Primary Mitochondrial Diseases:
A Rare Disease Virtual Workshop
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Afternoon Transcript

Current Approaches, Challenges, and Opportunities

Chad Glasser, PharmD, MPH, Tisento Therapeutics
Magnus Hansson, MD, PhD, Abliva AB, A Member of Pharming Froup

Susan Winckler: All right everyone, welcome back. I hope that you had a chance to engage in some other activities during the break or just take some time to yourself, but now we are ready to kick off for our afternoon session, or for those of you who aren't on the East coast, for our next session. Now we are going to hear to presentations from regulated industry, each sharing their unique experiences and perspectives on current approaches and challenges in developing therapeutics [00:00:30] for primary mitochondrial diseases. Following those two presentations, we'll have a 20 minute question and answer with the presenters ,and then we will move to a closing panel. So let's turn right to the content. First we're going to hear from Dr. Magnus Hansson, who serves as the executive medical director and KL 1333 global program team lead at Abliva AB. Dr. Hansson, I am going to step out of the way so that we can hear what [00:01:00] you have to say.

Dr. Magnus Hansson: Thank you so much Dr. Winckler, and thank you for inviting me to this important workshop for primary mitochondrial disease. At the last workshop back in 2019, I was in the audience at the FDA campus and I was really inspired by the talks and the discussions, the conversations between regulators, clinicians, and patients in that unique setting. And that actually helped shape our development [00:01:30] program quite a lot. So I'm therefore thrilled to be back today to share our strategies, how to overcome some of these challenges of developing drugs for rare disease like mitochondrial disease, and to share the opportunities we see to make a positive impact in this devastating condition. So the most important point of my talk today is that this collaboration between several stakeholders, which are represented here today, have enabled us to run a patient [00:02:00] centric study with two primary objectives and two primary endpoints reflecting the highest ranked needs from the Voice of the Patients.

And this collaboration also enabled the development of a patient reported outcome measure for fatigue specific for mitochondrial disease, which is now one of our two primary endpoints in a registrational trial. So Abliva is a member of Pharming Group, a company dedicated to developing treatments for rare and serious conditions. [00:02:30] And the specific mission for Abliva is what you can

read here, targeting the powerhouse of cells to improve the lives of primary mitochondrial disease patients. So we have developed a portfolio of novel compounds and strategies to do that, and I'll speak today about the program for KL one triple three.

These are my disclaimers. And to put my talk in context, we have an ongoing trial [00:03:00] and it's called the Falcon Study. And this is a randomized placebo-controlled study evaluating the efficacy and safety of KL one-triple-three. The study has a registrational study design and focuses on adult patients with multisystemic disease, including fatigue and myopathy, in patients with known pathogenic point mutations or a large-scale deletion of the mitochondrial genome. [00:03:30] The title of this session included challenges and opportunities. One challenge that we've heard speaking about earlier today is that mitochondria disease is a multisystemic condition which can affect almost any part of the body. And specific combinations of symptoms lead to some syndromic presentations, whereas other patients don't fit well into those descriptions. And as has described previously today, when we run studies, [00:04:00] do we include patients with only one specific symptom or do we include patients with very different types of symptoms where we may have to measure different endpoints in each patient? How do we compare treatments affect them?

And we've heard some approaches, statistical approaches, but one approach that we wanted to consider at the beginning of this program is if we can target debilitating symptoms which are common for a majority of the patients. Well, another challenge is, of course, that since there [00:04:30] are no approved therapies, there's no established pathway that we can follow to approval, but of course general guidance. But on the other hand, that means that what we develop has the opportunity to make a substantial impact on a high unmet need. So we faced these challenges by initially listening carefully to the patient voice. So back in 2019, in addition to the FDA workshop, there was also [00:05:00] an externally led patient-focused drug development meeting leading to a Voice of the Patient report. And in that meeting and the connecting surveys, it was clear that the two symptoms which are most frequent and which patient really highlight that as being the most burdensome are fatigue and muscle weakness.

And this is an example of one of the questions. So when asked, which abilities or symptoms would you rank as most important for a possible drug treatment today? [00:05:30] The top one response was fatigue, and the second was muscle weakness. So we decided to listen to the patient voice and to explore, can we focus our program on these two symptoms? Also because it really makes sense for our mechanism of action and the drug properties of KL-one-triple-three. But before I go further, I think it's important to define what fatigue is and how we use it in this context. [00:06:00] So when we speak of fatigue, it is the feeling of fatigue we are referring to. And on this slide you can see a couple of extracts from patient testimonies, from the same Voice of the Patient report. To the left, it reads, "I started missing work because I was too exhausted to even

get up to use the restroom." And here is the feeling of exhaustion, which is referred to. To the [00:06:30] right it reads, "I am afraid of what the progressive muscle weakness will do to me. Not being able to care for myself is a concern."

In contrast, here is the muscle function which is referred to. In our program, we separate the feeling of fatigue and the muscular abilities, the function. So in regulatory language, as you heard previously today, these are separate concepts of interest for the disease. [00:07:00] And we define fatigue as an overwhelming sense of tiredness, exhaustion or lack of energy, physical or mental energy, that interferes with daily life. And this definition of fatigue is similar to that used in several academic studies of fatigue. So one initial question for us as well was, if we are able to study both fatigue [00:07:30] and myopathy in a clinical trial, it means that those symptoms has to be common enough so that we can recruit sufficient number of patients. Because of course patients need to have the symptoms, but there are also more nuances how we set inclusion and exclusion criteria. For fatigue, there was good data available in the literature and the studies demonstrate very consistent findings.

Shown on these slides are two of those studies, one [00:08:00] from the UK and one from the US. In both studies, excessive fatigue was common, and the magnitude of fatigue correlated with overall disease burden.Interestingly though, in both studies, fatigue did not correlate specifically with myopathy scores. Again, highlighting that fatigue and myopathy are two different and separate concepts of interest for mitochondrial disease. [00:08:30] So for myopathy on the other hand, to plan our program, we needed more quantitative data and more nuanced data compared to what was available in the literature and also from a broader mitochondrial disease population. So there we have the opportunity to dig into one of the sources of natural history data. So did a collaboration with the Wellcome Center for Mitochondrial Research at Newcastle University [00:09:00] to extract data from the UK National Registry for Mitochondrial Disease called the MITO Cohort. And this study included over 500 adults, and those were adults that had active entries into this cohort over the past three years to reflect the patient population we were most interested in.

And the data included scores from the multi-component mitochondrial disease scale, NMDAS, or Newcastle Mitochondrial Disease Adult [00:09:30] Scale. And the benefit there was that we could look both at the prevalence of the symptoms but also the severity of the symptoms. That was important to figure out which kind of functional assessment would be relevant and feasible to perform. As you can see from results on this slide, both exercise intolerance and proximal muscle weakness related to myopathy and affecting larger muscle groups are common [00:10:00] in adults with Mitochondria disease. So it's illustrated here. So the field circle represents the proportion of the patient pool with these symptoms, some degree of severity of either exercise intolerance or proximal muscle weakness. So the conclusion from these studies are that both fatigue and myopathy are common in adults with Mitochondria disease, and so

common that it seemed feasible to run a registrational placebo controlled study [00:10:30] which evaluates both.

We also heard earlier today the importance of test driving. And we actually had an opportunity and we wanted to test drive this strategy early on in the program and we had an opportunity to do that already in phase one. So in this study, we included both a couple of fatigue assessments and the 30 second sit to stand test for proximal myopathy. And our conclusion from this study was [00:11:00] that these type of clinical outcome assessments seem promising to implement in a larger study. So moving a bit deeper into the further preparatory work. To assess fatigue, we need to ask the participant of a trial how they feel and how the symptoms of fatigue impacts their daily lives. And the way we ask those questions [00:11:30] will make a big difference to how reliable, sensitive and reproducible these results will be. So in my own professional life prior to this program, I had no experience with qualitative research.

Well, in contrast, I trained as a physician using diagnostic assessment with very objective and advanced quantitative methodologies such as magnetic resonance imaging and cardiopulmonary exercise tests with gas exchange analysis. [00:12:00] And my PhD studies were also very quantitative, lab bench research, isolated mitochondria. But luckily, the FDA and others have thought long and hard about what makes a patient reported outcome a reliable and useful tool. So we follow the guidelines and also at several meetings with the agency to discuss the development of validation of a mitochondrial disease specific fatigue questionnaire. And this slide shows [00:12:30] the process for how we develop the PROMIS fatigue mitochondria disease short form and establish its content's validity. So essentially we did two rounds of interview and patients, and the patient were recruited with the help from the United Mitochondrial Disease Foundation. The patients were adults with genetic confirmed disease who experienced chronic fatigue and myopathy.

And the first interview was a concept elicitation interview where participants [00:13:00] answered open-ended questions about their experience of fatigue. And the emerging fatigue themes were coded and then mapped to existing short forms and item banks for fatigue. Specifically, we looked at the Neurocall and the more extensive PROMIS item bank or fatigue items and questions. So what we found was that the existing general short form lacked important themes, and they also had some [00:13:30] items where we suspected the flooring or ceiling effects could be anticipated, would make them much less sensitive to change. So a new selection was done. These questions were then explored in a second round of interviews with the same participants. And those items which performed best and was most relevant formed the final short form.

To give you a bit more nuance from the concept [00:14:00] elicitation results, this is an illustration from that study of the most frequent themes from the interviews divided into fatigue characteristics and fatigue impacts on activities of daily living. And the level of endorsement is proportional to the font size of the respective theme. The participants also reported how other mitochondrial

disease symptoms they had either were [00:14:30] worsened by fatigue or have those symptoms worsened fatigue, and these are seen in the middle here. And to give you a specific example of the process, something we've heard over and over again in our conversations and also from these interviews is how patients really feel misunderstood when they speak about fatigue, that people don't [00:15:00] understand how debilitating the fatigue is. And I think this description, it resonated really well with me because it's something that we can relate to thinking back of when my kids were babies.

So it reads, "I don't think there's any getting it unless somebody lives it. I think maybe like a new parent might get it. Somebody who spent the last week or something waking up with a newborn several times a night, [00:15:30] they might get that severe, severe exhaustion type of feeling." So this description was coded to the theme exhaustion and map well to an item in the PROMIS item bank reading in the last seven days, how often did you experience extreme exhaustion? So in the second set of interviews, the cognitive interviews or cognitive debriefing, we tested how these [00:16:00] mapped PROMIS items performed. Were they interpreted correctly? Were they easy to understand and answer? Were they relevant to the participant's fatigue experience? And were the participants able to select a response option? You can see two examples here. One item performing better than the other. The second question was interpreted correctly by all, but depending on the participant's different family situation, [00:16:30] several found this item to be difficult to answer or not relevant to their specific situation. This theme overlapped with another question, so this item was not included in the final short form.

So this is the resulting PROMIS fatigue mitochondria disease short form. It consists of nine items assessing both fatigue experiences and fatigue impacts. And [00:17:00] there is a manuscript describing this development and establishment of the content validity that has been submitted for publication, and as of yesterday, it's also accepted for publication. So the final paper should come out very soon, but it's also available online as a pre-print, and you can find the address here. And of course there is remaining validation work to be done and that needs longitudinal data, and that will be performed [00:17:30] using trial data from the ongoing interventional Falcon Study.

One benefit of a patient reported outcome, and this was also touched upon earlier today, is that if we use an electronic capture system, we can actually assess this outcome in the participant's usual environment, not after traveling to a clinical trial site, which may be exhausting in [00:18:00] itself and exacerbate the fatigue. In this ongoing study, the participants answered the questionnaires in their home before traveling to the sites. So the preparations for the ongoing Falcon Study, based on the work I've shown you, came to the conclusion that it would be valuable and feasible to assess both fatigue and myopathy as primary objectives in the study and to have clinical [00:18:30] outcome assessments for each as primary endpoints. We have two primary endpoints, the fatigue scale and the 30 second sit to stand test for myopathy, and they are alternative primary endpoints. We're using a Hochberg step up

procedure for the statistical analysis. And that means that the study is positive if either of the two endpoints or both demonstrate benefits.

[00:19:00] The Falcon Study also includes several other important design features. Especially for fatigue, we wanted to ensure consistent levels of chronic fatigue. For example, avoid regression to the mean phenomena if we happen to assess the patient on an especially bad day or week. So we therefore have an extended screening period or run in phase where we assess fatigue every week. And the study also included an interim analysis which was completed last [00:19:30] year. And this interim analysis assessed safety, futility and sample size reassessment. This was done by an independent data monitoring committee, and they assessed that there were no safety concerns and that the study could continue as planned. And both of the endpoints passed the futility threshold, and the study is now in its second wave of recruitment to include in a total 180 patients.

[00:20:00] So the conclusion from the KL one triple three development program, leading up to and including the first part of the Falcon study, is that it is feasible to study both fatigue and myopathy in an interventional trial for mitochondrial disease. Both symptoms are common in adults. And collaboration between stakeholders, including the FDA, patient advocacy groups and expert clinicians and industry enable the successful development of a mitochondrial disease specific [00:20:30] fatigue, COA, to be used as a primary endpoint. And we have established content validity for the PROMIS fatigue short form. And this has enabled a patient centric study with two primary objectives and endpoints reflecting the highest ranked needs from the Voice of the Patient. Thank you.

Susan Winckler: Thank you so much Dr. Hansson. We're going to hear one more presentation and then we'll invite you back for [00:21:00] a question and answer session. So thank you for that comprehensive overview. I'm going to turn now to Dr. Chad Glasser who serves as the senior director of clinical research at Tisento Therapeutics. Dr. Glasser, we are looking forward to your presentation. Please proceed.

Dr. Chad Glasser: All right, thank you so much. I think my presentation is the last formal presentation of the day, so it's definitely going to be a reiteration of a number of points that other speakers [00:21:30] have made, but hopefully it'll serve as kind of a case study of how one may go about addressing all the challenges that we've been discussing and pulling all of that together. So I did want to quickly talk about who we are and give you an idea of why we were invited to speak. Now, me personally, I've worked on this molecule in this program for a little over six years now and was part of a prior Phase 2A MELAS trial that was conducted by Cyclerion Therapeutics. And that study generated some encouraging [00:22:00] results that spurred the creation of Tisento almost two years ago. Since then, we've been focused on developing new medications to treat serious diseases, and the first disease we chose was MELAS.

I don't plan to talk a lot about our investigational drugs, but in short, it's an oral once daily soluble guanylate cyclase stimulator, and that it is CNS penetrant, which is one of the main reasons that we did choose MELAS as our first indication. [00:22:30] As you can see, this is our only program, Zagociguat, and the phase 2B study, which we've branded as PRIZM, has been and still is our entire focus as a company. You can see we're based in Cambridge and much like other sponsors that are still dedicated to the space, we are relatively small. We have a committed team of 12 internal employees. And I think that's important to note because unlike other larger sponsors that might have maybe more funding or more diversified portfolios, the stakes are really high for small companies like us that are [00:23:00] really dedicated to a super challenging rare disease such as MELAS. And because those stakes are so high, we are spending a lot of time and a lot of energy and thought and putting as much rigor into the program as we possibly can. So that's all I wanted to say about Tisento.

The way that the presentation is kind set up is I'm going to go through four key challenges or milestones that we had to kind of progress through as we designed our study and as we conduct it. I do want to mention upfront that this entire presentation is focused on [00:23:30] the challenges we are encountering developing a drug for adults with MELAS. I know up until this point, we've talked a lot about PMD in general, but this is really a specific example of challenges within that [inaudible 00:23:44] patients. So I think the first challenge is, to me, foundational and arguably the most important challenge because it impacts everything else that I'm about to talk about. Obviously the sponsor can determine whoever they want to enroll in a study and define that population however they want, [00:24:00] but it's always been our goal to say that this study is truly a MELAS study and have that be supported by the medical community. And unfortunately that did take us a bit of time and a lot of work to get to a point where we do feel like that is indeed the case.

So why does it matter to have a consistent disease definition? Well, obviously if you have different disease definitions or a morphing of how a disease is defined over the years, you can't go back and look at prior research and estimate prevalence accurately, you can't really predict how feasible your clinical trial is going to be, [00:24:30] so you're kind of starting from scratch. So what do we do? We talked to a lot of experts in mitochondrial disease very early on, we talked to patient advocates, we learned about how they were talking about their disease, and we quickly realized that the field was wrestling with this and they did not know how to group patients together into these multifaceted syndromes that oftentimes ended up overlapping. The KOLs would actually ask us, "What is your definition of MELAS?" And we were like, "No, you tell us. You're the experts." [00:25:00] And I think in a perfect world, the community would be aligned and the sponsor would not have to do all that extra work, but unfortunately that really wasn't the case for us.

We did our best to scour literature and search for any MELAS relevant publications, but as you start to dig into those papers over the years and look at how MELAS was defined, you realize that only a small subset of the MELAS

patients truly had MELAS. We talked a little bit about diagnostic criteria for MELAS, and that goes back 30 plus years, [00:25:30] which was the first attempt published by Dr. Hirano. And then since then, there's been a few other iterations and varying approaches to defining MELAS. And I think also important to note is that in more informal settings, MELAS has also been used almost interchangeably with someone that has a 3 2 4 3 mutation and that has some degree of symptoms, and that's kind of shown here. This has greatly overestimated, I think, the number of true MELAS patients that are out there. And I think [00:26:00] in the spirit of transparency, when we went into the study, we thought that there would be a lot more enrollable patients.

And as of now, as we talk to clinical trial sites and they look at their individual patients, that number does start to dwindle as they look at the new patient or the patients with kind of the new criteria. So what is the most accurate disease definition that we're working towards? I think as we've gotten closer to present day, the nomenclature has gotten better and we're starting to equate MELAS patients with patients that do have a history of stroke- [00:26:30] like episodes, but then the question became whether you should group nuclear DNA patients with mitochondrial DNA patients. Are they different or are they the same? And this is basically where we landed after doing our best, again, to tap all of the experts in that MELAS is defined as only MTDNA, does not have to be 3 2 4 3 combined with the history of stroke-like episodes. And so going back to our protocol and our eligibility criteria, we knew that we had to provide pretty strict guidelines to ensure that we are [00:27:00] enrolling the right patients and not adding additional variability.

The other key part is embedded in the definition of MELAS is what a stroke-like episode is, and so that was another challenge that I won't go into. Just mentioning that we had to deal with that as well. So what did we do? On the right, I'll start to build this slide with all the things that we've done to kind of design PRIZM. We, again, talked to all of the key stakeholders. We had a lot of conversations with [00:27:30] them early on, we met with the FDA, got their feedback and support on our disease definition, brought [inaudible 00:27:35] to that interaction and talked to advocates along the way. There's also been a handful of disease definition meetings that have been focused initially on defining MELAS that we've tried to catalyze and really support, without biasing of course. And from what we've heard, it's still challenging to get everyone on the same page, but I think in general there's an appetite to kind of change how syndromes are grouped together because it can be relatively [00:28:00] limiting and also cause a lot of confusion that's unnecessary.

And I think moving the field more towards a place where you're defining a patient based on what their genetic mutation is combined with what their key symptoms are makes things a lot more clear. So that's really our approach with our MELAS study is saying that these are NTDNA patients that do have a history of stroke-like episodes, so we feel pretty confident in that definition. So now we had some acceptable criteria for MELAS, and then we had to do some work to really define that [00:28:30] specific patient pool and understand that disease

experience. And remember that the definition of MELAS has kind of morphed over the years, so we couldn't easily go back and refer to prior work. Again, we've talked about a lot of this earlier on in presentations, but we know it's complex, it's multi-system, it's heterogeneous, and that's shown by the graphic showing pretty much everything that could happen.

As we know, not all patients have every one of these. Some have a few, some have a lot, some have milder manifestations in some organs and more severe ones than others. [00:29:00] And they also all differ in terms of how they progress. And important to note, key symptoms like stroke-like episodes and seizures are relatively infrequent in most patients and are also super difficult to predict. And also kind of thinking about where this graphic came from, it came from clinicians and researchers, and it also doesn't necessarily take into account the patient experience. So we're looking at a lot of these things in our trial, but given that the patient numbers are so small, not every patient will have each one of these, [00:29:30] it's difficult to figure out where you should focus your efforts and, again, what you should put in your primary outcome measure. So like others, and like has been discussed earlier, we turned to patients and really asked what the most frequent and bothersome symptoms of their daily life was.

And again, similar to other work that's been done in broader PMD, which is very valuable, we wanted to do similar work specifically in MELAS because we know it is a unique disease presentation. So that's what we did. We conducted a patient and expert qualitative interview study very similar [00:30:00] to what Dr. Hansson just discussed, but this time we, again, entirely focused on patients with MELAS based on our definition. And by doing this, we were able to really focus the selection of our outcome measures on what is most frequent and most meaningful to patients and use that to build our overall endpoint model. So, we don't have a lot of time to go into the detailed methods or findings from the study, but this is probably the most important takeaway from the study. We asked open-ended questions to patients with MELAS and basically continued [00:30:30] until we reached saturation. And so we ended up with 16 patients and these were the most frequent symptoms or concepts that were most frequently reported by patients and we also have the physician percentages here as well.

Similar to the graphic that I showed on a previous slide, this is again, a very long list, but at least there's only nine terms that are in more than half of the patients. And when you start to look at themes and types of complaints, it's a combination of what we've been hearing a lot from other presentations [00:31:00] of being tired and energy depleted, AKA different aspects of fatigue, but also unique to MELAS are the mental processing challenges and cognitive difficulties. In addressing the note two are some of the other symptoms like stroke-like episodes and seizures, which we talk about a lot in the medical community. Those are reported less frequently, most likely because they are occurring less frequently and because there are more important symptoms from the patient perspective like fatigue and cognitive impairment that are more

continuous, more chronic and are actually impacting every day [00:31:30] of their life.

So, challenge number three, we have an accurate definition. Now we have an understanding of what the most frequent aspects of MELAS are. For the patient, now the question becomes how do you assess improvements in the disease? And as we've said, we went into this knowing that there's really no one-size-fits-all, sensitive, validated outcome measure that's able to assess treatment effects specifically in patients with MELAS. And I think the most historically [00:32:00] referenced validated measure that is generalizable is the NMDAS score in the context of mitochondrial disease. And it's great that it is all-inclusive and assesses pretty much anything and everything that could be impacted by mitochondrial disease. But because of that, many of the individuals or many of the questions and the assessments, they don't apply to every individual that the test is administered on, which of course decreases the sensitivity and makes it difficult to use in a study that is a year or less [00:32:30] in duration.

In terms of biomarkers, we've talked about limitations there. I think there's some front-runners like GDF-15, but there's still nothing established or widely accepted. Luckily, Abliva and Dr. Hansson and the team did a lot of the legwork and came up with their PMD short form specific to fatigue. And so that was a great place for us to start to measure fatigue. And so we further adapted that a little bit based on some of the findings from our qualitative interview study to make it more specific [00:33:00] to MELAS. So, we had a path for fatigue, but cognitive health and cognitive impairment has always been an enigma, I think, in mitochondrial disease. And so we knew we needed to do a lot more work there. And in terms of other studies that have enrolled MELAS patients, they were more focused on myopathy symptoms and muscle function. So, again, six-minute walk test was used a lot. But none really tried to evaluate some of the neurological manifestations.

When we went to the FDA had initially [00:33:30] proposed a PRO approach to assess cognitive challenges using some PROMIS scales, but they encouraged us to look into performance outcome measures that could more objectively measure cognition. So, that was really the approach that we prioritized from that point forward. We're also going to be doing some exit interviews at the end of our trial to better understand what improvements on those cognitive tests actually mean to the patient. And then finally, we've been talking a lot about adequately [inaudible 00:34:00] [00:34:00] the study. That will always be a challenge in rare disease because, obviously, the limited number of patients. So, we looked at any and all study design options and ways of combining endpoints and basically came up with the following.

So, our PRIZM study I think has two very important attributes that are very, very key to both, one, increasing power and also increasing our ability to overcome patient heterogeneity. And that's the fact that it's a crossover design and that we're [00:34:30] using a GST analysis approach, which is predefined the primary endpoint. The other key aspect, and again this is similar to Abliva's program, is

that we are collecting data at home on fatigue and cognition using both PROs and cognitive performance measures. And so this allows us to collect more continuous data and remove some of the confounders that impact performance at in-clinic visits.

So, this is a high-level study to design. Pretty standard, [00:35:00] randomized, double-blind placebo controlled crossover study. We have a three to six-week screening period, two twelve-week treatment period separated by a four-week washout. We're looking at two dose levels. So, participants are randomized to one of four sequences, and so they'll both receive active drug for 12 weeks and placebo for 12 weeks. And obviously the reason that this is important is because each patient will serve as their own control and that increases power and removes the need to stratify as [00:35:30] you would need to if you were doing a parallel study. We will be comparing weeks eight through 12 on active and weeks eight through 12 on placebo. And so we'll be averaging those last four weeks of each treatment within each subject. We're also, as you can see, planning to do an open-label extension study to collect long-term safety data as well as some additional biomarker data and more objective assessments, and some other clinician-administered assessments of disease.

And with this design, we're able to get pretty good power with just 44 [00:36:00] participants. And I'll talk a little bit about another way we were able to increase our power on the next slide and also address some of that issue of heterogeneity. So, like Abliva, we're also trying to find ways to incorporate multiple outcome measures into our primary endpoint. Of course, we have our primary objective of safety that's related to safety, but when it comes to our approach to measuring efficacy, we've combined three separate outcome measures aimed at assessing fatigue and various aspects of cognitive [00:36:30] function into, again, a global statistical test. So, the one measure is the fatigue-MELAS PRO, which I just spoke about. And then we'll have two other tests of very distinct cognitive functioning that we learned from the prior interview study and also from baseline data from this current study, are quite impaired in this patient population.

So, one of those is going to assess executive function. That's the Groton Maze test and the other assesses attention and processing speed, and [00:37:00] that's the Digit Symbol Substitution test. Now, all of these are done either weekly or biweekly at home, and if they are trending in the same direction and if they're not significantly correlated, each should theoretically contribute to an overall greater effect size or greater global treatment effect. These approaches, our GST approach and the crossover design, they have their own sets of assumptions and associated risks. We heard about carryover earlier on, but in comparison, a parallel placebo-controlled study with a single primary outcome measure [00:37:30] would require three times the number of participants to achieve similar statistical power as the study that we are conducting. And of course, that more traditional approach is oftentimes preferred by regulators, but it would have its own risks because it would be almost impossible to fully enroll, especially within the context of MELAS.

So, speaking of enrollment, this is where we are right now and where we're putting all of our efforts. Enrolling a MELAS study will say has been much harder than we anticipated. [00:38:00] We knew that other studies have failed due to heterogeneity in their patient population. That was one of the keys to our potential success. But obviously, when you're really thoughtful about the patients you're enrolling and ensuring that homogeneity, you're really limiting an already small patient pool. In terms of timelines and enrollments, they're extremely hard to predict for a lot of reasons here. There's no precedent or similar MELAS trials for comparison. I know a number of other trials have been termed MELAS studies, but they didn't [00:38:30] actually enroll MELAS patients, meaning they didn't have history of stroke-like episodes.

Regulatory environment is also very unpredictable and can be quite long. Site delays is a huge challenge for us. There's a lot of red tape and a lot of budget and contracting that needs to be done. Sites are stretched thin. There's a lot of work that they have to distribute across their teams. There's training we're requesting them to complete. Even scheduling an SIV takes time. There's also a limited number of sites with [00:39:00] mitochondrial expertise. They're primarily academic institutions. So, again, typically a slower startup. And these are complicated patients. So, we're looking at patients, we're trying to find patients that are pretty stable and they're not too severe, not too mild, just so we can see a pretty clear treatment effect, but again, that's limiting our pool even more. And then finally, I think we just had a number of patients that have said right out of the gate that they don't want to participate in clinical research, which is extremely discouraging, but I totally appreciate that there are patients [00:39:30] that don't want to rock the boat and it is a burden to take on. So, we're wrestling with that as well.

So, what are we doing? Well, we're making the study as attractive as we can. We have at-home visits. We're doing all of our outcome measures and our primary endpoint remotely. We're trying to reimburse patients for their travel expenses. We're also trying to get them access to drugs. So, as part of the crossover design, they will get access to study drug no matter what, and then we'll have the open label extension on the heels [00:40:00] of that. Beyond the study design, along the lines of execution, we have just initiated more sites. We have 25 sites to be exact, globally, which means one to two patients per site to get 44 patients, which seems extremely doable. But for the reasons that I've outlined on the previous slide, it has been slower than we had hoped for despite having, what I would say, are pretty good relationships with most of our trial sites.

One of the more recent challenges we encountered I think is important to mention was a string [00:40:30] of screen failures due to how rigorous our entry criteria were. We were realizing that we were unnecessarily screen failing patients that did have true cognitive deficits because they were doing too well on their memory tests that we had prioritized. So, we collected data from the first eight patients screened, and it would show that the deficits that the patient reported as memory were actually more so related to deficits in processing

speed and executive function, which was a huge realization because again, cognitive health is underappreciated [00:41:00] in this population and a lot of work needs to be done.

The last word on this slide unfortunately is weight. And I think it's a sad realization that sometimes these things just take time, but it's still no reason for us to not continue trying to do everything we can to speed things up. And I think that really does take all of us. It's not just on our shoulders. It requires regulators and clinicians and sites, patients to engage and participate, think outside of the box and problem solve. And I think honestly, we [00:41:30] can do even more than what we're currently doing.

So, in summary, I'm obviously biased, but I think the best approach, this is the approach that we've taken, and I think it's the best approach we could have taken given the cards that we were dealt. I think we wouldn't change a thing based on what we know right now, and it remains to be seen whether these approaches would be successful, but I hope that they will at least spark some additional conversation. I think the last comment I do want to make, and similar [00:42:00] to what Dr. Keras said earlier, is that I think we all have to be open to new ways and thoughtful ways of doing things and recognize that practically any research that we do in this space, despite our absolute best efforts, are still going to have limitations. And so I think these are complex diseases and we need new innovative ways to assess them. So, sorry I went over by a minute, but I want to thank the folks [inaudible 00:42:25] for the invite and welcome any questions.

Susan Winckler: Excellent. Thanks [00:42:30] so much Dr. Glasser. And we're going to invite Dr. Hansson back to the stage. I've got some questions that have been coming in the Zoom Q&A function. So, I've got one specific for Dr. Hansson and one specific for Dr. Glasser, and then I have some broader ones. But Dr. Hansson, there was a question related to, and you addressed this a bit, but I think it's worth giving a little more [00:43:00] time to it. A question related to potential perceptions of redundancy between exhaustion and loss of energy. And the question the individual said that as a patient they might be irritated by the redundancy or mystified by it. Just tell us a little bit more about your teasing out the exhaustion and loss of energy.

Dr. Magnus Hansson: [00:43:30] Well, in the short form we developed, there are a few different questions, but the whole idea is to capture the different nuances of fatigue. So, as a question, how often did you feel tired? How often did you feel extreme exhaustion? So, those are slightly different nuances where one may respond differently. Maybe you and I would also [00:44:00] say, "Well, sometimes we're tired, but very rarely extreme exhaustion," unless we've done a marathon or something similar. So, that was the whole purpose to try to capture as many aspects of fatigue as possible, but still not making the form too extensive because as Dr. Glasser said, if you have a lot of questions that may not be relevant to some patients, you lose [00:44:30] sensitivity. And here, it's also the risk of creating fatigue by having too many questions for patient to answer.

And that's something that I think we've all faced when we develop these files that in the beginning we may think it's good to include this and this and that, but in the end, we have to keep patient in trial. They have to be able to [00:45:00] address the questions accurately, and we cannot create too much trial fatigue. And that's also sometimes a question we need to have with the regulators because we may get pressure, well, why don't you include several functional tests? Well, of course there's that aspect that it may not be feasible to run it anymore, but it's also that then we need to set inclusion and exclusion criteria that are fit for purpose for each individual test, and in the end, we may have no [00:45:30] patient left to include. I don't know if that exactly addressed the question, but some nuances to it at least.

Susan Winckler: Yes. No, that's very helpful. And then Dr. Glasser, there was a question related to what you were speaking about towards the end of your remarks and the challenges in recruiting, and particularly that there were individuals who may have been eligible, but they were hesitant to participate in clinical research. [00:46:00] The question was a bit more of an observation of there are, [inaudible 00:46:08], there's often folks who are ready and anxious to participate. And so did you want to say anything more about how you've reflected on and navigated that? I know you had some interventions, but I want to give you space to say something more if you'd like to.

Dr. Chad Glasser: Yeah. I don't have a ton more to add. I think it's something [00:46:30] that we're still trying to better understand. I think tracking pre-screen failures at clinical trial sites is difficult. We tend to track more the patients that actually come in and that review the consent and decide that they don't want to participate. But we are hearing from sites that there are some patients that, for a number of reasons, like I said, I think probably the number one reason is that despite our best efforts, the patients do have to still come into the clinic a handful of times over the course of seven months [00:47:00] and it can be a lot to ask. We're trying to do things at home, we're trying to pay for travel expenses, but there's really not much more I think that we can do on our end to make the study more attractive to patients.

I think we're trying to do as much work as we can with UNTF and MitoAction and other kind of global patient advocacy groups to build some understanding of clinical trials and make people feel comfortable with that. But I think, again, it takes all of us. It takes sites having good relationships [00:47:30] with the patients as well to be able to articulate what the study is and why it may or may not be a good fit for them and build that trust. So, I think it really has to, dependent on the site and dependent on the investigator, but it is definitely something that we're trying to better understand as we go forward.

Susan Winckler: I'm struck, as you say that that it may be, we've been talking about how the community is doing more and aspiring to work together, that this idea of the value of participating [00:48:00] in clinical research may be even a place where that would be helpful to have the entire community talking about that because it would seem to be a barrier that cannot be overcome without patients. We will

not see therapeutic development in this area, absent patient participation in the clinical research.

Dr. Chad Glasser: [00:48:30] Absolutely. Yeah. We're stuck.

Susan Winckler: Yeah. Threshold challenge. So, then let me still focus on the patient component, but this is a broader question and earlier in the recruitment stage, I guess. Are there efforts that can be done to help ensure that patients and potential patients are properly diagnosed and diagnosed faster in the PMD space? [00:49:00] And I know Dr. Glasser, you had mentioned this a bit in narrowing down the MELAS place, but I'd welcome you Dr. Hansson, if there's thoughts about, either of you, thoughts about is there an opportunity to improve diagnosis generally and speed to diagnosis?

Dr. Chad Glasser: Yeah. I can start. I think the question is what diagnosis do we want [00:49:30] to have and how do we want to approach that? And what do the patients want? I think a lot of patients want to know, I have MELAS, for example, and that's what they've been telling everyone. If we do move away from that, and like I said, if the field starts moving more towards, let's make sure that you have your genetic diagnosis, we know what is causing the phenotype, and then just describe the phenotype in the most accurate way. And again, knowing that every patient is so different, if a patient is comfortable with saying, "I have this mutation [00:50:00] and also have these impairments and I have muscle weakness and X, Y, and Z," that is a diagnosis in and of itself.

And I think sometimes we're how we're trying to group patients together. And a lot of that is on the sponsor side because they're trying to do it for their studies. But I think that's the thing that we're wrestling with is, what is the diagnosis itself and making sure that we're not over-complicating things. [00:50:30] I don't know. Dr. Hansson, if you have anything to add to that?

Dr. Magnus Hansson: Well, one comment, represented here, we have a group of very dedicated physicians who are both on the research and care side. And I think that is especially rewarding to work in this area, that there is this sense of collaboration and genuine interest from different sites. But I think a lot [00:51:00] of patients may not have access to those few specialist centers that are out there. And I know there's a huge effort to try to spread awareness. And there are also some central repository, for instance, how to interpret genetic tests. And I know that those are used throughout the world. So, a big shout out to all of you who are doing so much important work.

In relation to diagnosis, I know there can be some access [00:51:30] issues to get genetic testing, especially here in the US and I know there are also efforts underway to try to spread that. Then we also discussed, or we talked about the natural history studies that have been initiated, and I think that's a fantastic source for us to learn more, but also purpose of them [00:52:00] are to try to guide patients to an appropriate interventional trial because most of them may not see the doctors of the trial sites that we have engaged. So, the wishlist from

my side would also be this visibility of one site, transferring patients to one of the sites that both have the expertise in mitochondria disease and have the clinical trial experience because those are two different sets of expertise. [00:52:30] And up until now, there's been only a few centers that have that expertise. But with the groundwork from Stealth, for example, those number of sites have really expanded and been really helpful for our program.

Susan Winckler: Great. That's helpful and just important as we think about the different dynamics there. I want to note that we did get a question that was more of a, I'll [00:53:00] say it was a tip for the two of you, which you probably already knew, but I think it's a good reminder to all of us. And it came from an individual who is a clinical research coordinator, and that individual noted that consistent sharing of treatment outcomes, sorry, the trial outcomes, consistent dissemination of trial outcomes is a [00:53:30] great incentive for the participants in seeing what it is that they've contributed to. So, I'm confident that that's in the plans that each of you have, but wanted to share more broadly because it was a great comment from one of the folks who has joined the event. So, now I want to ask, yep, go ahead.

Dr. Magnus Hansson: Yeah. Dr. [inaudible 00:53:56] mentioned the initiative, TREAT MITO, which is an [00:54:00] effort to collect that data from different sponsors after the trials and that's a really important initiative.

Susan Winckler: Yes. To share and say, "All right. Here is what we've learned and how it's been contributed." So, now I want to ask a question. Earlier today, this question got asked to FDA, and so now I'm going to adapt it for both of you. And that question is, it's the question that's asked in [00:54:30] every program every day. How are you thinking about applying artificial intelligence and machine learning in these? So, I'll say, or are you, my assumption that it is probably being applied in ways and thinking about setting baselines and clarity around endpoint selection and evaluation. But I'll throw it to the two of you or maybe it's what are you thinking about in the AI [00:55:00] and ML space? Is there, and I should preface it, is there an application here?

Dr. Magnus Hansson: Well, I think, sorry, go ahead [inaudible 00:55:07].

Susan Winckler: No, go ahead.

Dr. Magnus Hansson: Okay. Well, I think there are tremendous possibilities, but right now my understanding is it's like the million-dollar question. Whoever figures out how to use it the best first will have a huge benefit. And of course, the benefit to the whole community. And I think we're all [00:55:30] learning to use these tools and agents slowly, but I'm pretty sure it will soon explode.

Susan Winckler: And explode in a good way. That's how I heard it. Dr. Glasser, what might you add to that, if anything?

Dr. Chad Glasser: Yeah. We're definitely not there yet. I think we've talked about it as a team and places that we could potentially incorporate it. I think one thing that we've tried to do a little bit is some literature reviews and [00:56:00] papers, and being able to feed different manuscripts into that and have it summarized, that's been somewhat helpful. Sometimes you obviously have to double or triple check the outputs from that. But obviously any source of big data, really challenging outcome measures. We talked about mobility assessments and at-home monitoring and actigraphy, I think that's one of the opportunities that just keeps coming up over and over and over again. [00:56:30] It's like consider that, but no one has figured out how to deal with that amount of data. So, I think that is just one example of many where I think AI could come into play.

Susan Winckler: Yeah. Excellent. I want to give you one last question before we allow you to wrap up your time with us. And this one has to do, each of you is clearly, you're having interactions with FDA and other regulators. What might you say is an [00:57:00] ideal way to engage with regulators in this space? Is there one thing that you've found has been helpful? I'll give you a stage to say, what have you learned and what has worked well in regulator engagement?

Dr. Magnus Hansson: It's a good question. I remember when I first bought a house, the recommendation is [00:57:30] that in order to buy a house, you need to have done it before, to know what you're actually doing. And it's almost the same doing a clinical trial. And I think Dr. Glasser described that quite well, that taking a step back and thinking. We certainly had an opportunity due to the interim analysis to also look, okay, what can we learn in relation to screen failures, etc. But specifically, I think it's [00:58:00] worth, and I think the agency staff already know this, but the preparations that we do and all the parallel activities, that's several years activities. So, the hints and suggestions we get are very useful, but they often take a long time to implement. So, some of the advice that we maybe received four years ago, well, now [00:58:30] we can implement it. So, it's important also from the sponsor side that the recommendations from the teams are consistent throughout the years. Of course, we need to implement what we learn, but consistency is really important for us.

Susan Winckler: And it would seem with that sort of temporality, just being diligent in what is it that you've been told and when can you apply it? Chad, we'll give you the last word there.

Dr. Chad Glasser: Yeah. I think obviously [00:59:00] the guidance from the FDA has come early and come often and keep that line of communication open. So, I think we're trying to find that balance. There's going to be a lot that we will know at the end of this trial, and there's a lot of things that we've thrown into the study that will hopefully prove to be successful. So, I think that's really a key milestone for us where we can have really robust discussions. But as we've gotten to this point, we've been as transparent as we can. Share reports from [00:59:30] our interview study, for example, and keep them updated on how we're thinking about outcome measures. And we're generating more data, which we'll eventually be ready to discuss in more detail. So, I think it's providing that

context when the time is right, and I think, again, engaging as much as we possibly can.

Using What We've Learned To Move Forward

Jason Colquitt, Across Healthcare
Amel Karaa, MD, Massachusetts General Hospital & Harvard Medical School
Kerry Jo Lee, MD, Center Drug Evaluation and Research, FDA
Sophia Zilber, Lived Experience Perspective

Susan Winckler: Excellent. Well, doctors, Hansson and Glasser, that was just so instructive in giving us practical examples in the things that you've worked through. So, thank you for [01:00:00] sharing your insights with us today. We greatly appreciate it, and now we're going to turn to our final panel. And so, let me gather, I'm going to have folks who are joining me on the screen here, and particularly, we're going to gather perspectives from four corners of this community, and challenge them to engage and reflect on the content that was shared throughout today, and to help us align for the future. How do we apply the learnings to [01:00:30] help patients with primary mitochondrial diseases? And so, I think we've got all four of our folks who are on camera and ready to go. And so, I'm going to introduce each of them as I call on them, and first, I'm going to turn to Sophia Zilber. Sophia, you wear many hats in this space, including that of a parent of an affected child. Could you share a snapshot of your story and what you found most impactful [01:01:00] in today's presentation?

Sophia Zilber: Thank you so much. As you said, I wear multiple hats. I Am a mom. I lost my daughter, Miriam, to Leigh Syndrome when she was just an infant, which is what first brought me into this community. This happened in 2017. I'm also blessed to be a mom to three healthy boys. They're wonderful, and they keep my life very full. I'm also professional. [01:01:30] I've worked in a pharmaceutical industry and still working, and I have been there for over 20 years in statistical programming, focusing on clinical trials, data analysis. This background gives me unique perspective on how data is used to support decisions in drug development. In the Mito community. I also wear several hats. I lead the Leigh Syndrome Global Patient Registry with Cure Mito. It's where I've been able to really bring together both sides of my life, my personal [01:02:00] story, and my professional expertise, and be able to build something that can accelerate research and support families.

I'm also trying to fill in the gaps that I experienced myself as a parent. I worked closely with Critical Paths Institute for the past four years to promote the importance of data sharing within the Mito community and help launch the Mitochondrial Disease Task force, which has over 20 members currently, and I'll share more about the task force [01:02:30] during this panel. Beyond that, I also support many rare disease groups with their patient registry when needed. I've led workshops. I've led and participated in multiple working groups on registries, data federation, data analysis, and things like that. I've created educational tools and have done a lot in this space. I would like to thank the FDA

and the Reagan [inaudible 01:02:57] Foundation for organizing this meeting and for inviting [01:03:00] me to speak here. I would like to thank all speakers and panelists who spoke so far. It's very encouraging to see that the FDA is focusing on myocondrial disease, and that FDA has provided several very thoughtful presentations that really help guide our community forward.

I'm going to highlight a couple of them. I found Dr. Chow's talk very informative. I think, first of all, it was great to see the definitions of how FDA defines [01:03:30] safe, effective, evidence of effectiveness, either put in well-controlled studies. In a meeting like this, where we have many people from different backgrounds, it's really great to bring everybody on the same page and understand what does FDA really mean? What are we talking about when they say the drug is safe and effective? This context is extremely helpful. It was very, very helpful to hear the thinking behind their endpoints and population selection. I think we all [01:04:00] know these topics are very frequently discussed in these communities, so it's very reassuring to see that there's really careful consideration behind it. Also, thank you for sharing the links to the relevant draft guidances. I haven't read them yet, but I definitely will go and look back into them.

It was also helpful to see examples of recent drug approvals in our other rare diseases. I also would like to thank Dr. Noble and Dr. Yang for their very important and very helpful presentations. [01:04:30] Again, it was great to see the definitions of clinical outcomes, assessments, endpoints, and other key terms that are used. It was really great to hear about the flexibility in trial design, such as the option to use different primary endpoints for different subsets of patients, hearing about clinical outcomes' assessment, using a variety of measurements of measurement tools to assess whether treatment is working. It's really, really good to see these very innovative [01:05:00] approaches being considered. It gives us hope. I look forward to learning more about this later on, and these are my reflections on the meeting so far. Thank you.

Susan Winckler: Excellent. Thank you so much, Sophia, and thank you for your contributions to this community as well. So I want to then turn to Jason Colquitt, and we'll all stay on screen and contribute to the conversation, but Jason, as CEO [01:05:30] and founder of Across Healthcare, you bring a technology bent to the table, which we've brought up a little bit in some of our Q&A, but it hasn't been a significant focus, but what inspired your thinking or challenged your assumptions in today's program?

Jason Colquitt: Thanks for the opportunity to speak, and this meeting has been great. It fills my heart with warmth to know people are focused, [01:06:00] because I actually have a mitochondrial disease that I didn't get diagnosed until 32, so like Sophia, this is a personal passion of mine, but I also support over 120 patient advocacy groups in the rare disease space, collect data, and this whole meeting is about data. How can we use that data, improve getting therapies to market? So, a lot of passion behind what I do professionally. I've been in this space for 25 years,

collecting data in the healthcare space, so [01:06:30] lots of insight, and that's kind of the lens at which I look at this meeting today, so it's been awesome to see the collaboration and the actual stakeholders you brought to the table today. Just thinking about this, a lot of times I see, because I've been in this clinical research world, the clinical researchers will come up with their endpoints, ask their questions of patients, and we've heard a lot about, "We want the patient voice into the equation.

So I loved hearing the pros that are being [01:07:00] developed, the assessments that we're looking at to better gather data, and I think it was in several the sessions, actually having feedback loops to those patients and caregivers about what is occurring. Then, I think in the last panel you actually talked about the data going back if somebody asked that question, so I think that's hugely important. All this is good, and to talk about the positivity and all the great things that are happening is good, but we all know there's good and bad [01:07:30] that occurs across the trials, the research that we're doing, and sharing that type information is hugely important. So, I think that's an important thing, and not that I came into this not knowing this, but listening to the conversations and hearing the variability of the different distinctions between the diseases and disorders, and deficiencies and things within this space, is huge.

So, trying to come up with the commonalities across those things [01:08:00] that we can apply, but also the distinctions between those that we can draw out was a big, big importance. We heard pediatric versus adult populations. We heard different body systems affected, so I think all of that is an important distinction that you brought to the table today, but then the thing that's happened to me is, I am not a statistician either, but hearing the numbers to power, some of these models, and the fact that we have really small [01:08:30] populations in some of these areas, breaks my heart. I want to make sure the technology side is not a factor in that for participation, and you talked about that in the last panel as well, so that's a huge pull on my heart of, how do we get significant populations to build these models so that we can model this stuff out?

So, those are just some of the reflections that I saw from my lens, as a technologist, and you're right, we touched a little bit on the technology side. [01:09:00] My heart is to make sure technology is not the drag, and we can empower. I'm a huge Clayton Christensen, disruptive innovation advocate, so how can we keep thinking of how can these digital technologies and these different ways to use technology software to better empower the agency, the sponsors, the CROs, the academics that are doing research in the space is a big pull on me. So with that, I'll say that, [01:09:30] just thanks for having me. Enjoy listening to the rest of reactions and the rest of this session.

Susan Winckler: Great. Thank you so much, Jason. Dr. Karaa, I'm going to turn to you, as we have talked with you, and we know you've been in many discussions about primary mitochondrial diseases and invested much of your career in this space, and we

appreciate your presentation from earlier today, but what other components of today's discussion [01:10:00] would you highlight?

Dr. Amel Karaa: Yes, thank you. This has been excellent so far. What I heard today from the patient advocate, from the clinicians, from the FDA, is how complex mitochondrial diseases is, so it's heartening to be all on the same page and understand the complexity of what we're dealing with. What I also heard is that everyone, all the stakeholders that we've heard from today, are very open [01:10:30] to learning from each other and to change the way they have been doing things, which is a really positive thing to see within this community. I think, over the years, since 2014 when we first started these clinical trials, we are already seeing a lot of changes happening with how we design the trials, how we select our patient. We've moved away from the basket trials and the heterogeneous population.

We're focusing more on genes, we're focusing more on specific [01:11:00] phenotype. We're also moving away from the six-minute walk test, which everyone really disliked in the past, and moving towards more innovative approaches to outcome, measure selection and the statistical analysis that might be better suited for this complex group of disorders. I think the most important message that I heard today is that we have a very committed community, and that we are all willing to share and work with [01:11:30] each other, and we are all willing to change the way we do things, and we remain very positive and committed to moving things along and moving forward. That is really the positive optimistic point that I want us to leap with today is that, yes, the task at hand is huge and it's very complicated, but we are all committed and we're all moving this forward together.

Susan Winckler: Fabulous. Thank you so much, Dr. Karaa. [01:12:00] So, we've got one more voice that we haven't yet heard. So let's round out this opening response. Dr. Lee, we're going to turn to you for the view from the regulatory realm. Now, your role within CDER and leading the Accelerator Rare Disease Cures program, you have this very broad view as it relates to the rare disease landscape, and so was there anything you heard [01:12:30] today that has the potential for impact for primary mitochondrial disease treatment development, and then something that might be more broadly applicable for the rare disease community? So, you get a two part.

Dr. Kerry Jo Lee: Fantastic. I'm happy to be here. Dr. Kerry Jo Lee, and I would say that reflecting on today, I think that the presentations, exactly as Dr. Karaa said, have really underscored the complexity, the diverse constellations [01:13:00] of mitochondrial diseases that we're seeing, and their phenotypes, not only across mitochondrial diseases, but within specific conditions themselves, and that can make it incredibly challenging, that level of heterogeneity, to really plan for and carry out successful drug development, particularly in rare diseases when you have very limited and small populations. And so, what I feel as though we have learned or heard today, that I think are particularly important to underscore,

[01:13:30] the understanding that defining and understanding the natural history is critical to inform drug development programs.

You really do have to spend time on the forefront in rare diseases planning these trials, because you don't want to find out in the middle of a trial. You don't have multi-phase development often, and there is not a population to just sort of try again, try again, and try again, and so natural history studies are really important. They characterize your patient populations, the heterogeneity within these conditions, [01:14:00] which covers the variance in characteristics, such as disease progression, onset, an expected course. Whether clinical courses naturally wax and wane, that's critical. Whether or not they simply decline, and if they decline, do they decline steadily or do they start and stop? Those are aspects that you really need to build into your trial or at least the adaptability to deal with those challenges as they come up. You don't want to find it out and not have built in any adaptability into your trial design in the [01:14:30] middle of a trial. You can also utilize natural history study to help you determine those subsets, right?

So, looking at your therapy, do you expect your therapy to have an effect or the same effect in all patients in the conditions that you're studying, or do you need to enrich for certain populations related to age or how the disease course progresses based on subsets or stratify patients in order to get an answer at the end of a trial? It also helps you identify and describe various types of clinical manifestations, their severity [01:15:00] and their time course and progression, and that is critical to determine endpoint selection, and not just what endpoint are you going to pick that you could expect to see, but within what duration, at what time point, when are you going to collect that endpoint in the trial? Because you don't want to get into a trial and just realize you could have run it a little bit longer and understood whether or not that therapy would've worked. So, those are the types of things that natural history studies are really invaluable to pull to inform.

So, therefore, they actually need to be conducted with rigor [01:15:30] and with an eye to what type of data collection should occur in that study to make it applicable to drug development. I think that that's one of the reasons that, as you know, Susan, we had the Reagan Udall, NIH, and Cedars Rare Diseases team's Natural History Study Workshop just last year, that you can still find online at various websites, including AHRQ or Reagan Udall, that really delved into those aspects. So, there's that, and then I'd say the other learning that I would just sort of point out, that I think I heard a little bit about, but sounds like it's early [01:16:00] in this space, is that there are people starting to look at biomarker development. Now, this is an evolving area, it sounds like, in primary mitochondrial diseases, but if you're exploring this type of work, in translational science, is really critical to drug development programs, illustrating the importance of translational science through AHRQ's cross-center collaborations.

We published two papers in the past year looking at two things, and non-oncological rare disease approvals [01:16:30] over the past several years. One

looked at endpoints over about a decade, and found that biomarkers are utilized as primary endpoints equally to clinical outcomes in rare disease drug development. Now, that's important, because these are often novel biomarkers, so they are not all slam-dunk, perfect, and have been completely related to clinical outcomes that we've approved. And so, therefore, the translational science packages that you're putting together to support the selection of those biomarkers is [01:17:00] critically important. Then, the last part on translational science, the majority of rare disease drug development programs are approved on one adequate and well-controlled trial and confirmatory evidence. Now, what makes up that confirmatory evidence? Often mechanistic and the pharmacodynamic data, as well as at times animal studies, non-clinical data from drug development. Those are aspects that are critical to utilize and investigate in your programs. AHRQ, actually, has [01:17:30] a translational science team that works with review teams to assess these types of data in rare disease drug development programs. I'll pause there.

Susan Winckler: Dr. Lee, I feel like we should all pause and then make sure that we've captured all of that, because that was so helpful. I had, throughout the day, thought back to that natural history meeting and thought, "Oh, yes. There's applicability," and "How is it that we might see the connection [01:18:00] and use the power of that potential and apply it here?" So, really appreciate that, and so I think we covered our reflecting on the day, what we heard, and some things that we're pulling together. I want to now turn us to be thinking about next steps, and what do we think the future might hold. And so, Jason, I'll give you the warning. I'm going to turn to you first, but would love for [01:18:30] you to share what you think a natural next step might be in this space.

Jason Colquitt: Sorry. I got to get off mute first. I didn't say one of the hats I wear, is I actually, my platform powers the Mighty Share, UMDF mighty share platform, so one of the things I really harp on, and [01:19:00] look across the community and see a lot of islands, and I think this meeting has been great to come together and I think we've talked about the unity and reflecting back, but how do we take that energy out of this meeting and take forth outside of this meeting? So, my next step is how do we centralize a lot of these efforts, or if there's something new that's going to be developed, does it look to others to tag onto [01:19:30] that island, rather than create its own distinct island? When we talked a lot about the Instruments that we use, I do a lot of migration of data from existing, you talked about natural history study, so I'm migrating data from one natural history study to on top of my platform.

It's interesting to see how different groups create their own data, not thinking about how the [01:20:00] standards, and I know Sophia works a lot in C dash, trying to create these standards, but it's how do we make sure we're all using standard, and we've talked a lot about that here, the standard instruments, the standard assessments so that we can share this data and reflect on it. We talked about the distinction of the community at large, tie a lot of this data together, so I think thinking a lot about that is what I was thinking about when thinking about the question you just posed of, "What do we take [01:20:30] next? How

do we centralize, work together, take the energy from this meeting and collaboration, and move that to the next level and put it to action in how we work and act in the days ahead?"

Susan Winckler: Yeah. Jason, that's really powerful, and then I'm struck, right? And in a way that would recognize the heterogeneity of the diseases that we're talking about, right? So, it's a space where there is [01:21:00] great value in the collective and working together, and then remembering the uniqueness of and just recognizing that there's heterogeneity there too. Yeah, great. Dr. Lee, do you want to go next, and help us think about what might be next?

Dr. Kerry Jo Lee: Yeah, sure. I think an important thing to remember is, as this community comes together and sort of hits the next [01:21:30] phase of what's on the horizon for drug development, you have to do it with the regulatory context in mind, upfront. I think that that's incredibly important. At FDA and CDER, what we've been doing, really, we've been working hard on the dissemination of information that we hope will really be helpful in moving the needle forward in addressing study design challenges for regulatory purposes. I would encourage the community to utilize and have an awareness of those resources. Some of them have to do, you saw a case study today presented from ARC's Leader [01:22:00] 3D program regarding the development of a clinical outcome assessment. That learning and education to advance and empower rare disease drug developers program or leader 3D, as we like to call it because we like acronyms and it's a lot shorter, it was really created to develop and expand educational resources that were identified as priorities from the rare disease community, as what they wanted to know more about how to create in sort of a regulatory context.

And so, we currently have three videos that are sort of describing [01:22:30] core principles in drug development that are helpful in rare diseases, as well as multiple case studies available on that website for use. We also love to come to workshops. We love to put on workshops and sort of help disseminate that information, but what we're also doing is creating sort of a repository in the website of those workshops, the AHRQ website for the workshops in perpetuity, right? Because you need those in time and the time that you need. You're not going to remember, say, [01:23:00] all the talking points we made two years from now when you need the information. So, we've been doing that. We've really been working towards cross disciplinary efforts to look at rare disease drug development design as well under AHRQ, and we're hoping to disseminate learnings and information from those efforts as well, because we understand that trial design in these heterogeneic communities is incredibly hard, particularly with small progressive, slowly progressive diseases and therapies that have modest effect.

Dr. [inaudible 01:23:30]'s presentation [01:23:30] was a good example of some of the approaches we've been looking at with the global statistic test. Then, lastly, I just wanted to point out the Rare disease Endpoint Advancement program, which is a pilot [inaudible 01:23:40] program that's looking at

endpoint construction. That has a disclosure clause that enables us to share learnings prior to the approval of therapies, and it's really a mechanism that enables sponsors to work more closely with us on their endpoint development. That is really critical, because you have to have a measure that you believe will reasonably detect the effect of your therapy [01:24:00] in a reliable and reproducible way, and the website itself has a wealth of resources that I would hope the community could avail themselves up when it comes to endpoint construction. All of those efforts are ways we're hoping to support the community, understand the regulatory context of the work that they're doing, and how to really ready themselves and position themselves for success when they bring drug development programs forward.

Susan Winckler: And the phrase that kept coming up in my mind, as you articulated those resources, Dr. [01:24:30] Lee, is that the work here has to be regulatorly relevant, right? It's the relevance and then the standard, and the only way to do that is to have a good sense of, what does good look like? You have to go into it with that construct, or we won't get to the therapeutic development that is thought here. I want to make sure that we get to [01:25:00] everyone with this question of, what does the next step look like? So Dr. Karaa, what might a natural next step be?

Dr. Amel Karaa: Yeah, thank you. I would echo what Jason said, about not trying to reinvent the wheel, to support existing islands, and build bridges from those. In that regards, I feel like the natural next step is to deconstruct and re-centralize, [01:25:30] and let me explain what I mean by that. A lot of the experiences that we've had so far have heavily relied on academic centers and single investigators doing a lot of the work within their institution, but there's so much red tape within those institutions. With the current funding environment, it's really hard to know what's going to happen in the future, where the data that has been gathered for many years is going to survive, where is it going [01:26:00] to end up, and who can have access to it? At the same time, when I look at rare disease drug approval, most of the successful programs have heavily relied on advocacy group, natural history, and registries that have been run by advocacy group.

To me, deconstructing is really steering a little bit away from academic center being the driver for all of this and putting the honors on the advocacy groups and having them [01:26:30] support these efforts. To that regard, what I have been trying, and I have to disclose that, at the moment, I am the chair of the Scientific and Medical Advisory Board for the UMDF. During my tenure, I really have been trying to, while creating this clinical trial consortium to treat Mito to try to look at the strengths of all the infrastructures that we have within our community, and how we can leverage those strength and trying to build [01:27:00] a robust, centralized infrastructure to hold all of the knowledge that we have acquired over the years.

We settled on having the UMDF be the custodian for all of these infrastructures. That is helping us support this new regulatory approved database that Jason has been running. And so, we rely heavily on people like Jason to make sure that all

we're doing is regulatory grade proof, [01:27:30] and that every changes that are implemented are implemented within what we are doing. And so, basically, centralizing these natural history studies that we have been talking about, which are so important for drug development into one place that is readily accessible to patients, but at the same time, that are also connected to those patients' clinician, where we can input information from both the patient perspective [01:28:00] and the clinician expert perspective all in one place, and we have had buy-in from industry now.

We are in the process of showing that this model might be the perfect model, not perfect, but one of the models that might work in the future. And so, I think we are still learning as we go, and obviously, there are going to be some changes that will need to be made over time, [01:28:30] but the interesting piece is that, with this approach, we have been able to engage other advocacy group. We are partnering with other advocacy group and with our international colleagues to try to build these harmonized, standardized, natural history study for specific primary mitochondrial disorders so that when we enter data here in the US, it's going to be the same data entered in Europe and eventually in Asia and South America, so that [01:29:00] we are all looking at the same problem from the same perspective, gathering the same information.

So, when we go to the FDA and EMA and other regulatory bodies, we have information that we gather from all the international cohorts of patients, because one thing that I have noticed by looking at data from all these past trials is that patients are different. Even though they have the same disease, the same mutation, a patient with MYELOS in the US is different from a patient with [01:29:30] Myelos in the UK or in Italy. That is really speaking to the other added complexity of environmental exposures, genetic modifiers, and where patients are born and what they have been exposed to, and so we can't just rely on one country or one advocacy group. We really have to put all our efforts together to try to have the most information about each one of these primary mitochondrial diseases, [01:30:00] so that's my de-constructed and re-centralized approach.

PART 3 OF 4 ENDS [01:30:04]

Dr. Amel Karaa: ... so that's my deconstruct and re-centralize approach, otherwise, I think the next wave of things that need to be done, and there are so many things that we need to be working on, is really the use of technology and digitized outcome measures, and tools that can support clinical trials and lessen the burden for patients so that they don't have to-

Susan Winckler: Sure.

Dr. Amel Karaa: ... go to the clinical trial sites as often [01:30:30] as they are doing now. Then lastly, I think giving what we heard from Chad about clinical trial site initiation and interaction, it's been really hard, especially after COVID. We have had a lot of issues enrolling our PND trials. Before COVID, we were turning people away

from trials. After COVID, we've had a huge issue trying to fill in our trials. [01:31:00] And that in part relates to issues with these clinical trial initiations at the sites, and the additional burden that these academic centers are putting on the sites. Is there a place for decentralized clinical trial sites, and a more unified approach that also gets patients away from these academic centers to a more knowledgeable expert decentralized trial model? I'll stop here-

Susan Winckler: [inaudible 01:31:30].

Dr. Amel Karaa: ... because don't want to [01:31:30] take too much time.

Susan Winckler: Yes. No, but that that's helpful in particularly thinking about do we... Addressing that threshold challenge of having patients who are then going to enroll in that trial so that we can continue to learn more. Sophia, I want to make sure that you provide your voice on a natural next step here.

Sophia Zilber: Thank you so much. So I have a couple of next steps in mind. So one, as we talked here a lot, each [01:32:00] patient with mitochondrial disease is different, but in addition to that, each mitochondrial disease is also different from each other. As we know, some primarily affect vision, some impact muscles. In my case, I said some diseases like Leigh syndrome are neurodegenerative, and are fatal in child. And so we know from previous research that when we are looking at the mitochondrial disease as a whole, it actually takes patients many years to get diagnosed. But the interesting thing [01:32:30] in our registry for Leigh syndrome, we are actually seeing something different. We are seeing that over 60% of patients receive diagnosis in a year or less, which makes sense, because these children with Leigh syndrome become very sick very quickly, and so that leads to faster testing and faster diagnosis.

So one of the next steps I see would be to have more discussions, possibly similar meetings, and think about the pediatric patients. That's one of my [01:33:00] next steps. And the second key next step is finding ways to learn better from the data that already exists. Like Jason also said, we have many patient registries, and we have many data collection efforts that remain unaligned at this point. We do have a task force with Critical Path Institute, which currently has over 20 members, 15 of them are patient organizations, and the full list can be seen at Cure Mito website.

[01:33:30] C-Path acts as a neutral convener. I think that point is really critical. That neutrality is what helps us build trust, and it's really critical in our space, where we have efforts that are not always coordinated, and some of the work is done in silence. RDCA-DAP is an FDA-funded platform, and it allows for integration of various data types, registries, clinical trials, natural history studies, and any other data.

In other diseases, C- [01:34:00] Path has built clinical trial simulation tools to help optimize endpoints and clinical trial design. This is really important for us,

and it's possible for us if everyone joins this effort, and if enough data will be shared to the RDCA-DAP. Right now, we are working with C-Path on aligning data dictionaries across several mitochondrial disease registries. I can't say how exciting it is. This is something that we needed to do for a very long time, [01:34:30] and we are really doing it, we're literally looking at these data dictionaries, and we are seeing what are we doing the same? What are we doing differently? And based on this, C-Path will be able to make recommendations on how we can collect data in a more uniform way. What's very important is that organizations that share data through RDCA-DAP retain full ownership of their data, and they continue to be encouraged to share their data with other efforts, other platforms. This truly [01:35:00] promotes open collaboration and data sharing. So this is an amazing next step that I see for our community.

Susan Winckler: Yeah. And I'm struck, Sophia, you say that both you and Dr. Karaa, and actually all four of you, in both your reflections and in thinking about the next steps, that it's this power of collaboration, and the potential power of collaboration, and that we need to... [01:35:30] There's an opportunity for the community to do more together. And Dr. Karaa, this is essential part of your next step, and in fact, you gave me... I was trying to come up with, what's the metaphor for the collaboration here? And I think your bridges between islands makes a lot of sense, in that the island allows the various... It allows us to protect the heterogeneity, [01:36:00] but having the bridges allows the data, and the learning, and the information to flow for patients and clinicians. But what else might you say about the power of collaboration and opportunities to do more together?

Dr. Amel Karaa: Yeah. I think collaboration has become a buzzword that is thrown out there at every meeting. Everyone is theoretically very open to collaborating, [01:36:30] but practically, it's harder to do-

Susan Winckler: Yeah, it's hard.

Dr. Amel Karaa: ... than talking about it, right?

Susan Winckler: It is hard.

Dr. Amel Karaa: Yeah, it is hard to align objectives, goals, priorities, personalities, all of that. So I think collaboration really has to be done at every level of stakeholdership. Like what I said earlier about stakeholders being responsible [01:37:00] for communicating and developing outcome measures, and helping develop outcome measures, collaboration has to happen at the beginning within and across all advocacy group for primary mitochondrial diseases.

In recent years, we have seen a bit of a splintering of advocacy for mitochondrial disease, which is great, because a lot more people are interested in fundraising, [01:37:30] and developing, and educating people in the

community about their specific disease. But splintering into smaller groups that deal with just one gene, or one syndrome, or one disease it really kind of dilutes a little bit the efforts. And so it's great to have all of these advocacy groups, but I think at the end, they all have to come together, and work together towards the same goal.

And so working together, collaborating, what does it mean for advocacy? First of all, like it [01:38:00] was mentioned before, improving diagnostics. We still are struggling with diagnosing all mitochondrial disease patients, even though we know 1 in 5,000 people have the disease. Our North American Mitochondrial Disease Consortium only has about 3,000 patients, so we're missing 45,000 patients. Where are they? We need to be better at diagnosing them.

We need to be better at collaborating to conduct these natural history studies across all of these advocacy groups, and use, as Sophia said, [01:38:30] the same language to collect the data. We also need collaboration between academic centers, key opinion leaders, researchers that do this work. There's a lot hinging on publication, and discoveries, and all of that, and that sometimes makes collaboration a little bit harder between academic centers, so that also has to change, especially for a small group of diseases like mitochondrial diseases.

[01:39:00] Collaboration in the next step really involves sponsors, and industry, and pharma. At one point in the mitochondrial disease field, there were five different clinical trials looking at primary mitochondrial myopathy, all pretty much using very similar outcome measures, wouldn't it have been great to collaborate, and share information during that time to allow better enrollment in the trial and better design of this trial? So how can we [01:39:30] support our sponsors to collaborate better? And to their credit, they have been transparent amongst each other, discussing their progress, and sharing some data that they have gathered, but we can do better.

And so one of the things that we were successful in having them collaborate on is to share their clinical trial data, so that we can put all of that in one unified place, aggregate it, and reanalyze it, and share it with everyone.

And then finally, collaboration [01:40:00] within regulatory bodies, FDA, EMA, other regulations. So I'm very heartened to see that the regular discussions between EMA and FDA are happening. And that's really important, because we have sponsors that do international trials both in the U.S. and in Europe, and sometimes for the same trial we have different directives, we have different acceptance of outcome measures. So even the regulatory agencies are not agreeing to agree. And so we [01:40:30] need collaboration at every level of our stakeholders, and that is not easy to do, but that's really what needs to happen to move things along.

Susan Winckler: Yeah. Well, and in fact, I'm going to pick up on that idea of needing the regulatory collaboration, because... Dr. Lee, I am aware that that is far easier said than done, but that there are also opportunities... And to think about

collaboration not just among [01:41:00] regulators, but where there's regulator collaboration through communication. I mean, clearly the example of all the guidance documents you gave is an example of that. But what would you add to this conversation about collaboration?

Dr. Kerry Jo Lee: Yeah. I would say, definitely the international regulatory collaborations are still ongoing regularly. That is a very valuable source, I think, on our part, and is a benefit for the community as well. And I'll just add that for the international [01:41:30] rare diseases cluster, we additionally have Health Canada, so it's not just the EMA and the FDA, it's also Health Canada having those conversations, so that's very important.

I would say that as well as improving diagnostics, that was just spoken about, definitions is really important. So are we actually talking about the same patient population we all think we're talking about? Because that can really hinder all the other collaborations that are ongoing if we think we're all talking about apples, and it's a basket of lots of different [01:42:00] types of patients.

We really need to leverage our collective experiences and knowledge. Patients just don't have time for silos. If we're all doing this independently, we're not going to get very far, and we may make the same mistakes over and over. So as much, as regulators, we can partner with the community, and the community can partner as well, particularly in the pre-competitive space. There's a number of consortia we partake in, there's the workshops here. Those are, I think, really, really valuable collaborations.

[01:42:30] We can learn from sharing examples and approaches across conditions. I know that conditions are unique, but the reality is, a lot of the challenges are similar. So how do I deal with heterogeneity, even extreme heterogeneity within patient populations in trial design? How do I adapt a COA to my patient population when we don't have our own... Rather than develop our own instrument? How do I strengthen translational science to support this biomarker or confirmatory evidence? Those are all things that other rare disease communities [01:43:00] have also taken on, and I think we can learn from everyone else's experience.

And finally, I'll just say, I was glad to hear the Rare Disease Cures Accelerator-Data Analytics Platform was brought up. It's an effort that CDER supports and believes very strongly in, because we believe in the aggregation of data. These are very small populations, and even one patient's experience can have an outsize effect on how you view data, or the experience in the condition. So that's particularly important. I know that the FDA is very dedicated [01:43:30] to supporting collaboration, as is evidenced by my colleagues that were here today, and the numbers you cannot see that are watching online, we are deeply committed to this community, and helping to move therapeutics forward in this space. So I hope that we continue to strengthen our collective dialogue. I also hope that the Rare Disease Innovation Hub, which is now a single external point

of communication, can help to do that when there's cross-center collaboration that needs to take place, and I think we can really sustain this.

Susan Winckler: Yeah. [01:44:00] In fact, the Rare Disease Innovation Hub is an example of driving collaboration within the agency, which is so very helpful. Yeah. Excellent. Sophia, you too mentioned the power of collaboration in your next step, what would you add to our, yes, collaboration is hard and we need to do it? What would you add to that component?

Sophia Zilber: Thank you so much. So I want to highlight a couple of opportunities. So one, is the [inaudible 01:44:28] task force which I already talked [01:44:30] about. Additionally, I would like to share a little bit about Leigh syndrome, our registry at Cure Mito is doing as another opportunity to collaborate, and I just want everybody to know more about it.

We started registry in 2021 with a goal that we're not just collecting data, we're not just providing hope, but we're providing real results right now. And so I can say that right now, we have close to 400 participants. We have had two peer-reviewed papers, we're about to submit [01:45:00] our third paper, and we have five posters.

What's important, Jason said, I love data standards, our data is fully interoperable into both [inaudible 01:45:10] and OMOP standards, and we have shared our learnings from these data transformations, and we are continuing to share. We analyze our data on a regular basis to ensure data quality, and as recommended by the FDA registry guidance. We have had two listening sessions on the registry with the FDA Real-World Evidence [01:45:30] team, and so we've had a chance to share with FDA, and hear their questions, and their input.

Researchers can collaborate with us, they can request data, they can share their clinical trials or studies through the registry, it's very easy. There's a way to link the registry data with patient bio samples or other research where the same patients participate. And they can always meet with us, and we can show really detailed summaries of the data, and walk them through the entire registry data.

[01:46:00] Now, we were talking that collaboration is not always easy. I would like to say that when we're forming new consortiums, new initiatives within our community, there should always be a transparent and clear path for others to join, so that everyone can find out what it is, have a chance to have a seat at the table, and contribute in a meaningful way. I've seen this across all of rare disease communities, I talk to many [01:46:30] groups regarding the registries, I see that duplicate and parallel efforts happen when there is no way to join existing efforts. And so new people come in, they're motivated, they see that they can't participate, they have no other opportunity except start something independent. Unfortunately, I see this all the time.

We do try to follow this collaborative approach with our registry and with Cure Mito, [01:47:00] we make sure that the community knows about our registry, our data, and we made sure to be responsive to all who wanted to become involved. Because of this, we've actually been able to form really valuable relationships across the entire rare disease community, and we've been able to meet the researchers who are not a part of the Mito community, but who brought really unique perspectives to our work, contributed to our registry publications, and we really gained from their participation.

[01:47:30] Our registry is on [inaudible 01:47:32] platform. We collaborated with the Hope for PDCD Foundation, and there is now a PDCD registry on the same platform. And so as there is an overlap between Leigh syndrome and PDCD, we actually set it up in a way that those patients who have both of these diseases only register once, and only respond to many of the questions once, which reduces the burden on the patients, and also improves our data quality. I always say when I talk about the registry, it's an open [01:48:00] door policy, we have an open door mindset. If anyone has feedback, questions, concerns, we want to hear them... All of this is welcome. And so those who want to collaborate, please be in touch with us.

Susan Winckler: Yeah. Excellent. Thanks, Sophia. Jason, what else do we need to know about collaborations? And then we're going to turn to everybody for a lightning round. So final word on collaboration.

Jason Colquitt: Yep. You've covered a lot of ground. Well, I was blessed [01:48:30] for seven years to work with the Cystic Fibrosis Foundation in their data collection effort, and they embodied this concept, and I talk about it a lot, co-production of care. So this is not about researchers getting answers and that's it. It's about this whole learning healthcare system, and as we're creating all this data, it should be shared all different ways. So that's a big part on the collaboration. It's hard, but thinking about that ahead, as you're building your protocols, you're thinking about this, you're thinking [01:49:00] about even your informed consensus of, where's the data going to go after this study, and what can it be used for? So that's a huge part of this collaboration with patients, I think, talking to industry, and thinking about that.

I had the opportunity to lead the patient data track. Sophia actually was one of the speakers at the World Orphan Drug Congress, and it was, I don't know, disheartening, some of the things like duplicative tests that patients have to... So I think just collaborating on, what am I thinking about doing in my trial, [01:49:30] and what effect... If I'm getting an EEG or an MRI and the patient has to have one also, how can I share that data across? So there's simple things like that just thinking about the pure research we don't think about, but the practicality, collaborating with the patient community, I think is hugely important.

And then we talked about this a little bit, about sharing that data. I've seen this across many of the rare diseases I work in, is, how do you collaborate? And

again, back to the good, bad or ugly, or even if [01:50:00] you shelve that product and it goes no further, how can we make good use of that data no matter what it is, and allow that data to be seen outside of somebody's four walls? So I'll end there, but good collaborative talk about collaboration. Thank you.

Susan Winckler: Excellent. Thanks, Jason. So we're closing out our time together, and I'm going to give you each a lightning-fast last word, and I'm going to give you... I think I will give you three options [01:50:30] for that last word. One, take a magic wand approach. So if there's one thing you would change about developing treatments for primary mitochondrial disease, or even rare diseases more broadly, what would that be? That's option one. Magic wand. Option two, a remember this approach, what would you challenge our speakers and attendees to take away from today's discussion to be sure that they remember? So that's the remember this. Or third, if there's [01:51:00] something that we didn't get to, take this opportunity to share it so you can make sure it's communicated, and you've got just under two minutes for each one, so we're going to go in this order, Dr. Lee, you get to go first, then we're going to turn to Jason, then we'll turn to Dr. Karaa, and we'll close out with Sophia. But Dr. Lee, your two minutes, magic wand, remember, or something new. Fire away.

Dr. Kerry Jo Lee: Well, I'm a regulator, so pragmatic, and I will give [01:51:30] you something to remember as you're considering drug development. So I want people to remember that, while we are leveraging each other's experiences, individual drug development programs are unique. What does that mean? You have to look at your therapeutic product, you have to think about, how does it work? In whom? What is the expected effect? Is this something that ameliorates a condition, or is this something that just sort of holds decline or slows decline? Those types of things matter greatly in trial design considerations.

[01:52:00] Other things are, not every program is the same. You've heard one-size-fits-all, even in the same condition or indication. One program has a well-defined natural history study, another one has a robust translational science program, another one has an objective, well-defined endpoint. Another one has a subjective, noisy endpoint, or any combination of all of these things. All of those different elements are what goes into specific program considerations and trial design, the regulatory approaches and pathways you take, and ultimately, decision-making.

[01:52:30] And so finally, I'd just really like to end with, while learning from others, understand your development program's strengths, weaknesses, elements, and then come talk to us early, because some of the most important decisions that you make are very difficult to undo, or make up for later. So if you come and talk to the FDA early about what you have and your approaches, we can really help to inform you to get a program that will generate data is interpretable as to whether or not the drug is safe and effective, and that's the [01:53:00] goal.

Susan Winckler: Excellent. Thanks so much, Dr. Lee. Jason, I'm turning to you. Magic wand, remember, or something we have to say.

Jason Colquitt: I love magic wands, and almost went that route, but I think there's one that we didn't talk about. I know it's an audacious goal from my perspective, but in collecting this natural history data, I really want to build a dataset. I know this is hard, and you'll tell me, "Can he do it?" But build that, so that we don't have to have all these control arms. That hits off of what [01:53:30] Casey said, and you heard the quote from The Champ Foundation of... Personally, I've been affected by that with people around me that had gone into trials and potentially on that placebo, so can I build a natural history study with enough data? And that's my audacious goal, and I just wanted to... I know there's examples of that within the agency where that has happened, that we have enough data, it has to be the right data, and I understand all of those nuances, but that's a huge [01:54:00] goal that I put on myself of, how can I expand to as many rare diseases as possible? And how can I collect as much data to make that a possibility as well?

Susan Winckler: Awesome. Thanks, Jason. Dr. Karaa?

Dr. Amel Karaa: Thank you. So I think I would choose option number two. I like everyone to remember that it takes a village to get these clinical trials going, and I think that one key takeaway is that if you are a sponsor and you're interested, [01:54:30] you really have to reach out very early, and reach out to as many stakeholders as you can, because it's better to spend a lot of time upfront thinking through what needs to be done, gathering information, gathering data, and doing it the right way with FDA input than to start something in a rush, and then end up stuck in the middle of a trial. So collaboration, early [01:55:00] input, and it takes a village. But with an optimistic final word, which is, we're all committed to help you, so just reach out.

Susan Winckler: Yeah. Fabulous. Thanks, Dr. Karaa. Sophia, you have your three options, and you're just under two minutes. Fire away.

Sophia Zilber: Thank you. I'm going to take the remember this approach, and I want to share a couple of reflections. First, remember that each patient is a person. I'd like to share a story [01:55:30] from when my husband and I received our daughter's MRI results. At that point, we didn't know anything at all what was wrong with her, and her neurologist said, "The MRI revealed some findings. Do you want me to show you the images, or would you prefer just talk about them?" We thought it was incredible. It may seem like such a small thing, and we agreed, we said yes to seeing the images, but we thought it was incredible that, at that time, when he had these important medical news to share with us, [01:56:00] he was able to just kind of pause and step back, and just see us not just as a medical case, but just as two parents whose lives were about to change forever, and be split into before and after. We noticed that then, what he said, and we still remember it now.

Second reflection. This meeting is only the beginning. We don't have any treatments yet, and we have to remember there's still a lot to do. The clinical trials we talked about today are for [01:56:30] adult patients, and again, we have a Leigh syndrome community that's very interested in clinical trials. Almost every month when we send our newsletter, we're including a piece about a child who died that month. We have to collaborate in a real way, and we have to continue working hard towards treatment. Finally, I would like to acknowledge the dedication that it takes to be a part of this community. If you are here listening, and if the path feels challenging to [01:57:00] you now, I want to leave you with this, your presence here matters, there is a reason why you're here, your voice is important, keep working hard, and keep going. Thank you.

Susan Winckler: Well, Sophia, just brilliant, and powerful, so thank you.

Sophia Zilber: Thank you.

Susan Winckler: Thank you to-

Sophia Zilber: [inaudible 01:57:24] this panel. Thank you.

Closing Remarks and Adjourn

Susan C. Winckler, RPh, Esq., Reagan-Udall Foundation for the FDA

Susan Winckler: Yes. Well, thank you. Thank you all for joining [01:57:30] us. I want to thank all of our speakers today, what powerful contributions each of you made, and I am leaving the meeting encouraged, as well as with some clarity, and thinking through the opportunities, having that better sense of the challenges that were shared throughout the day, and that we can move forward and make a difference. I'll just remind everyone that the meeting recording and the transcript will be posted [01:58:00] at our website, which is reaganudall.org, within the next few days, and then will become part of that repository as well that FDA can connect to, so that all of the components that help rare disease therapeutic development move forward collectively. With that, I'm going to thank you for joining us today, for sticking with us for five and a half hours of content sharing and learning, and we just [01:58:30] really appreciate each and every one of you. Be well, take care, and we'll see you soon.