr. ElZarrad will return for questions and answers with our presenters.

Here's [00:02:00] one more reminder for why we're all here today. We are engaging with experts who have participated in conducting clinical trials with pragmatic or decentralized features so that we can understand the opportunities and challenges of conducting trials with innovative design features to help inform the development of responsive policies and guidelines that encourage innovation while protecting participants and safeguarding the

reliability of trial results. Finally, FDA [00:02:30] wants to hear questions from the public, so please feel free to submit yours through the Zoom Q&A box.

Now, it is my pleasure to introduce our first speaker, Dr. Khair ElZarrad. Dr. ElZarrad serves as the Director of Office of Medical Policy in the Center for Drug Evaluation and Research at the FDA, the US Food and Drug Administration. Dr. ElZarrad, please pick up the microphone.

**03:00 Introduction: Dr. Khair ElZarrad**

Dr. Khair ElZarrad: Thank you so much, Amar. Do you hear me well?

Amar Bhat: Yes.

Dr. Khair ElZarrad: [00:03:00] Perfect. Thank you so much for the introduction. Just a few opening remarks before we go to really the core of the meeting, our speakers. I want to thank, actually, the speakers first, for joining this meeting. I know we have some of the busiest group of experts here and I want to thank you for joining us. We're all grateful to hear your expertise today. I want to thank also my FDA colleagues, and the Reagan-Udall team as well, for organizing this meeting, [00:03:30] relatively in a very short period of time. I also want to thank the almost 3000 individuals who actually registered for this meeting, it's really a testimony for the importance of this topic, and the interest in this topic, and I think it behooves us all to really advance the field.

This meeting is a part of FDA's effort to modernize the clinical trial ecosystem overall, and really to advance innovation and efficiency in the design and conduct of clinical trials. We want to continue to engage and to hear from all involved stakeholders. [00:04:00] This meeting, again, is intended to hear from academics with experiences in conducting trials with decentralized or pragmatic features. As FDA and other agencies around the world are continuing to develop guidance and policies on clinical trial design and conduct, we must incorporate learnings and experiences such as those that we will be hearing from our experts today. This will help make our policies more responsive, more appropriate, more agile, to protect trial participants and the reliability of the trial results [00:04:30] while at the same time encourage and facilitate innovation.

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 know that pragmatic features are generally described to include the broad eligibility criteria, a simplified protocol, a streamlined data collection that typically incorporates healthcare infrastructure [00:05:00] including the data from routine healthcare, among many other features, of course.

I view decentralization and pragmatic features as elements that can be incorporated in a different variety into a trial, and as appropriate, to streamline

the trial processes, making the trial less burdensome, and to incorporate available infrastructure and data sources. Ultimately, the goal is to produce reliable [00:05:30] results in the most efficient fashion.

So just a couple of points regarding the input that we received from all of you during registration. This meeting is designed to hear from three esteemed experts every day, followed by a generous time for dialogue, specifically to hear elaborations, to hear additional inputs on the critical aspects that we're hearing about. I want to thank all of you for submitting questions and comments during registrations, we have received hundreds of comments. We are very grateful for that. Clearly, we cannot address all those comments [00:06:00] and questions during the meeting, but we tried to consolidate this input into themes that we hope to touch on during the panel discussion.

We will also have the Q&A chat box, as Amar mentioned, open, with colleagues monitoring it, and if time allows, we may be able to incorporate some of that input into the discussion. However, it's assured that no question or comments will go un-reviewed, we intend to look and see if there are themes that can be addressed as we continue to engage with different stakeholders, [00:06:30] and ultimately really to inform policy development.

I want to thank you, again, all, for making this meeting happen, and without further delay I'll turn it to Dr. Lenze. Thank you, Dr. Lenze, and I'll turn the podium to you.

**07:00 Presentation 1: Dr. Eric Lenze**

Amar Bhat: Thank you Dr. ElZarrad. I appreciate that. Now, I'm pleased to introduce our next speaker, who will be providing an overview of clinical trials in the remote world. Dr. Eric Lenze is a Professor, Head of Psychiatry and Director of the Healthy Mind Lab at the Washington [00:07:00] University School of Medicine in St. Louis. Dr. Lenze, please begin.

Dr. Eric Lenze: Thank you very much, and thanks for that introduction, Dr. ElZarrad, and good morning everyone. I'm pleased to provide my perspective of today's discussion about decentralized and other pragmatic features of clinical trials.

A brief background about me, I'm a psychiatrist and a clinical trialist. I've led clinical trials for over 20 [00:07:30] years, focusing on mental health conditions such as depression, and more recently, my research team has also focused on COVID clinical trials. Next slide, please.

My perspective is that of a scientist who believes that clinical trials lead to scientific progress, and this progress can be accelerated by improving both the speed and quality of our clinical trials. In my field, mental [00:08:00] health, there has been less scientific progress than we would hope, and one reason for this gap is the slow speed and less than optimal quality of our clinical trials. We

need to improve both to accelerate scientific progress, and that's not just in mental health, but also throughout clinical medicine. Next slide, please.

We all know science is innately a trial and error process, and this is [00:08:30] true in clinical trials. One clinical trial may fail to demonstrate an expected result, so you adjust the treatment or other parameters and try again to succeed, and then you follow with other studies to optimize treatment. But, for example, in mental health, when each clinical trial can take many years to complete and success is unsure, the resulting progress is slow. [00:09:00] Next slide, please.

Now, this is from a recent article in which my colleagues and I argued that moving to fully remote trials could improve both their speed and quality. That's because the slow pace of traditional onsite recruitment means that larger studies must include numerous trial sites, and this is costly and slow. It also leads to a high failure rate as these numerous trial sites [00:09:30] are each recruiting only a few participants, which makes the trial's quality lower.

Finally, studies often have an inadequate diversity of patients. An answer for this is moving to decentralized trials, or my preferred term, fully remote trials. By this method, a small number, or even a single trial site, can recruit patients from a wide geographic area. The trial's [00:10:00] speed is enhanced by increasing the recruitment rate, and then a greater diversity of patients can participate because of the reduced burden.

Beyond that, the clinical trial quality is enhanced by allowing the study to be completed by fewer sites, which means that expert and fully committed trial teams can complete this study. In my history of conducting clinical trials, we gain experience with each patient recruited, and we iteratively [00:10:30] improve quality during the trial, including the recruitment rate, retention rate, and the data acquisition. Imagine, for example, in a thousand patient trial of an antidepressant medication, how much better quality of an experiment can be conducted when it's done by five sites, recruiting 200 patients each, rather than a hundred sites recruiting 10 patients each. Next slide, please.

[00:11:00] Our team recently completed a multi-site trial where we compared different antidepressant strategies for difficult to treat depression in older adults. This study was funded by the Patient-Centered Outcomes Research Institute, or PCORI, because of the public health need to understand which strategies were most effective and safest, such as augmentation with either aripiprazole or bupropion, two popular [00:11:30] antidepressant augmentation strategies. This study allowed for fully remote participation, and in this study approximately one third of the participants were recruited, assessed, and managed in that way.

Fully remote participation allowed us to randomize over 700 participants across five sites, and it allowed us to continue the trial during COVID. This in turn allowed us to have well [00:12:00] powered tests of effectiveness and safety,

which as seen in the graphic on the right below, showed for the first time in my field, a safety difference between treatment strategies, namely, a higher rate of falls in participants randomized to bupropion augmentation versus aripiprazole augmentation. This is important because falls are a common and serious sequelae of depression treatment in this age group, and our study [00:12:30] allows patients and clinicians to make evidence-based treatment choices that could reduce the risk of treatment associated falls. Next slide, please.

The fully remote experience we gained from that study also gave us confidence to conduct clinical trials for the treatment of COVID. In 2020 and 2021, we conducted a sequence of placebo controlled trials where we tested the drug [00:13:00] fluvoxamine, an antidepressant with potential immunomodulatory activity. Despite the incredible challenge imposed by conducting a clinical trial during the pandemic, we were able to recruit over 150 patients for a preliminary study in Spring of 2020. You can see in the photos on the left and center that we recruited patients through phone and e-consent, and then for those patients randomized, [00:13:30] we delivered study medication and assessment supplies by bringing it to the patient's home. By this technique, over 90% of participants started their study medication on the same day that we first reached and screened them.

Then, in a larger follow-up trial, we shipped medication and study supplies to geographically remote participants throughout the US and Canada, as seen in the photo on the right. The point, again, [00:14:00] is that a single site or a small number of sites could recruit large number of patients throughout a large area, and I'll add that the fully remote participation also improved the diversity of our study samples. For example, in that first COVID trial, 25% of our participants were Black. Next slide, please.

Now, fully remote trials are the norm. In fact, we recently [00:14:30] established a center, funded by the National Institute of Mental Health, focused on clinical trials for perioperative mental health such as depression and anxiety. In that center, we conduct the trials fully remotely. As with our previous studies, we're finding this improves both the recruitment rate and the participant diversity while maintaining a high quality in terms of managing patients with complex conditions [00:15:00] by our team of experts. Next slide.

Now, there's another way to increase trial quality, and that's by increasing the quality of the assessments. In mental health and cognitive research, single time point outcome assessments are the norm, but they often have a low measurement reliability, and this increases the chance of study failure, or at minimum adds to the sample size requirements. [00:15:30] Also, there's great interest in precision medicine in mental health, finding the right treatment for the right patient, but precision medicine requires precision assessment. That is, the analysis needed to find the patients who benefit most from a treatment require a very high level of measurement reliability, both of the mediator or moderator assessment and of the outcome assessment.

For many of our measures, it's [00:16:00] doubtful they have this level of reliability. The solution is to use technology, smartphones and sensors, to increase the quality of the assessments by increasing their frequency. Highly reliable assessments reduce sample size requirements, and they're also a necessary step to get to precision medicine using those mediation and moderation analysis. Next slide, please.

Now, how does a frequent [00:16:30] assessment improve reliability and validity? Well, you can do this thought experiment. Looking at the graphic on the left, how many of you can accurately answer the question depicted here, which is, how has your energy been over the last week? That's challenging, right? And if an answer does come into your head, it's likely following the rule I've depicted on the right, which is that when we humans are asked [00:17:00] to retrospectively describe our experience, we either think of the peak, the extreme, or the end or most recent. That means for any experience we're asked about, like mood or energy or sleep, we will give a snapshot answer, which may be an outlier if that experience varies over time. And this variability is also seen in more objective measures such as cognitive or physical performance. [00:17:30] Yet our studies rely on single time point assessments that ignore this variability. So an alternative is frequent assessments. Daily, or even multiple times daily, that can then be summed together to provide a more accurate, reliable assessment. Next slide, please.

My team first used a smartphone-based assessment strategy in this study funded by the FDA [00:18:00] several years ago. The goal of the study was to test different generic versions of the drug Bupropion XL that were on the market. The rationale for the study was that patients were then providing feedback to the FDA, that they thought some of the generic versions were not as potent as the original brand name version. So we conducted a crossover clinical trial in which patients were randomized to six week intervals [00:18:30] where they received one of three generic versions of Bupropion XL, or the original brand name. To capture those potential subtle differences in clinical effect, we assessed daily depressive symptoms using smartphones that the participants used throughout the study. We then summarize those daily reports into weekly scores, as you can see on the graphic on the right.

Now, that figure shows two things. First, [00:19:00] that there was no difference between any generic versions or the brand name version in the patient's level of depressive symptoms. And second, that those depressive symptoms continue to remain low for the six weeks on each of the medication versions. Thus, the patients continue to benefit as they used each generic version with no differences between them. This was the first time we used, in our lab, frequent technology-based [00:19:30] assessments of outcome in a clinical trial, but we've since done this in many of our studies. Next slide, please.

Another example was in the COVID clinical trials that I previously mentioned. Patients in those studies were medically ill, at home, and in isolation, so we needed to assess them medically, and for safety, while they were receiving

study medication. In fact, the frequent at-home self- [00:20:00] assessments improved our ability to assess them medically and for safety compared to coming to the study site.

Patients self-monitored with the equipment we provided them, twice daily in the case of vital signs. The figure on the right shows an example of just one participant's vital signs throughout the 15-day long clinical trial. You can see that we were able to see that this participant did not have a problem with [00:20:30] low blood pressure, the red trend line at the top, and that while there were some instances of bradycardia, the blue line at the bottom, the overall measurement showed little or no trend in drop in pulse, and those were some initial concerns we had in this study. So, precise measurement through frequent assessments and fully remote clinical trials extends the safety evaluations as well as effectiveness. [00:21:00] Next slide.

Our most recent clinical trial, an ongoing study testing fluvoxamine for long COVID problems, such as cognitive difficulties, shows just how far we've come. In this case, the entire study is fully remote capable, so we recruit participants across two US states for a study run by our team in St. Louis. Not only is recruitment and consent done fully [00:21:30] remotely, study assessments are conducted through participant's phones, as shown on the left. This includes cognitive performance tests, shown on the top right, and ecological momentary assessment of symptoms, shown on the bottom right. We shipped study medication and supplies to them. In this study, about one half of the participants so far have been fully remote, and this aids both recruitment and diversity of the sample. [00:22:00] Next and final slide.

In summary, three points I've made in this talk are, first, fully remote trials have become the norm. Second, that using fully remote techniques, greater speed and better quality are now possible compared to traditional techniques. And finally, I am hopeful that embracing these techniques will accelerate our scientific progress. Thank you for [00:22:30] your attention.

## **22:30 Presentation 2: Craig Lipset**

Amar Bhat: Dr. Lenze, thank you very much for that fascinating look into the world of remote trials. Just a reminder, the slides from today's presentation will be posted on the website after the event. Now, I'm pleased to introduce our next speaker who will provide perspectives on decentralized clinical trials. Craig Lipset is Co-Chair of Decentralized Trials and Research [00:23:00] Alliance, and an Adjunct Professor at Rutgers University, Vice President at the Foundation for Sarcoidosis Research, and Managing Partner at Clinical Innovation Partners. Craig, will you please pick up the microphone?

Craig Lipset: Thank you so much, Amar. It's a pleasure to follow Dr. Lenze and to address this audience. We can move forward to the next slide, and to the next.

As Amar just mentioned, I have a few different affiliations, but the perspectives I [00:23:30] will share do represent my own views on today's topic. Next slide, please.

I'd like to just begin by sharing some perspective on jargon because we are talking about both pragmatic and decentralized trials. The term decentralized, it's worth mentioning or reiterating, is far from ideal. As far as jargon goes, it implies that we're decentralized in the perspective of the site, but when it comes to the participant, [00:24:00] we're actually centralized.

On the other hand, many other terms that are tried all have their various limitations or restrictions. Virtual, as an example, implies perhaps that we're using modeling based approaches to reduce or eliminate the number of patients in the trial itself.

On the other hand, decentralized is now being normalized, it's being used more consistently across organizations and globally. [00:24:30] And so, perhaps the term decentralized, despite its shortcomings, is a good reminder for us of a truth that trials have historically been centered around the site, and it's only in recent years that we, as a research community, have begun to shift that center over to the participant.

On the next slide is just a recap of how broadly we're seeing this term being utilized today, and these are just reflections of some of the types of guidance [00:25:00] and recommendations that we see issued both in the US with draft guidance on decentralized trials in Europe, with EMA recommendations that were issued back in December, as well as with authorities now around the world. Next slide.

Now, we began with a brief definition from Dr. ElZarrad regarding decentralized trials, it's worth reiterating. This is a definition [00:25:30] from the FDA's draft guidance, a clinical trial where some or all trial related activities are current locations other than traditional clinical trial sites. There are two themes to this definition I want to call out. One is that this is an umbrella term, it's inclusive of multiple archetypes. We have some or all trial related activities, and so it's inclusive of both hybrid studies, as well as those that might be fully remote, and starts to set us up for futures [00:26:00] where clinical trial participants may have more choice and flexibility. Also, noteworthy here is the definition does not explicitly state home, but simply other than traditional clinical trial sites, and therefore gives us a very expansive range of where visits may be able to take place. Home, pharmacy, community centers, local providers offices, mobile units, can all be in scope. Next slide.

We [00:26:30] do see definitions around the world capturing the same spirit, and so when we look at definitions, whether it be from the EMA, from CTTI, the Clinical Trials Transformation Initiative, from DTRA, the Decentralized Trials Research Alliance, from trials at home, in Europe under the IMI. While they use different words, we see many of the same themes start to recur, that the term



decentralized is meant as an umbrella term, capturing multiple [00:27:00] archetypes, including both hybrid and fully remote, that this represents a collection of decentralized methods and tools, both processes and technologies, that support this model, and that the focus is simply on enabling participants to be able to access trials from outside of a traditional site. Next slide.

It's also worth noting why we're engaging today around decentralization, [00:27:30] because on the one hand, it's easy for us to point to patient factors, and there is ample data now in the public domain demonstrating patient's perspective around experience and access, and as we saw from the presentation from Dr. Lenze, even the ability for these approaches to open up improvements in representation and equity. So those patient factors are certainly central to decentralizing today. However, the adoption that we've seen over the last three years [00:28:00] were largely triggered by issues around business continuity. The adoption triggered during the pandemic wasn't because we were suddenly sensitive to patient access issues, it was because clinical trials were at risk of shutting down during a global pandemic, and suddenly these approaches were viewed as a resilience measure. And that remains to be true. We are operating global development programs in an unpredictable environment, whether triggered by pandemics, war, [00:28:30] weather events, or other circumstances, that may stand in the way of a patient being able to access a research site with consistency around the world, and so for resilience factors alone, these decentralized approaches should continue to be introduced.

A third factor that we see, primarily coming out of Europe today, is the impact of clinical research on the environment and what the role of decentralization may be to help [00:29:00] mitigate the burden on the planet of clinical research, and how might decentralized approaches help to support ESG efforts and other efforts to improve our carbon footprint, including around clinical research. There are some noteworthy initiatives taking place today to help to quantify the carbon impact of clinical trial procedures traditionally, as compared with those that may involve decentralized [00:29:30] approaches. Next slide, please.

Within industry today, we tend to see a recurring theme around what implementation looks like. For most organizations today, implementation has been something of a pairing of a set of decentralized tools and methods with specific studies in the portfolio. With Dr. Lenze a moment ago, we got a sense of what some [00:30:00] of those decentralized tools and methods look like. For most organizations today, this has been an opportunity to look at electronic technologies like electronic consent, video visits, remote patient monitoring technologies, the digitization of our endpoints, but also process innovations. How can we introduce home health and visiting nurses, our ability to ship investigational product directly to [00:30:30] participants and help them to access investigational product outside of a traditional site. Our supply chain considerations, our ability to take advantage of local labs or local imaging centers. Those process innovations can be just as important as the technology innovations that help power these decentralized approaches. For many

organizations over the last two, three years, they've been normalizing some of those tools to become [00:31:00] more available for their study teams in their own organizations.

Craig Lipset:

... more available for their study teams in their own organizations, refreshing SOPs, training and so on. The part that gets tricky for many organizations is to consistently evaluate which studies in the portfolio are most appropriate to use, which decentralized methods, looking at the visit schedule, and understanding attributes around the molecule, looking at what countries around the planet the study may have plans for [00:31:30] execution. Still, more often than not, the true rate limiter in terms of where decentralized approaches are being introduced in studies in the industry today, tends to be limited by culture within the organization, change readiness, how receptive organizations are to embracing new approaches, and accepting and managing some level of additional risk using new approaches in their studies. [00:32:00] We manage risk in our clinical trials every day. It's not a new concept for us to identify and implement risk mitigation plans, but this still is perceived as additional work and potentially just enough friction to create a barrier for many to implement. Next slide please.

Now, with industry, what we've been doing for the last two years has largely been sort of a version 1.0 [00:32:30] of decentralizing. Coming out of the pandemic, mostly focusing on this dichotomy of visits taking place in the clinic or in the home, mostly by leveraging some entry level technologies for decentralizing, electronic consent, video visits, some process change like home visits, as I mentioned, extending the supply chain, perhaps some specimen acquisition, more local to home. But we're already starting to see what the second level of decentralizing [00:33:00] will start to look like, because while many organizations are normalizing those methods and tools of DCT 1.0, they're still experimenting with these, that I'll call DCT 2.0. These are in many cases, the areas of opportunity that most organizations may not have yet committed to scale, but are certainly experimenting with internally.

These include our ability to look at locations beyond the home. It's in particular in [00:33:30] light of the draft guidance from FDA, taking a fresh look at the role of the HCP, the healthcare provider, and how might those HCPs in local communities help to support routine care activities in clinical trials, thereby opening up another point of access that's trusted and familiar for patients to participate. We see many putting increased attention, on what I'll call next generation participant support, in appreciation that the participant [00:34:00] in a decentralized trial should not feel that they're being left alone with unfamiliar technology and a box of investigational medicine. As Dr. Lenz mentioned when he was reflecting on safety, decentralized studies done right should make a person feel more connected and engaged, both as we're thinking about safety surveillance, but also overall support of the individual. Whether thinking about their operational needs, their safety and oversight needs, or just the level [00:34:30] of empathy that they've come to embrace and appreciate coming from an in-person coordinator and investigator.

That should not be compromised just because the individual is participating from home, and so we have to level up, in this case, what support looks like for those individuals to make sure that there is no compromise in the level of engagement and support in individual fields. We see increased appreciation of [00:35:00] this concept of choice, flexibility, optionality for the participant. When we're implementing studies that may be hybrid today, and that tends to be where a lot of the industry is still landing right now with many of their investigational medicines, all too often hybrid still means a prescriptive schedule of which visits may be in the clinic and which visits will be at home. What we as consumers, what we as patients in healthcare today, are increasingly [00:35:30] expecting is to have more choice and flexibility. It's greater respect and appreciation of my journey as a patient and that some of these encounters may work best for me to take place at home and others I might prefer to go into a nearby clinic and others I may prefer to go to the research site.

And so how do we start to structure models where we can give individuals more choice and flexibility without compromising data integrity, without running the risk [00:36:00] that we're capturing our fragile data in different places and somehow because our data acquisition methods are so temperamental that we have less confidence in data integrity. One of the best countermeasures we'll come to, and Dr. Lenz mentioned a moment ago, is our ability to modernize and digitize our endpoints. Because when we can modernize and digitize our endpoints, they're more resilient to location and don't care whether they're being acquired in a home or in the clinic, [00:36:30] thereby giving people more choice and flexibility. Now, many research sites in decentralized trials today, many of the site staff are having challenges implementing these decentralized approaches. In large part because when participating in a multicenter trial that may be sponsored with industry, they're being confronted with unfamiliar technology that may be redundant with what they're using for their own studies.

[00:37:00] Tools like electronic consent or video that a research center may be using for investigator initiated in grant-funded studies, may suddenly have to be replaced by something that's being centrally selected by a pharma sponsor and a CRO. And so that friction, again, is causing challenges. It causes quality issues, retraining issues, and so it's a call now for the industry to start to embrace more [00:37:30] interoperability, and define minimum quality standards that can let sites use more of their own existing technology infrastructure. Now, as we're looking more and more at these decentralized approaches, where people may not be coming to a site for some or all visits, this of course is also now an opportunity for us to place greater emphasis on capturing real world data, such as data from the electronic health record for the participant.

Now, [00:38:00] many of our eSource, our electronic health record data acquisition strategies have assumed that the investigators electronic health record has the data about me as the participant. But what we're increasingly appreciating is, as we increase the distance between a participant and the research site, we decrease the probability that the investigator's electronic

health record has any knowledge about me as the patient. And so we have [00:38:30] to shift our focus on how we're collecting real world data, how we're accessing electronic health record data, and rely less on the assumption that the investigator's EHR knows about me and shift to rely more on the power of the individual, the participant, to give permission to connect their EHR data into my study. And we know that there are ways that are increasingly accessible to us in the United States using these approaches, [00:39:00] whether it may involve privacy, preserving tokens with real world data, HIPAA right of access, other ways to tap into fire data polls, and increasingly some of those standards-based approaches are available to us outside of the US as well.

I'm not going to belabor the point around endpoint modernization, we talked about that a moment ago about the location flexibility. We are able to realize when our endpoints are modernized. What I will call out though is that [00:39:30] the investment to shift and modernize an endpoint has to happen months, sometimes years ahead of when that clinical trial start may take place. And so this is not a countermeasure that one can introduce in the middle of a pandemic and suddenly shift from an endpoint, like a six minute walk test of having an individual walk the hallway for a movement disorder or congestive heart failure study, and suddenly switched to a mobile app. [00:40:00] It required advanced planning to validate and qualify that digital measurement, all of which can be done, but simply requires advanced planning and investment on the part of the research sponsor and investigators. I'm going to move on from there. These are some of the themes though that we, again, see experimentation today and expect to see more of introduced within how industry has been scaling decentralized.

Next slide please. [00:40:30] DTRA is a nonprofit collaboration that I co-chair that is focused on the global adoption of decentralized methods. And the reason that I wanted to just call out DTRA here today is we've just updated on the next slide, a website that includes this tube stop framework of the process of drug development with resources for the global research community that are looking to increase their utilization of decentralized methods. [00:41:00] Those resources whether created by DTRA, or other organizations and consortia, as long as those resources are available in the public domain, we've been working to centralize those to make these available for researchers around the world, to be able to better understand, to be able to better plan, design, and execute their studies with decentralized methods leveraging the ecosystem of tools, solutions, and guidance that have been made available [00:41:30] across the ecosystem over the last two years. Next slide please.

I don't want to sound Pollyanna, but there are significant barriers that remain around driving global adoption and scale of decentralized methods, especially with industry for multicenter trials. The regulatory community has done a tremendous job of addressing ambiguity. I think for many in the industry, there were concerns [00:42:00] about whether regulatory flexibility is introduced during the pandemic will out last the pandemic, and that ambiguity is being lifted more and more at global scale. We do still have some remaining

challenges, just domestically in areas like the US as it relates to policy, and interstate licensing, which remains a barrier for some when working with investigators who may be supporting research participants across state lines. Areas where, perhaps [00:42:30] from a policy perspective, we could introduce opportunities that can remove this ambiguity. It's not necessarily a question of providing medical care across state lines, simply being able to support their participation as an individual in a research study. Now, global variability, certainly, remains a challenge for those implementing studies at global scale.

ICH will, certainly, help in terms of some level of [00:43:00] harmonization, but will likely still land with some level of variability across different regions. That's not a true barrier to implementation. We have that as the case for many technologies and processes in clinical trials, but it will still slow and create some level of friction. Technology data flow, interoperability, these do remain issues as we hinted at before with decentralized approaches, we simply are introducing often [00:43:30] many more data sources. Whether related to connected devices as was mentioned earlier, real world data, or other ways in which data are flowing into our studies. These may be less familiar to organizations and there may be interoperability issues that we're not able to take advantage of, perhaps optimized processes, like we mentioned earlier, around electronic informed consent. These do create some challenges for investigators in the research [00:44:00] site community.

Investigators need readiness both around these different technologies, but also how they can provide proper oversight for the study participant in this new reality when data may be flowing in new directions from a connected device or other data stream where there may be third parties such as visiting nurses, home health, or local community healthcare providers involved. What are the right tools and processes [00:44:30] to ensure and demonstrate that investigators have the proper oversight that they need, not only in fully remote trials, but perhaps even more difficult in those hybrid scenarios, where some patients may be going down different paths from another. We talked a bit about those endpoint limitations and investing early in modernizing our endpoints, but as we hinted at earlier, more often than not, the ultimate barrier is just organizational culture. And that's not just among research [00:45:00] sponsors, that's our entire ecosystem. Many research sites are pushing back on decentralized approaches perhaps because of ambiguity around oversight, perhaps ambiguity around respect for budget when those sites still have responsibilities, even if a third party is say, providing a visit. And so this friction is still causing issues around global adoption. Next slide please.

[00:45:30] I think it's reasonable, just as a closing note for us to forecast a bit about what adoption has looked like and where it will head from here. In many cases, pre-pandemic, we were in largely a state of experimentation, interesting studies in different pockets, but mostly anecdote within industry, perhaps a couple of experiments in the portfolio. But it was certainly during mid pandemic that [00:46:00] we saw an important spike in adoption, as we mentioned earlier, mostly because of reasons of business continuity rather than for reasons say

around access, experience, diversity, representation. But it's those patient factors that will pull us through with adoption beyond the pandemic. For many in industry, we're still at a place with some post-pandemic hesitation that was largely driven by regulatory ambiguity and normalizing processes, but for where we [00:46:30] are in 2023, it's also due, in many cases, to the macroeconomic factors that many in industry are confronting today, whether it's ambiguity around reimbursement, inflation rates, or other factors that are standing in the way.

A lot of these are causing many an industry to pause or hesitate with their innovation investments, their IT enterprise spends, and other types of places where they invest in these types [00:47:00] of initiatives. As we see regulatory ambiguity removed in particular, as we see different regulatory decisions on studies that have been running using these approaches over the last two years, each time there's a decision made will be an opportunity for clarity. Sometimes that clarity could cause a little bit of hesitation. Sometimes there may be regulators that make a decision that isn't favorable around the way a decentralized [00:47:30] approach was used, and that's still helpful to the environment because it gives the ecosystem an opportunity to react and get better. In other cases, they may see favorable decision that continues to enhance confidence. I would argue that the last spike in adoption around decentralized approaches will largely come from IRBs and ethics committees.

I would argue that this is the case, because when we get to a place of having [00:48:00] operational confidence and regulatory confidence, when we know that we can introduce these methods without sacrificing in any way on patient safety or data integrity, and we have full confidence in our engagement with regulatory authorities, that these approaches will be acceptable. I believe that it will then become an ethical imperative. How do we deny access for those patients that are relying on these approaches in order to participate? How [00:48:30] do we deny access to those individuals simply because we're not using methods that we know we can use successfully from an operational and regulatory perspective? We're certainly not at that place of confidence yet, but we will be and I think that's what will drive the final nudge in the adoption curve. I'm going to stop over here and turn things back over to the moderator and look forward to the Q&A session.

**49:00**      **Presentation 3: Dr. Kenichi Nakamura**

Amar Bhat:      Thank you, Craig, that [00:49:00] was fascinating and I appreciate your helping us define better what decentralized means, and also as well the look into the future of decentralized clinical trials. I'm looking forward to that future. Next, I'd like to introduce our last speaker for this webinar for today who will provide an overview of fully decentralized clinical trials in oncology. Dr. Kenichi Nakamura is the director of the Department of International Clinical Development [00:49:30] and Chief Management Officer at the Clinical Research Support Office at the National Cancer Center Hospital in Tokyo. Dr. Nakamura, please take it away.

Dr. Nakamura:

Thank you so much for the kind introduction and good evening, Gabriel. I'm Kenichi Nakamura from the National Cancer Center Hospital in Japan. And today I'll talk about a fully decentralized clinical trials in oncology. So previously cancer drugs are considered less suitable [00:50:00] for DCTs due to their toxicity. Recently in Japan, there have been severe DCTs conducted in cancer field. So today I will talk about our recent challenges in three decentralized clinical trials in oncology. So yeah, let's begin with why DCT oncology. So now the comprehensive genomic profiling tests or CGP tests can be done in Japan under national health insurance. [00:50:30] But only 9.1% of patients can receive the matched drug. I heard the percentage is around 10% even in the US or European countries. One of the main reasons of the small percentage is the difficulty in clinical trial access, especially for patients living in rural areas.

So there are many clinical trials conducted only in Tokyo. For example, our [00:51:00] hospital, National Cancer Center Hospital has more than 500 IND clinical trials, but the number is less than 10 even in university hospitals in distant area. So patients living in rural areas often need to travel four or five hours to visit our hospital to join our clinical trials. So I can say there's a significant regional disparity we must address. Next, please. [00:51:30] This is a scheme of our free decentralized clinical trials. Previously, a patient living in distant area, you can see on the top, she had to take a flight to Tokyo, it takes five hours. But in this scheme, this patient can join the clinical trials using telemedicine. Investigators at the National Cancer Center, you can see him in the right row or corner, he [00:52:00] makes eligibility check, informed consent, go or no go decision on treatment continuation, and efficacy or safety evaluation all online.

And the investigational drugs are directly delivered from National Cancer Center to the patient's home. But patients still needs to receive some examinations such as blood testing, CT and MRI. Then the patient visit a neighboring hospital, [00:52:30] we call it the partner site, at the left row corner. So patient will receive such examinations here. On the partner site, we'll share the examination results on the internet. The partner site here is not a clinical authorized site on the ICHGCP, but National Cancer Center concludes a contract and delegates examinations to the partner sites. So the partner [00:53:00] site does not need to receive IRB review and they don't need to make a data entry to EDC system. And basically, we don't make onsite monitoring because satisfied copies of examination results are shared on the internet and which is another benefit of DCT. Next please. So what are the benefits of this scheme?

So first, [00:53:30] clinical trial access from a distant area is significantly improved, but its most important part. Because partner sites are not a clinical trial site under GCP, but the site that undertakes delegative tasks, so ethical review, education, and the monitoring can be significantly simplified. The benefit of clinical trial site like National Cancer Center is that we can recruit [00:54:00] patients from overall Japan, which will make patient accrual much faster. And cost reduction is another important benefit. We can shorten the accrual period and make remote monitoring, so possibly we can reduce the total

clinical trial cost. Next, please. So this is our first three decentralized clinical trial, which is a phase two investigator-initiated registration- [00:54:30] directed trial for tazemetstat. Our target disease is Epithelioid sarcoma, which is ultra rare cancer. Although the sample size is just 15 patients, the patient accrual is expected to be very difficult. And actually we enroll just one patient in the first six months, that is why we introduced DCT in this trial.

The delegated [00:55:00] examinations to partner sites, blood tests, pregnancy tests, ECG, imaging tests such as CT or MRI, and echocardiography, all of which are performed even in a daily clinical practice. Next, please. DCT works particularly well in specific situations such as when the patient's condition is stable or the drug is already administered [00:55:30] with non-safety profiles. It's especially useful for rare cancers or rare fractions. That means a rare genetic abnormalities, because at this moment DCT requires a lot of burden for investigators and the support staff in our hospital. So we cannot handle tens of DCT patients every day. But when it comes to rare cancer patients, they appear once [00:56:00] or twice a month and we need to enroll every single patient. And DCT enables us to enroll patients from [inaudible 00:56:09] Japan. That is why rare cancers or rare fractions are good indications of DCT. Next, please. The most important part of the DCT scheme is a partnership between the National Cancer Center and remote partner sites.

Telemedicine [00:56:30] is conducted in the presence of the physicians at the partner site, which can put the patient at ease. A touchpad is provided to the partner site with a telemedicine system installed. And the patient will give electric consent by digital signature on touchpad. And the drugs are shipped directly from NCC to the patient's home. That is the basic scheme of our fully decentralized clinical [00:57:00] trials. Next, please. This is an established DCT platform connecting our hospital to the partner sites. And the elements we introduced are eConsent, telemedicine, and the eSource, direct drug delivery, and the medical expense payment system. The first, we obtain electric consent via the middle house system developed by [inaudible 00:57:30], [00:57:30] which is a Japanese IT company. And the E source system is under development as an in-house system because now the existing systems is compliant with Japanese strict regulations of online medical information sharing.

Drug delivery is done by Sagawa Express, which is a regular [inaudible 00:57:51], and the Findme system is a medical expense payment system. The medical affairs [00:58:00] divisions makes patient record on EHR by using a patient information registered in the Findme system. A patient has to register their credit card information in the system. And as for the partner site, we ask the physicians to assign a liaison staff who helps patients join the DCT smoothly. And I will discuss detailed proceeds in each element under [00:58:30] regulatory or operational issues we encounter when we prepared. Next, please. First, I talked about the selection of partner sites. We have set relatively strict criteria for selecting partner sites because this is the first case and we focused on the patient safety and the necessary infrastructure. So partner sites should be



familiar [00:59:00] with genomic medicine and have certain experiences for GCP compliant clinical trials.

They also need sufficient staff and facilities to implement the DCT. And in this scheme, although we identified candidate sites in advance, but the offshore contract as a partner site is concluded after eligible patient appear so that [00:59:30] we can save the site set up fee. In rare cancer clinical trials, if we set up a certain number of clinical trial sites, sometimes the number of indoor patients from those sites is zero, so that is why we took such a procedure. Next, please. There are some rare issues on partner sites. For example, what kind of tasks can be delegated [01:00:00] to partner sites? We discussed this point with the regulatory authority. So for example, first question is whether it is possible to delegate examinations, not performed in daily practice. So basically I think it's okay if the quality of examination results does not deteriorate. And another question is whether it is possible to delegate an invasive procedure such as biopsy for correlative study. I think maybe [01:00:30] no, because if the procedure requires a certain level of invasiveness, the partner site cannot take on the responsibility.

Another question is if it is possible to delegate intravenous infusion as a part of protocol treatment. So maybe no, it is because Japanese regulations specify that protocol treatment cannot be delegated to the partner site. And the other discussion points [01:01:00] include to what extent do we need to give training or information to partner sites? What is the responsibility division point in a emergency situation? In a usual situation, National Cancer Center needs to take care of adverse events remotely by sharing information with the partner site. But if the patient is hospitalized at the partner [01:01:30] site, there is no choice but to rely on the partner site. Next, please. So the eConsent process should be secure and efficient. So first, we provide the partner site a touchpad with the eConsent on telemedicine system installed. The patient at the partner site sits aside to share the medical information and put the patient at ease. That is what we call the [01:02:00] D to P with D style, doctor to patient with doctor style.

Dr. Nakamura:

D two P with this style, doctor to patient with doctor style. The PI on side, NCC makes a patient identification to check the patient's ID card such as a driver's license. And if the patient agrees to join the trials, the patient gives eConsent by digital signature on the touchpad like that.

One of the discussion points is compliance with DCT regulations in Japan. [01:02:30] It actually became an issue because Japanese regulations strongly recommend multi-factor authentication when using some IT systems. But in our process, the patient gives eConsent in the remote presence of GRC at National Cancer Center, and we can assure that patients themselves give an eConsent. So at this moment, we don't make a multi-factor authentication. Next, please.

[01:03:00] Next is telemedicine procedures. Telemedicine is performed using the touchpad in the D two P with D style, but before that, the liaison at the partner site should upload the delegated examination results and CRC ensures

all the required results provided. And our telemedicine procedures are designed to facilitate the effective communication among all parties [01:03:30] involved, but scheduling remains a realistical challenge that needs to be addressed. Next, please.

In terms of eSource, initially it was difficult to share medical information on the internet due to the strict Japanese regulations of medical information security. The risk of information leakage and identity theft should be minimized [01:04:00] at the system. Therefore, test results were shared by fax and CD-R, by mail, initially. It was difficult to share the information in a timely manner with the partner sites. A new system is under development to securely share medical information on the internet by providing a laptop PC with client certificates installed. And I know some countries have already set up a well-designed medical information [01:04:30] sharing service as a national system, but Japan does not have a good system at this moment. I believe a good medical information sharing service will play a key role in facilitating the spread of DCT in Japan. Next, please.

We directly deliver the investigational drugs from NCC to the patient's home with a temperature logger enclosed. The CRC at the National Cancer Center [01:05:00] remotely manages a number of residual drugs, and the patient has to send them back to NCC. One of the key regulatory issues here is whether direct drug shipment from the depot is possible under the supervision of the sponsor. Now, ICGCP specialized responsibility of drug prescription for not a sponsor, but an unknown investigator. However, direct [01:05:30] shipment from the depot to the patient's home will improve the drug delivery much more efficiently. It will be a regulatory discussion point in Annex 2. Next, please.

So far, I have introduced detailed procedures of our DCT, and I would like to slightly touch on the Japanese regulations on DCT. The Japanese government has already issued guidelines for eConsent, [01:06:00] which include patient authentication, IT system, location, procedures, digital signature and so on. There are other DCT guidances under development such partner sites, IT platform, remote data acquisition, direct drug delivery. Now, various countries have issued their own DCT guidance, so harmonization of those guidelines is expected. Next, please.

[01:06:30] From now on, DCT is expected to be utilized even in international clinical trials, and it is likely that DCT systems are prepared and owned not by a sponsor, but by each institution. Different DCT systems and procedures may be used in a single clinical trial. It is expected that Annex 2 will include [01:07:00] descriptions that promote a high level standardization across the countries. Then, DCT procedures in each country will not be very different. Next, please.

Last but not least, I would introduce an ongoing project with Thailand, which is a cross-border DCT. The basic scheme is all same as what I introduced so far. My idea is a same scheme can be applied even for [01:07:30] overseas countries. Next, please.

One of the most difficult issues is medical license. When I first discussed my idea, cross-border DCT idea, with the Thai government, they said Japanese doctors who don't have a medical license in Thailand cannot perform online medical care for patients living in Thailand.

I almost gave up my idea, [01:08:00] but someone told me that in a special circumstance, such as a skilled surgeon makes a demonstration surgery, they are allowed to have a temporary medical license and to practice medicine in Thailand under the supervision of Thai doctors.

Then, after a long-term discussion with the Thai government, finally, the Thai Ministry of Public Health and the National Health Center agreed to issue a temporary medical license for Japanese medical oncologists [01:08:30] engaged in DCTs. Next, please.

This is a photo of the MoU signing ceremony between Thai MoPH and NCC. And this MoU intends to promote cross-border DCTs between Japan and Thailand, including issuing temporary medical licenses. Next, please.

Through the discussion with the Thai MoPH, we modified some procedures, and in this cross-border DCT, [01:09:00] the partner site is not just the sites undertaking delegated examinations but clinical trial sites under ICDCP.

PI is assigned in Thailand, IRB review is performed and the application is submitted to the Thai FDA and the investigation of drugs are prescribed from the partner site in Thailand. But the benefits of DCT are said are the same between this cross-border [01:09:30] DCT. Cost reduction can be achieved by sharing examination results online and simplifying the monitoring process. And the clinical trial access and the faster patient accrual can of course be achieved by the cross-border DCT.

We are still preparing the cross-border, and we have to overcome some more barriers before we actually start it. I believe such initiatives will significantly make a [01:10:00] clinical trial much more efficient and eventually benefit many patients in the world. Next, please.

This is the final slide. The realization of the DCT would not have been possible without the cooperation of many stakeholders and colleagues. I'd like to thank all those involved. That's all from me. Thank you for your kind attention.

**1:10:30**

**Moderated Discussion**

Dr. Khair ElZarrad:

Thank you very much, [01:10:30] Dr. Nakamura. May I ask the speakers to go on camera, please, with us? Thank you so much everybody for such a wonderful talk. The chat, the Q&A and the chat were really hopping with many aspects and many questions. Thanks to all of you.

Before we jump into some of the questions, while you guys were talking, we were trying to also summarize some of the questions. One key area that seems to be coming up quite a [01:11:00] bit, just to clarify before we start, is what we mean by pragmatic trials. And I just want to, maybe at certain points, you can elaborate on that, but without getting stuck into definitions, I just want to highlight that for us, pragmatic refers to, sometimes, as point of care. The idea is that they have flexible inclusion criteria, they use routine healthcare data. Some people describe those as real world data. They utilize [01:11:30] healthcare infrastructures, often such studies called embedded trials or embedded in healthcare.

They have the potential to be more inclusive, to be more efficient. Many of you are familiar with the [inaudible 01:11:42], the scale for pragmatism, but I think that the idea here is that we are trying to avoid the all or nothing approach and focus on features, design features that will make clinical trials more efficient and more inclusive. Dr Nakamura's talk actually ended up with some really good anecdotes for considerations around those trials that are conducted [01:12:00] at a global stage, for example, differences in standard of care, differences in licensure, requirements for healthcare provider. We heard about Thailand and Japan working together on those.

I just want to provide that clarification because there are multiple points on that. But let me go into a question, and I was very intrigued by Dr. Lenze's, actually, first slide, accelerating speed and quality. And I think there couldn't be any nicer way of saying [01:12:30] what we're trying to do in a very simple word, accelerating both the speed and the quality here.

One of the questions we have that really sums quite a bit of the comments we received, are there specific consideration for data quality when conducting a trial with decentralized or pragmatic elements? For example, certain trials use digital tools, as many of you discussed, to capture data directly from patients, or use healthcare data directly. Are there specific considerations to ensure data quality? [01:13:00] A lot of the comments we receive, really, are about data quality on those settings that all of you discussed. I'm going to go to you, Eric, first, and then, others can elaborate.

Dr. Eric Lenze:

Thank you. That's a really good question. And I would say, first of all, that there are opportunities, as I think Dr. Lipset referred to for increased data quality through these decentralized techniques. But I think [01:13:30] maybe the issue is regarding when we move to data directly from patients, for example, ecological momentary assessment, data where we ask a patient a question over and over, there's an opportunity for more valid data from the scientific sense, but these measures are often not validated yet in the psychometric, or particularly, the regulatory sense.

[01:14:00] There needs to be more effort to come to consensus on what are validated measures that are going to be acceptable to regulators and have consensus. That's a key data quality issue that's just going to need to be

answered over time. I think there are other issues with data quality as far as what can go wrong with patients intersect with technology, which highlights what I was saying about the need [01:14:30] for expert study teams that need to be really on top of this in real time.

We found our clinical trial team often acts like an IT team to deal with the challenges with technology. And then, finally, there is a final concern that fully remote or decentralized participants might be more likely to be fraudulent patients, which I think is probably in the backs of many of our [01:15:00] minds when we're thinking of these remote trials. In the article I referred to, we talked about this challenge and potential solutions to it. In my own experience, we have not seen this as a problem but I think that's because that's an experience in academic trials where we just have a lot more innate guardrails to fraudulent participants than an industry study may have.

Dr. Khair ElZarrad: [01:15:30] Thanks so much for that.

Craig Lipset: What I might add for that discussion is, it's helpful for me when we separate out data quality into considerations around the data sources themselves as compared with the role of systems and processes for data oversight. Now, the technologies that we're looking at for data acquisition are not unique to decentralized trials. We have many studies that look at digital health technologies, [01:16:00] tapping into connected devices and sensors, looking to digitize and modernize endpoints, looking at ways to pull in electronic health records. Many brick and mortar studies are actively using these approaches as well. Our expectations and standards for data quality are no different for a decentralized trial, and the same considerations around ensuring that those methods are qualified and validated as fit for purpose count.

The second half of that [01:16:30] is, do we have the right processes for data oversight by either the investigator or other supporting roles in the study? And there, of course, the answer has to be yes, and increasingly, we see that made clear in guidance and recommendations from regulators calling to make sure that oversight plans are in place and demonstrate the ability for investigators to have full visibility and span of control over these different data sources when they're coming in. A connected [01:17:00] device can't just feed data into some remote database, it still has to go through the investigator for proper oversight. And then, we have these two elements mastered, just as we do for our brick and mortar studies, considerations around how the data's being sourced and making sure we have confidence in the process for review and oversight of that data.

Dr. Khair ElZarrad: Thank you for that. Ken, I don't know if you want to add anything to that.

Dr. Nakamura: Yeah. From my perspective, [01:17:30] our example clinical trial is research injected trial, so the data quality is really important. And in our ongoing DCT, we take some countermeasures to keep the data quality good. For example, in

terms of the efficacy in the points such as progression-free survival or response rate, we delegate imaging examinations like CTs or MRIs to partner sites.

[01:18:00] One of the discussion points we had with Japanese regulatory authority is, what kind of examinations can we delegate to the partner sites? And the key point is, the quality of the examination result would not change. If the accuracy of the delegated examination results deteriorates, it's not acceptable. We only delegate examinations that are usually performed in [01:18:30] the usual normal clinical trials such as blood testing or CT or MRI.

And all assessments are performed not by the partner site, but by the investigator defined by the ICH E6 [inaudible 01:18:47] at the clinical trial site. By taking such countermeasures, now, I think the data quality of efficacy endpoints in our DCTs is essentially the same as non DCT cases.

[01:19:00] In terms of the safety endpoints, some endpoints can be assessed by remote communication with a patient, but it is sometimes difficult to take physical findings precisely because we cannot look closer to patients or touch the patient's body. Under our mitigation plan is that the site selection criteria include the physicians at the partner site should have certain experiences [01:19:30] to join the DCT compliant clinical trials as an investigator, and the assistance from them or information sharing by them would help to keep the data quality good. But overall, I think that it's possible to ensure the data quality or both efficacy and safety endpoints by taking such appropriate countermeasures even in decentralized clinical trials.

Dr. Khair ElZarrad: [01:20:00] Thank you very much for that. You really highlighted some of the points that we tried also to stress during the work of ICH E6 in clinical practice, the draft that's available for public comments right now where we highlighted a couple of points. Those entities who will be delegated certain tasks like, let's say, clinical tasks, simply, they should be qualified to do that task.

And I like the point, we highlighted the fit for purpose approach as well, with the understanding that we're not seeking perfection here, there's no data set [01:20:30] that's perfect in that sense, but also is it fit for purpose, I think that's the question. And thank you for making that point about safety and efficacy. I think we really should think about them in those pockets as well. Thanks for the input here.

One key theme, and this is not a prepared question, actually. This is something that came up from the Q&A right now, during the discussion that we try to summarize here. A lot of the questions are trying to address the logistics of decentralization, specifically [01:21:00] regarding the supply chain, regarding the shipment of the investigational product directly to subjects. Many of you brought in the idea of shipping to homes, for example, and how do we maintain product accountability and the appropriate administration of the product during those trials.

Again, many of your presentations really touched on that, but I just want to provide an opportunity for you to elaborate. This is a two part question. There is another part, but let's start with this one first, about the logistics, the supply [01:21:30] chain, the shipment of the IP directly, and how do we maintain product accountability during that process. I don't know who would like to start. I think all of you touched on this. Maybe I'll start with you, Craig, and then, see if others would like to chime in as well.

Craig Lipset:

It's a complex topic, and it's made more complex as we think about the range of investigational medicine, small molecules and large, that we may be introducing. Certainly, as relates to small molecules [01:22:00] with temperatures that we're able to control, our ability to ship those directly to patients is a little better understood and we can have more confidence in their management, but for many they still fall back on language detailing that the investigator shall provide investigational product to the patient. That does raise some concerns for some that shipping directly from a depot does not seem to feel like it's consistent [01:22:30] with the investigator providing that investigational product. For some, they have their IP still flowing through a site to then reship to the participant. There's ambiguity there that we can do better to demystify and render more consistent.

With large molecules, it's obviously much more complex, including for those that may be self-administered. But we do know that video is a great democratizer, and our ability to leverage video, simple [01:23:00] video, just as we're doing today, should not be underestimated. Our ability to actively monitor how a self-administered investigational product is being utilized in the home is a great resource, having either coordinators or other investigator site staff on the other side.

In other cases, we will still be relying on either home health staff or other stakeholders to support administration. And it's interesting, now, [01:23:30] for us to consider, again, that role of the local healthcare provider, that role of the local HCP, especially if there is a concomitant medication that's more routine care or control that's more routine care that that local HCP can support supply chain and administration around.

Dr. Khair ElZarrad:

Thank you very much for that. And do you want to add anything to that?

Dr. Eric Lenze:

Yeah. I [01:24:00] can just add some pragmatic considerations of that. In our academic clinical trials, we have less worry about following the regulatory rules, some of which Craig described. We have a lot of experience with what can happen in the real world. I know, when we were doing the second COVID clinical trial, unfortunately, [01:24:30] it was happening during the winter and there were ice storms throughout the country, including in Texas, famously, back in early 2021, and it really did a number on our ability to provide investigational product directly to patients. I think, in one case, a patient actually found the box that we had shipped half a mile down the road in a snowbank where it was left there. The point is [01:25:00] that there are these kinds of shipping issues that

occur, and I think, as Craig said, maybe less of an issue for small molecules that are more stable with shipping in that case.

Dr. Khair ElZarrad: Yeah, absolutely. This is an intriguing example. Ken, you would like to chime in? Please go ahead.

Dr. Nakamura: Yeah. When I found our DCT, there were two options. One is table two patients and the other [01:25:30] one is the NCC, National Cancer Center to patients. And we finally chose the NCC to patients. The reason why is, now, the ICGCP, the responsibility of drug prescriptions on the investigators, and if we ship the investigation drug from a depot, so we have to control the depot, but management of the depot from the NCC [01:26:00] is really difficult. That's why we chose the second option.

Now, the pharmacy division in NCC directory makes the drug shipment to the patient's home. And the other thing with temperature control is an issue, but we enclose a temperature logger with the shipped drug and we check that temperature variation does not happen during the shipment [01:26:30] process. Yeah, that's what we are doing right now.

Dr. Khair ElZarrad: Yeah, that's fascinating. And our work, again, I'm referencing back to the GCP work in ICH as well, if we highlighted, obviously, the investigator is really responsible for the rights and safety of the participants, and we highlighted that any entities involved, they should be qualified entity to do the task, including the shipping and the handling. And that the product, the IP, the investigational product, should arrive [01:27:00] with the right specifications. I know it's a higher level, but I think, ultimately, we try clarifying the goal, ultimately, here. And I think your example of what you gave, temperature control, is a key example. That's something should be considered, especially at the global stage where you have a variation even in the environment where the product will be handled and shipped. That, I think, should be considered from a specification perspective. Thank you for that great input.

One other aspect here, from the same question, actually, there is the [01:27:30] issue of training, the required training, and I think some of you also highlighted that. One of the highlight of our work on GCB is that we're trying to correspond any required training to the role being played in the trial.

For example, if a healthcare provider is part of the trial and what they're doing is simply a task, a healthcare task that they're qualified and trained to do, that we do not necessarily impose additional training on those settings. Training should [01:28:00] correspond with the expected role. There are quite a bit of questions, however, on the type of training that will be required, especially when it comes to the administration of this product. And I know, Dr. Nakamura, you are working in cancer specifically, and the complexity of that environment may be something to consider as well. I don't know if you want to mention your perspective a little bit on training and requirements around that, and then, maybe we can open it for others as well.



Dr. Nakamura: Thank you for the question. And we actually [01:28:30] discussed to what extent we have to give training to the partner sites. Because we just delegate the examinations to partner sites, we will provide the necessary information on examinations, but the problem is, sometimes, emergency situations happen even in the partner sites, so we have to give a training for safety. [01:29:00] What kind of safety information should we give to the partner sites? That's a very big discussion for us.

For example, the investigator brochures will be updated so frequently. Do we need to send IVs every time it is updated? It was a discussion point. But essentially, it depends on the [01:29:30] importance of the information. If it is essentially related to the patient safety or necessary information to perform the delegated examinations, then, we will give a training. We need to think about what is essentially needed for the partner sites. It's a lot of background [01:30:00] simple questions, but we have to consider what kind of training to the partner sites, depending on the situation.

Dr. Khair ElZarrad: Thank you very much. Eric or Craig, would you like to chime in here?

Dr. Eric Lenze: Yeah. I would only add just that, sometimes, the engage in research language [01:30:30] will spur some institutional review boards to mandate additional, and I will say, in my experience, often excessive ethical training by healthcare providers who are simply performing a medical task, what would be seemingly a routine medical task like infusing a product, or I think [01:31:00] even handing a product to a patient. And it seems that this then creates a large barrier to actually be conducting this research because these healthcare providers, it may be of a significant network of providers, will often change over time as well. The idea that each provider needs to undergo, potentially, [01:31:30] many hours of ethical training in order to do that seems to be not a good fit for the research.

Dr. Khair ElZarrad: Mm-hmm.

Craig Lipset: It almost feels like ... It goes back to that phrase we used around safety measures and data around being fit for purpose, and for some of our stakeholders, triggering extensive advanced training curricula is not going to necessarily improve the quality of the specific [01:32:00] task that they're being asked to support if it's for routine care. And perhaps, in some cases, our attention is better placed on tools that support orchestration, that can help to just guide the individual around what is needed at that moment, if that particular tube is going to travel in a different direction from the other tubes that they're more routinely collecting, just simple technologies and tools that can help with orchestration. That's not a training [01:32:30] issue, and they don't need special GCP training. They just need to know, at that moment, have the right tools to make sure they're handling that tube differently from the other tube that they just drew.

Dr. Khair ElZarrad: Great point. I wasn't going to go to the IRBs, unless we have time in the end, but this seems to be something that's been coming up quite a bit, even in the chat

as well. Maybe we can elaborate a little bit more because I see, potentially, this is an area in need of more work. [01:33:00] One thing, from a regulatory perspective, we're trying to highlight that, in a-

Dr. Khair ElZarrad: ... one thing from a [inaudible 01:33:02] perspective, we're trying to highlight that innovation should be understood in the context of the trial and innovations themselves may not constitute necessarily additional risks per se. They may constitute different considerations but not necessarily additional risks.

And the IRB obviously play an essential role for research. I'm wondering are we looking potentially at needing a little bit more expertise on the IRB, are we [01:33:30] asking a little bit better understanding of the research ecosystems from the IRB perspective. I'm not an IRB expert so my questions may not be making perfect sense here, but I'm wondering if that's something we're highlighting a little bit here both via your comments and in the chat a little bit. I don't know if anybody would like to elaborate more on that.

Craig Lipset: I will not claim to bring expertise specifically on IRB and ethics committees, however, [01:34:00] I will point to resources available from MRCT, the Multi-regional Clinical Trial Center at their [mrcctcenter.org](http://mrcctcenter.org) website where they have developed some specific considerations for IRBs and ethics committees when reviewing studies with decentralized elements.

Now, how widely used or known of those resources may be may be part of the challenge that you're raising in terms of just awareness [01:34:30] and familiarity with these approaches.

Dr. Khair ElZarrad: Thank you. Eric, I saw you unmuting so go ahead.

Dr. Eric Lenze: I'll just add, my experience usually as a recipient of the rulings of IRBs and I have the scars to prove it in that case, often we're dealing with regional or even local IRBs who are really struggling to keep up with the innovations in this area. [01:35:00] They really rely on, as Craig had said, national guidance including guidance from the FDA. So any kind of guidance that IRBs can look to, to clarify or contextualize things in the area of decentralized or fully remote trials, would be very well received I think.

Dr. Khair ElZarrad: [01:35:30] Thank you for that. Ken, I see you unmuting as well so please go ahead.

Dr. Nakamura: The DCT has just begun in Japan so we need a training for IRB reviewers because they don't familiar with basically DCT scheme. So sometimes I give a training for IRB reviewers.

One of the discussion point we have when we prepare our DCT is do we need IRB review [01:36:00] even in the partner site. So in our case we just delegate the examination to the partner sites that is not invasive. So in most cases, the

IRB review is not required. But if we delegate, for example, invasive procedures such as biopsy to the patient, that would essentially increase the risk of patients. In that case, the partner's [01:36:30] site should be a clinical trial site and they need IRB review. That was what we discussed when we prepared our DCT process.

Dr. Khair ElZarrad: And that IRB review at that specific site, that's a little bit separate from the IRB review of the initial study, just to make sure I understand it?

Dr. Nakamura: Also, if the procedure is invasive enough, so the partner site should be joined as a clinical [01:37:00] trial site, formal clinical trial site.

Dr. Khair ElZarrad: I see. So the work goes beyond the standard of care, if you would, because of the complexity of the procedures involved. Okay.

Dr. Nakamura: And one more thing. So when we talked with Thailand, so the cross-border DCT is completely new for Thai sites, so they require the IRB review because it's quite new.

Dr. Khair ElZarrad: Okay. Just [01:37:30] kind of the novelty of the method, yeah. That's helpful. Thank you for that.

Just a few points also from the chat. The audience are asking about resources. We will provide a link to the ICHE 6R3. That's available in draft version right now on the ICH website. We'll also provide a link to the MRCT resources that Eric mentioned as well. So stay tuned. No problem.

Let me move to another area and this is [01:38:00] a question that we summarized. We prepared it from the comments during the registration process actually. A lot of people asked about safety and privacy in the context of using decentralized or rheumatic features. Specifically, that those trials a lot of times are embedded in healthcare and I think at least the perception is that you can have a conglomerate of data sources on the patients since the proximity to healthcare is a little bit closer. What are the safety and privacy considerations when conducting [01:38:30] those trials? And if you don't mind also commenting on potential strategies in how to best ensure the safety and privacy of those data. I don't know who would like to start us with this one?

Craig Lipset: I would say that safety is neither inherently better or worse in a decentralized trial. It sort of goes to the point that Dr. Lens was making earlier. It's how one is using these tools and methods. If done right, [01:39:00] safety monitoring should be the same or better than any other clinical trial because of more active engagement with the participant, with the ability to capture data beyond a typical schedule and visit based time sequence of when we would otherwise capture those data. But that's not necessarily just native to DCT. Simply using those tools does not natively make for better safety. [01:39:30] It takes active planning and strategies within the study to make sure that those measures are

being properly used, that there's proper active surveillance and monitoring of those data, that there's proper oversight.

Privacy is a bit different and it's an interesting thread to pull here because when we're using video, when we have home visits, when we have these, say, applications that may be leveraging location data, that does open [01:40:00] us up to additional types of data, additional observation that we might not otherwise see. Many of us have virtual backgrounds on today or blurred screens, but we can all remember fondly the images during the pandemic of things going on in the background on Zoom calls. And when we are opening up video and home visits, we may simply see things that we might not have otherwise had access to that do require us to have another level of privacy planning and consideration in place.

Dr. Khair ElZarrad: [01:40:30] Thanks so much, Craig. I think there is some intrigue around remote data capture specifically and I think sometimes we not always correctly associate that with the vulnerability for privacy and there are tools that's now used every day, encryptions for example, to really protect this data flow. One area I've been hearing about, for example, if you use a cellular network or wifi network to capture [01:41:00] the data and make it flow to a server, what will happen in between? Will that third party have access to the data? And that's not a question that can be answered simply by encryption.

So again, there are tools there that addresses that. And I think your point initially regarding the safety which is, you're right, it's a separate issue about this design potentially providing us with better safety data capture potentially and better safety parameters. I think Eric highlighted that quite a bit. With a little bit more frequent data capture, you really can see a little bit better what's happening to the participants and [01:41:30] the patients in the trial. So thanks for that elaboration. Ken or Eric, would you like to jump in here? Ken, go ahead.

Dr. Nakamura: So in terms of safety, in our DCT when some adverse event happens, the first choice is that the patient [inaudible 01:41:48] in our hospital. However, if the patient needs emergency treatment treatment, then the investigator in the hospital instructs the [01:42:00] patient to visit the partner site immediately. In that case, the timely information sharing with the physician at the partner site would be very important. So the data information sharing between [inaudible 01:42:15] and the partner site plays an important role in ensuring the patient safety. And the presentation by Dr. [inaudible 01:42:26] was so impressive for me so that I agree that frequent communication [01:42:30] with patient could help to measure the safety [inaudible 01:42:34] more precisely even in the oncology clinical trials.

And in terms of privacy, Japanese people are very sensitive to privacy issues. So in our DCT, patients have to come to the partner sites and we have telemedicine in the [inaudible 01:42:54]. So the telemedicine system keeps logs about [01:43:00] when who uses the system. Then we can assure that any outside person does not join that system. The other thing is how we can send the

examination results securely through a cloud system. As I mentioned in my presentation, we provide [inaudible 01:43:23] client certification, certificate installed so the partner site can send the examination results [01:43:30] securely. And simultaneously, we also keep logs about when and who sends the examination results so that we can prevent a leak of patient information. So anyway, Japanese data sharing regulations are very strict and we have to comply with that regulations so that the harmonization of such regulations will be [01:44:00] expected in the global [inaudible 01:44:04]. Thank you.

Dr. Khair ElZarrad: Thank you again. Dr. Nakamura, you constantly challenge us to harmonize globally and I think that the message is really well received here. So thank you for that. I was also corrected by my colleagues, it's not just encryption, there are other tools to bypass even the need for the data going to a third party server even. So again, there are multiple modalities here that we can utilize to assure [01:44:30] this and I think technology provide us with those opportunities as well.

I don't know, Eric, if you would like to jump in on this discussion as well?

Dr. Eric Lenze: Just real quick, I thought it was interesting to connect safety and privacy. I think there's I guess a great concern that data will be used by a third party in a way that would threaten a patient's safety. I don't know how often that that's really likely to be the [01:45:00] case, but the broader concern is trust. I think it's safe to say in America, in particular, and I think this is true elsewhere, that Americans do not trust health technology companies with their data and increasingly I think do not trust academic or medical research institutions with that. So I think one of the big concerns and [01:45:30] potential barriers to progress in this area is if there are data breaches or breaches in privacy that lead to a further erosion in trust.

Dr. Khair ElZarrad: Wow, that's such a poignant comment here. In previous life at NIH, we looked into recruitment barriers and you're absolutely right. Trust, especially for underrepresented populations, trust is such a key factor here and you can totally see how compromising [01:46:00] the data potentially, even unintentionally, would compromise such trust and that brings this to even a higher importance. So thanks for that mention and very well good point.

One other point that actually this reminds me of when you mention trust is really the patient centricity. One of the hope at least for those trial designs or trial features, if you would, is that we'll bring the trial a little bit closer to participants. We'll lessen the burden of participation. We [01:46:30] potentially reach communities historically at least not reached in clinical research. So there is a lot of hope there.

However, one of the comment that we summarized from registration questions and input is that regarding patient population specifically, are there specific considerations and challenges when it comes to using digital technology. Some of the comments highlighted the contribution to diversity. Does it contribute to

diversity or does it even create [01:47:00] roadblocks sometimes? And specifically addressing digital divide issues, favoring enrollment and engagement for those with access to technology over others. Without cornering just that part, can we discuss this a little bit here? How these designs contribute to diversity or create roadblocks and with the challenges associated with them? Not to pick on you, Eric, but you mentioned trust and that brought this question into light so maybe starting with you.

Dr. Eric Lenze: Yeah, thank you. And I think there's an assumption that these [01:47:30] digital tools will increase equity for those, for example, in rural areas that are geographically remote from academic or medical centers. But that ignores some key things. One is that many rural states in the US and low and middle income countries elsewhere have no broadband or unstable broadband and that makes the possibility of data collection [01:48:00] more challenging.

I know the US policy is moving towards trying to eradicate these digital disparities but they still exist as recently as when COVID started and our kids moved to remote learning, how many rural or poverty stricken areas, education just became inaccessible because of a lack of internet access and technology.

Dr. Khair ElZarrad: [01:48:30] Thank you for that. Ken or Craig, I think this is an important topic so I'm really curious what you guys have to say about it.

Dr. Nakamura: In our experience, actually we have some elderly cancer patients who don't have an email address or who are not used to using digital gadgets. So right now we don't require patients to roll into the DCT system when they [01:49:00] join the e-consent process or telemedicine system. Alternatively, physicians or [inaudible 01:49:07] at the partner sites log into the system in advance, then patients are coming into the loop and they can remotely communicate with investigator in [inaudible 01:49:19] without logging into the system.

But one of the issues here is Japanese [inaudible 01:49:26] guidelines strongly recommends a multifactor authentication [01:49:30] with a patient logging into the system. So in our current procedure, patient does not log into the system. So we discussed this issue with Japanese regulatory authority extensively and, as a result, we agreed on the current procedure but we need to record the IC process in detail to ensure compliance with pre-specified SOPs. And if we fail to [01:50:00] keep the record and cannot demonstrate IC processes conducted compressed with SOPs, it is likely that the regulatory authority would judge the IC process as ineffective. So the current procedure is of course user-friendly but I'm a little bit anxious about the integrity of IC process so that we are still assuring the best way [01:50:30] even now. That's my experience.

Dr. Khair ElZarrad: Thank you very much. Craig?

Craig Lipset: We can't exacerbate a digital divide. We can't establish eligibility criteria assuming that individuals have access to certain technology. We have to

continue to plan a provision technology where needed. And to the point made about even rural areas, I was on a call the other day with a team planning a decentralized trial in Pakistan. [01:51:00] There's great learnings from these regions just even for other more developed countries where there are technology gaps. We have to make sure that technologies can work asynchronously, that they cannot assume that the individual always has access. I'm in a bandwidth rich area in the northeast corridor in the US and, even here, I have dead zones and drops. So making sure that our technology appreciates [01:51:30] those gaps that individuals will face and can't just rely on assuming a constant stream.

Dr. Khair ElZarrad: Thank you very much. One thing that was pointed to me too is that you can resolve a lot of time the digital divide by providing hotspots or some tools but also there are other issues, for example. I think it's called the age divide or the potential for symptom population, older populations not to be [01:52:00] familiar with the tool as much as younger populations. And we do not necessarily want that to bias who's part of the trial as well.

I'm trying to see here. There's one request to hear about your opinion regarding the retention of trial participants in the absence of in-person visits. Do we see any kind of variation in that sense and, say, you rely more on the digital data capture, do you see a little bit more droppage, more [01:52:30] withdrawals potentially in those settings? Or that's not something that's been noticed? Starting with you, Craig, since you're still on unmute and then I'll go to Eric and Ken.

Craig Lipset: Similar to what we were saying with safety earlier, simply using these decentralized approaches does not make for a better or for a worse engaged individual, but we do know that, incorrectly deployed, individuals can be left to feel isolated with unfamiliar technology and an unfamiliar investigational [01:53:00] medicine. And those scenarios will be destined to fail because those individuals will feel disconnected.

On the flip side, decentralized and right should make an individual feel more supported, more connected. Like their connections, as Dr. Nakamura was mentioning earlier, that the participants should feel that they can engage with and reach out to study coordinators or investigational staff even more so [01:53:30] than at just a typical schedule driven visit encounter with a typical brick-and-mortar study. So the devil's in the details in terms of how these are being deployed and the process around it and it does require additional thought but, done right, should leave the individual feeling better supported and connected and better retained. But it would be very easy to point to examples where that was not the case in a study that used decentralized methods but didn't do [01:54:00] so with the proper level of support.

Dr. Khair ElZarrad: Thank you. You're really highlighting the thoughtfulness and the design for decentralization or for any trial really is important here. And then the idea of

being potentially even more supportive in those settings, it's a really interesting idea. So let me go to Eric and then Kim.

Dr. Eric Lenze: I totally agree with Dr. Lipset on that. Decentralized does not mean high tech, low touch and in our experience we have not noticed [01:54:30] a reduction in engagement or retention with fully remote participants, but we rely on a rather high touch approach through telephone contact and the expertise of our study team that has many years of clinical trial experience under our belt.

I would just add that, in addition to realizing that this does not mean [01:55:00] low touch, in fact it may mean more frequent contact with the study team to make sure we don't regulate our way out of opportunities for engagement and retention. There's lots of creative ways through incentives like, say, graduated incentives that increase in value over time, effort, recognition, and also return of information, which we haven't even talked about today, that many patients [01:55:30] probably value that feedback as much as or more than monetary rewards. The point here is I would argue we should not regulate it in such a way that prohibits these opportunities.

Dr. Khair ElZarrad: Thank you. Absolutely. And I think the point at least in part of this meeting is to inform those robust policies that will actually facilitate such approaches, such good approaches, not plug them in any formal shape. So [01:56:00] thanks for that point. Ken, I don't know if you would like to comment as well?

Dr. Nakamura: Our ongoing DCT is fully decentralized clinical trials, so also our patient visit NCC if they like to come to our hospital. So of course the free remote DCT has many benefits but [01:56:30] also the patient preference is also important. Sometimes patient may change their mind in the middle of clinical trials and they come to prefer coming directly to our hospital. So our style is not a hundred percent or zero percent. We prefer the hybrid style rather than the free remote model. [01:57:00] I think that can make a patient at ease when they join the clinical trials and eventually decrease, maintain the retention rate.

Dr. Khair ElZarrad: Great comments and a reminder to us as we're talking about a spectrum about hybrid of tools that we can use to make the trial more efficient. Absolutely. And not all or nothing here. So thank you for that.

I was just reminded that we have three more minutes left. [01:57:30] We have a lot of questions from the chat so I cannot go all over them, but I think we going to take those and really study them and try to understand better how again we be more responsive around policies.

But let me end with just giving everybody an opportunity, even 20, 30 seconds if you don't mind, just from your perspective, to share with us the most important advantages and key challenges. Sorry, just in a few seconds each for those trials with decentralized [inaudible 01:57:58] elements, just any final words you would like to share [01:58:00] with us.



Dr. Nakamura, let me start with you and then I'll go to Eric and Craig.

Dr. Nakamura: Thank you very much for inviting me to this very important discussion. So I think the DCT in oncology area brings many benefits for many stakeholders. For example, we can reduce the regional disparity in clinical trial access and we can increase patient satisfaction. We can accelerate patient accrual and we can reduce the total clinical trial [01:58:30] cost. So I think I would like to make this DCT [inaudible 01:58:38] in Japan and in Asia.

And the key challenges are the establishment of the nationwide secure data capturing system. So that's really challenging in Japan. And also the standardization of DCT procedures across trials and the sites, that is another difficult thing. And the [inaudible 01:58:59] DCT [01:59:00] platform that compliance with our Japanese regulations is what I would like to have right now. There are a lot of things we have to do from now on, but I would like to spread this wonderful scheme to various types of clinical trials. So thank you very much.

Dr. Khair ElZarrad: Thank you and thanks for your work. Eric?

Dr. Eric Lenze: Well, thanks and I appreciate people's sustained attention over this virtual format as well.

I'll [01:59:30] just go back to what I said at the beginning, which is about scientific progress and I guess I'll hone it in more in the area of mental health and related areas like brain health and cognitive outcomes. There's a lot of opportunity for innovation. I think in many ways some of the things we do in clinical trials is really quite primitive, like compared to my colleague, Dr. Nakamura, in cancer. And I would [02:00:00] just look for the opportunity for these digital endpoints, these novel ways of measuring both mechanisms and outcomes to potentially accelerate progress in the field in many ways.

Dr. Khair ElZarrad: Thank you and thanks for your work as well. Craig, final word?

Dr. Craig Lipset: We've talked extensively here about many of the advantages, whether it's facing participants with experience or diversity and equity, [02:00:30] whether it's around trial resilience or even environmental considerations. I think, for many researchers today, there is a dearth of evidence of which decentralized methods have worked in which scenarios. So it's a call for continuing to engage in spaces like this.

So thank you, Dr. ElZarrad, and the colleagues at Reagan-Udall for bringing today and tomorrow's sessions together, but also other spaces to make [02:01:00] sure that evidence of what's working and what is not is getting shared and amplified so we continue to make data-driven decisions around our study designs. Thanks.

Dr. Khair ElZarrad: Thank you so much. Very grateful for your time today and I will turn it now to my colleague, Amar. Thanks again, everybody.

Amar Bhat: Thanks everybody for presenting today. We look forward to another day or another morning depending on where you are, presentations tomorrow. And until [02:01:30] then, goodbye and have fun.