Natural History Studies and Registries in the Development of Rare Disease Treatments
Hybrid Public Workshop
May 13, 2024 | 10am-4pm *(eastern)*

Afternoon Transcript

Collecting Fit for Purpose Data to Inform Regulatory Decision Making
Collin Hovinga, PharmD, MS, FCCP, Critical Path Institute
Jennifer Farmer, MS, Friedreich's Ataxia Research Alliance
Reactor Panel
Benjamin Forred, MBA, ACRP-CP, Sanford Research
Donna Rivera, PharmD, MSc, Oncology Center of Excellence, FDA
Kimberly Smith, MD, MS, Center for Drug Evaluation and Research, FDA
Tiina Urv, PhD, National Center for Advancing Translational Sciences, NIH

Susan Winckler (00:00:05):

All right, it's 1:35 PM and we have two exciting sessions this afternoon, so we need to kick off right away, or I'm sure our speakers will let me know that I did not give them enough time. So let's jump in. We heard this morning about the what and why of registries and natural history studies, and now we need to turn to talking about collecting fit-for-purpose data to inform regulatory decision-mating, decision-making rather. I'm going to ask our reactor panelists to come up and take a seat on stage. We have a return engagement in the reactor panel for Ben Forred and for Dr. Tiina Urv from NIH NCATS who you had just heard from, and joining them are Dr. Donna Rivera from FDA's Oncology Center of Excellence and Dr. Kimberly Smith from FDA's Center for Drug Evaluation and Research. So we will make sure that Ben gets caught up by the time he comes in the room, but you all get extra time to ask questions since you're seated already.

(00:01:09):

But let's get ready to hear from our first presenter. We're going to hear from Dr. Collin Hovinga, who is Vice President of the Rare and Orphan Disease Programs at the Critical Path Institute. There he oversees the critical path for rare neurodegenerative diseases, public-private partnership, and C-Path's Disease Cures Accelerator and Analytics platform. Collin, I think you need a few more consonants in all of those things that you just made me say-

Dr. Collin Hovinga (00:01:40):

I just do stuff.

Susan Winckler (00:01:41):

But take it away and get to the substance.

Dr. Collin Hovinga (00:01:44):

Let's see if I can figure out how to advance the slides.

Susan Winckler (00:01:48):

Big green button.

Dr. Collin Hovinga (00:01:48):

Oh, big button. Okay.

(00:01:53):

In spite of all the acronyms, one of the things I'm going to try to convey in my talk is I come from a lot of backgrounds, so I've worked a lot with nonprofits, I've been an academic researcher, I've worked with pharma companies to design clinical trials, and I'm at C-Path now largely because in each of those roles I found sort of a gap in how to bridge the things that needed to come together to take the data that I wanted or the trial design that I wanted to get to something that would be deliverable for something that would meet regulatory approval. Because as an academic, there were a lot of things I didn't know, as a clinician, I didn't know, even as a research administrator who ran clinical trials, I didn't know. And as a person designing clinical trials, you use real-world data, didn't quite know everything I needed to.

(00:02:36):

So this talk will re-emphasize some of the things that we talked about earlier today. I'm going to give, I guess some pearls throughout the conversation so that you all can think about. And in my role at C-Path, one of the things we do is we take data from diverse types, everything from trial data to registry data, to Excel spreadsheets, et cetera. And we put them in standardized data formats, make them available publicly, given permissions that we have, but through that, there's a lot of lessons learned and that platform, which was among the acronyms there was RDCA-DAP. So if anybody wants to share data, please reach me after the talk. But that program was supported through FDA grant, through the ARC program, so a lot of lessons learned through that interaction and hopefully those will inform some of the conversation today. The focus here is going to be non-individual studies as the tone of the conversation. Registries, we're not really going to focus on EHR-based data. That's another deep pocket of resource. We're going to talk about data that's collected longitudinally. Some of the data sources that we talked about earlier today are cross-sectional and whatnot. We're going to talk about data-sharing considerations because that is the bane of my existence, and so if I have a soapbox to speech on, it will be that. And then we'll talk about the end. What do you do with this? And some of the tools that C-Path builds. I'll give you some examples. Jen is going to talk about external controls. And so she'll add a little bit to that. But I always think about, have the end in sight as you're thinking through things.

(00:04:20):

Now, when you think of fit-for-purpose data, the first what you think about is, is the data reliable> and Dr. Wagner and Dr. Hill today really spent a lot of time focusing about that. And really what that means is the data that it represents that you have is intended from the medical concepts and thus are considered trustworthy and credible. Taken in an English language, what that means is that what you put in and what you get out are the same and what you wanted to record is what you're getting out. It's something that you're collecting accurately and retrieving accurately and it's trustworthy.

(00:04:58):

The one that's probably more intuitive is that is it relevant, right? Relevancy is important and that's classically defined as that represents the population of interest and can answer the research questions

in the clinical context of interest, meaning that is that when you design the natural history study, think about what you wanted that natural history study to do at the end, and we'll talk about some examples of how this can be used in regulatory framework. But lots of times what I find when people are planning these, they have a lot of information. They're sort of in a fishing expedition, and so they don't really tie what they're collecting to what it's going to be used for. And so it's really important to sort of be really critical about that step to know your data is relevant.

(00:05:40):

The second part of that is timeliness, because one of the bans of my existence and planning trials was is that in many cases, natural history studies or whatnot were dated. They weren't recent and how we care for patients and the drugs that they're on and all the other things that are important weren't current. So when you're designing a clinical trial with a dated paper, it's really not a good way to design a clinical trial because your statistical power can be off and the sample size and whatnot.

(00:06:13):

Now, I will emphasize this again, begin with the end in mind. Know what you're going to be planning to do. Is this a statistical plan? Is it a fishing expedition? Are you thinking about exploring concepts important to patients? Is it a genomic-based study where you're looking at segmenting the population? Is it a pre-symptomatic trial where you're looking at natural history all the way through impacted disease? Think of those things as important.

(00:06:40):

The other part of this that I really can't stress enough is that don't reproduce the wheel if you don't have to. Patience, time, talent and treasure are important. People's time is important, resources are important, so do your homework. Get input with lived experience to understand the concepts that are important to them. It's very, very important. They're the ones that are most likely involved in the collection of the data. So make sure that you're collecting things that are important to them.

(00:07:10):

Literature review, understand what's being done, what natural history studies that have been done that you can build upon and define where the gaps were that you need to address. And then avoid duplication. I can say in many rare diseases there are multiple groups that are working on similar things. Try to either align data or aggregate data or address different questions so that we're not overburdening the system and whatnot. Who is going to collect the data? That's often important with regulatory decision. Is this a parent that's collecting the data? Is it the child collecting the data? Is it the adult that may have a journey of disease collecting the data? How does that impact who's collecting the data? Refine the collection strategy, sufficiently address questions over time, and make sure it's not overly burdensome. I will use an example. There's a study that I've been involved in, a natural history study being planned and they charted out the time period they expected the survey tools to be assessed and they added it up. I think it was about an hour and a half. Anybody in clinic for hour and a half doing clinical surveys, not going to... And imagine as the disease progresses, that hour and a half becomes half day, maybe a day, maybe not completing it at all. So be important to that. Think about this. The other thing is that patients are involved in lots of different studies with rare diseases. Think about global unique identifiers and don't put the burden of the person impacted with this to address that issue. You as researchers should do that.

(00:08:42):

Now I'm going to break through some of the concepts here of the protocol and their considerations. I'm going to stream through this. It's a lot. I apologize. I tried to think of a sub-way to do this. It would've probably been 50 slides if I would've done it otherwise. Think about the population that you're looking

at and define what the inclusion criteria is because that's going to tell you a lot of what your controlled population might look like or what conclusions, what generalizability you have, what population could be ultimately studied in a drug trial.

(00:09:13):

Demographic considerations in particular, where they're at. Sometimes jurisdictions are sensitive about whether or not patients come from a specific jurisdictions as they represent. Be aware of that. Concurrent therapies are a really big deal when you're talking about external controls because if there's a drug approval, I think that was talked about earlier today, that sort of level set. Otherwise, general rule of thumb, every five years, look at your data because timeliness of care will be important. The other thing is to decide, are you taking all comers? Are you taking an enriched trial population that may be a smaller subset that might be eligible for a clinical trial? The other one would be presymptomatic versus symptomatic because sometimes the assessment tools that you're looking on early in disease don't really have relevance until patients have symptoms. So be very clear of what your population would look like and what impact that is.

(00:10:06):

Disease-related concepts, a lot of these are sort of listed in different terms. What I really want to stress here is many rare diseases have diseases that impact multiple systems and organs, and you may want to concentrate on one of those. Right now, one of the ones that we work at C-Path is lysosomal storage disease. We are focusing on neurological right now, but there are other organ systems that are affected with some of those. There are many of the conditions that's similar. So very, very, very symptom and understand all those things need to be characterized.

(00:10:36):

Outcome assessments. This I could hold a whole talk on. What I really want to stress here is when you're thinking about these is that decide which ones might be closer to regulatory grade and you're considering measures and what's the reliability of the assessments. You might want to collect qualitative data as you're going along, because a lot of times patient-focused interviews that are done by pharma companies are oftentimes something that's needed. So addressing them so people understand their condition over time might be relevant to them.

(00:11:05):

And then the big thing I want to stress here, particularly for other measures like MRIs and scales and labs is have a procedural list. Do the things that require training in cross and iterative reliability and things like that. Some kind of quality control. Have that in your protocols so that it's outlined so that if someone's asking whether or not, "Oh, yeah, we have the variability. Once we look at this endpoint in the natural history, it's all over the place." Well, maybe it's because people just assume that this was a standard clinical scale and everybody did it the same. That's probably not a good assumption. It's probably the other way around.

(00:11:45):

General methods, this is about who does the assessments. That's really important for interpretability and whether or not it's the same person, individual sites. So having roles is really important because if, say, one site the child does the survey and then the parent does it at another site or the nurse does it at another site, that's probably a big deal, right? Duration of the study overall, and particularly for the subject, schedule events. It's important to have routine follow up. What I always think about is when do I want to anticipate change? And that's kind of how I think about it. And then I look from that threshold and then I ask feedback from the individuals that they're going to have to do the assessments of is this

too much? The reason for the frequency part of it, I want to detect as earliest change as possible for futility type of analysis. And so having that is really important.

(00:12:38):

Clear standards and definitions, I think people have talked about data dictionaries, we'll come to that in a minute, but you want to have as many standardized as you possibly can because then it is reproducible, particularly if there's things that are measurements or other things like that. Considering structured data. I think that's been echoed throughout this. The other thing I want to talk about is the analysis plan. The biggest factor that comes up to play is how you're going to be able to do loss to follow up. And then the typical type of analysis needs to be thought about before you do the data collection. Because thinking about that and ultimately how much samples you collect is going to be really very important and how many patients you consider.

(00:13:17):

Consider sources of bias and critical enrollment bias, how are you going to perform your outreach? I mean, I remember you have to go after real-world data sources and having data holders tell me, "You don't want my data because it's enriched for persons that were consulted to my service. I mean, that's not the general population that's impacted in that." So I also think with DHT's and other things that are being measured, it's important to understand other software or proprietary algorithms that are involved in whether or not that that's part of the equation. Because if it's going to be used, that has ramifications for if you're going to be using it in a clinical trial or are you going to get it endorsed for a drug development tool.

(00:13:56):

I won't go into a great deal for time for the quality, but there's a whole bunch of things. Remember, you're going to have an auditing and quality and QA program to look at your data, missing data and whatnot to make sure this is all done really well. And that's probably one of the larger things that happen where there's a lot of missing data. Sometimes I'll get within our platform data that that's one of the huge problems with it. Even data that's supposed to be good quality that you'll run and do a QC on it and you're like, "Wow, there's a lot of missing stuff."

(00:14:26):

I'm going to speed through for time. Clinical outcome assessments, I want to stress this. The reason that I want to stress this is that oftentimes people when they're doing, back to that fishing expedition, they're not thinking of clinical outcome assessments that might specifically be already measured in their field or how fit for purpose they are already. One of the things you want to be thinking about back to that field function, survive definition, you want to make sure that whatever's being collected is meaningful for the patient because that's where a COA is going to live. That's where an endpoint's going to live, right? The example I've seen used, and I'll thank Michelle Campbell for this example, is that in vibratory sense for someone may not be really clinical or meaningful, it doesn't change the way they function throughout their day, however, but if there's weakness or numbness enough that they can't hold the spoon or button, that's important. So you're going to try to quantify things that change their daily function level.

(00:15:22):

The other thing I wanted to do is reference that I think there's been different libraries referenced. C-Path has one that Lindsey Murray has been active at our rare disease program at C-Path. She looked at where there's substantive support for the use of different COAs, and you can find that resource on our website, but that's also a starting point where surveys and whatnot have more substantive evidence for their use. The key thing is how well does this for the population and how comfortable people feel with

extrapolating that to your rare disease. And the big thing that you should look at in any of your methods is the methods on how it's collected and how it is quality assessed.

(00:16:03):

Now, I'm going to switch gears quickly with the end here, and I'm going to give you some examples of projects. Some of these fall under fit-for-purpose use, others don't, but they give you some conceptual frameworks to think about as you're designing your own natural history studies. One of the things that C-Path's done under the encouragement of FDA has been biologically driven disease staging. Wonderful, wonderful thing. One, it sets up a standard currency that's not just clinically aligned so people can speak the same language. And what it usually entails is taking a disease, for example, I have ALS in an example because that's my next adventure, and you take different elements of that disease and you basically map them across the course of the disease. So you may take things like genetic diagnosis, pathology, demographic characteristics, if it's important, specific biomarkers or genes, and then clinical work from DHTs, and et cetera. And you map them across the disease state, so extrapolated so you can compare the same currency across different courses of the disease. That allows you to converse with others, but also to decide different disease progressions. I'm about to get done.

(00:17:16):

This one's a simulation tool. You saw a picture of a graph on the slide about a simulation. This is what that would look like. And you'll have the slides for this, but what I wanted to show in these slides is that it has study duration and parameters, frequency of visits for your national history study. It has patient characteristics, it has potential outcome variables. And these all with this data can be simulated. These do undergo regulatory endorsement. And data standards. Just a quick point, it was mentioned earlier, really important if you want to share your data, data standards both within your own data dictionary as one in a common data model. And the ones that if you wanted to discuss later on is CDISC and OMOP are probably the more common ones. CDISC is most likely for a regulatory purpose. So if you want to use it with other researchers.

(00:18:05):

And my last comment is I want to talk about IRB, because this is a lot of confusion, real quickly and if we want to get through the Q&A. I think Ben has talked about this as well, but normally data is datafied when it's shared. Most of the time the coded linked data is not shared individual and it's the data owner that owns that. So I want to frame that part one. So that's the most common way of a data is gone. Common consent language is a huge deal, and people ask this all the time because I don't know how many times they go and ask me about sharing data and then they go back and look at their consent form and they say, "We can't share data because we didn't include that in the data share." That happens to me out of all the data requests that I received, probably 25 to 40% of data conversations, I have realize that, oh, crap, I can't share my data.

(00:18:52):

And so this gives you, you can use these in the slides, but I want to wrap up here for Jen. You'll have the slides for that, but that's my secondary soapbox and I'll sit over here.

Susan Winckler (00:19:05):

Great, thanks Dr. Hovinga. I was waiting for the begin with the end in mind in the presentations this morning and we just got it. So thank you. So let's turn to our second presentation. As Dr. Hovinga mentioned, we will turn now to Jennifer Farmer, who is CEO of the Friedreich's Ataxia Research Alliance. I'm going to turn it to you. We'll talk about the how of collecting fit-for-purpose data and then turn to our discussion.

Jennifer Farmer (00:19:35):

Thank you. It's really a privilege to be here today and to participate and to have Dr. Cavazzoni open this morning and reference our experience in the Friedreich's Ataxia community with leveraging our natural history data as part of regulatory decision-making. That is not where we started. That was not the original goal, I promise you, because I was the first clinical coordinator to file our first IRB submission for our natural history study. That was not where we started. But the fact that the first treatment approved for FA is also helping other rare disease groups hopefully have a path forward for how to leverage their natural history studies data in regulatory decision making makes all of us really, really proud and thankful that we can share this with you.

(00:20:40):

As Leslie mentioned earlier, these natural history studies in our rare disease communities are only possible because our families are fundraising and making this happen. So we're 20 years in, and our natural history study has been solely funded by donations and events from our patient families. We had one government-funded supplemental study to our natural history study. So I think that's really important to recognize, especially when we also think about sustainability.

(00:21:19):

We started back in 2003 with a clinical outcome measure study that we parlayed into a natural history study. And I'll tell you a little bit about that, but I'll bring you along to what Dr. Cavazzoni talked about this morning. In 2003, one of our clinician researchers at a scientific conference said, "We need to understand FA better. We need to be able to understand the natural history and we need to be able to track disease progression over time if we are ever going to be able to do clinical trials." And it was a core group of clinician researchers who came together at that time and designed the first clinical outcome measure study. It was co-funded by FARA and MDA, and we had some disease-specific assessments that they developed and we piloted, but we also borrowed from multiple sclerosis from other diseases where they had endpoints that were being used in clinical trials, I think to Colin's point about what is going to be approvable and trying to think in that direction.

(00:22:34):

That clinical outcome measure study really did parlay then into our natural history study. And again, what we were focused on at that time was being able to facilitate clinical trials. We needed clinical outcome assessments. We needed to understand how to design a trial, how long should it be? How many people would we need? We needed the clinical sites who could carry out trials to be identified and to be trained and to be ready to do these kinds of things. And so that's kind of where we started with why would we do a natural history study and what do we hope to gain from it?

(00:23:11):

Just in terms of some of the study design aspects, we were really inclusive. We took all ages, all stages. Anybody genetically diagnosed with FA was eligible to enroll into the natural history study. We knew it was important that it would be prospective and longitudinal, and we knew for practical reasons as well as reasons related to the speed of the disease progression that probably annual visits would be sufficient. And we needed to ensure consistency of data collection across all the sites. So things like having a robust protocol, visit schedules, standard operating procedures, training for investigators, coordinators, those kinds of things. Quality of data, you've heard a lot about this today, so I won't spend too much time on it, but early advice we got in the process in about 2010 was to make sure we were using a robust electronic data capture system with querying and auditing. And so the early data that we collected on the Excel spreadsheets or in custom-made databases all quickly got converted to a robust system.

(00:24:41):

I can't emphasize enough the importance of the clinicians and the researchers in this process and their diligence to natural history to analyzing the data and publishing it and getting it out there. That's another part of making it accessible. It's one thing to have the data accessible that you're sharing it in its raw form, but I think these scientific peer-reviewed papers are really, really valuable. And I need to update my slide because now it's more than 50 publications from the clinician researchers who have been dedicated to this process.

(00:25:21):

But it's also important because we're analyzing the data, it tells us where to go next. And we realized early on that our natural history study was over-representing the adult population with Friedreich's ataxia. We did not have many children enrolled in the study, yet the majority of individuals with FA have onset of symptoms between the ages of five and 12 years of age. And when you actually look at our data, not only are individuals older, but if you look, the red dots are the baseline visits and the blue represents that period of age of onset. So we are missing a huge time period of natural history in this disease from the onset of symptoms till people are coming into our natural history study.

(00:26:22):

And so things like this, this is just one example of things that we've learned and try to respond to as we analyzed the data. With the FDA study that we did, we were able to enroll more children. And one of the standard outcome measures that we use in clinical trials is called the modified Friedreich's Ataxia Rating Scale. And what you're seeing here on the slide in red is that in children less than eight years of age, this scale is not very sensitive and it's not going to work in these young kids. And so we need to identify new clinical outcome assessments that are going to be sensitive and clinically relevant in our younger population.

(00:27:19):

I think you've heard a lot of these things, but I think in terms of our experience with natural history, sustainability, the outcome assessments, it's important to really be critical of this along the way. You've heard about fatiguing patients and overburdening them, get rid of the ones that don't work and continue to add the ones that do. And you also have just your core set of data that you're always collecting that you have something to compare to. And so there is a natural process to evolving your natural history data collection and your clinical outcome assessments. The investigators, again, I can't ever give them enough credit. And the importance of keeping your data contemporary, and this is kind of where I'm going to pivot a little bit to the regulatory decision-making part of what I want to share with FARA's experience.

(00:28:24):

Regulatory engagement is never one meeting, one point in time. Michelle Campbell always says, "Come early, come often." And it really is an engagement process that you should start when you start collecting your natural history data and continue throughout the process. And there's lots of different ways in which you can do that. You can have direct meetings with FDA, you can participate through sponsor meetings. We have a partnership with the Critical Path Institute where we've contributed the data to RDCA-DAP so that it's available for the research community, but there's also good engagement opportunities that come from that partnership. And then again, things like externally-led patient-focused drug development meetings. It's not just one of these, it's all of them that are important.

(00:29:16):

On this slide, what I'm sharing with you is kind of the path to approval for Skyclarys or omaveloxolone, which was the first approved treatment for Friedreich's Ataxia. It starts with basic science grants to academic investigators who identify a pathway that's abnormal in the disease. It was a parent of an FA child who pointed FARA in the direction of a drug company that was making molecules that targeted this pathway. And it was our outreach to the company that got them engaged in FA. They were not working on Friedreich's Ataxia, they were working on kidney disease. FA is a neurologic disease. And what allowed them though to develop this drug in FA was the fact that we did have a natural history study and we had that clinical research infrastructure because they could not have done that themselves.

(00:30:14):

So we worked together to leverage that natural history data to plan the first phase IIa study and then the second efficacy pivotal trial. It was important to have that data in getting a regulatory agreement about the primary outcome measure. And then later in the process after we completed the randomized placebo-controlled trial in terms of leveraging the natural history data as confirmatory evidence through a propensity matched natural history control study. And this is the part about keeping the dataset contemporary. A lot of concerns that you have with using natural history data as an external control for a clinical trial is that the clinical trial population for some reason is very different than your natural history dataset. And here we were able to ensure that the natural history data that we were applying did match the clinical trial population and matched them really well, matching them across five different variables that are disease related. So again, just to summarize that natural history data was important in the trial design, making sure that we ran the trial long enough and had enough people, consensus around the primary outcome measure, and then being able to contribute the confirmatory evidence.

(00:31:51):

So where do we go from here? Sharon Hesterly from MDA told me very early in my career and in this natural history journey process, I naively said to her, "Sharon, I think another four or five years we'll have this box checked. We'll be done. We'll have enough natural history data." And she laughed and she said, "Jen, I'm sorry. If you do your job right, you will never be done collecting natural history data." And that was hard to hear at that time. But I really to this day, really appreciate her honesty and putting a little pin in my balloon. But it was an important lesson to learn early.

(00:32:36):

So right now, we are focused on really expanding the infrastructure and the natural history study globally to where our FA community is around the world. And that has involved really collaborating with an existing natural history study in Europe and bringing those two together into a unified harmonized protocol and dataset and database, and forming this global clinical consortium with our academic partners around the world and really trying to provide the infrastructure to support that along with engaging the patient advocacy organizations.

(00:33:20):

Again, this is just a visual way to think about what we've tried to establish with the natural history study. You've got the core data elements that are assessed at every single visit. We've got supplementary assessments that are done based on stage of disease or ability to capture certain types of data. And with this platform and the consortium, we're hoping that we will be able to incorporate other types of supplemental and parallel studies that will further advance our understanding of the disease and therapeutic development.

(00:33:59):

Everyone asks what this costs, how do we do it? So we didn't start with where we were, remember? Most of what we started with was a lot of volunteer time and effort and funding our sites for pennies,

honestly, for the work that they were doing. And still today, to be able to have a global natural history study for what's going to cost us, this year, $2 million is really because of the grace and the generosity of the clinician research community who invest a lot into this process as well. And just again, where we're going with the global clinical network, we're trying to enroll those kids much earlier in their process when they're having onset of disease. We want to also understand later-stage disease and be able to assess impact of therapeutic development for those folks. And again, be able to understand the natural history and as it evolves, as treatments become available. And so with that, thank you for your attention and just really want to, again, acknowledge our FA community, both the patient families contributing all of their data as well as to our clinician and research community.

Susan Winckler (00:35:23):

Fabulous. Thank you, Jen. And now we're going to turn to our reactor panel dynamic here. So as I mentioned, we have two returning speakers. So you'll see Ben Forret and Dr. Tina Irv returning as reactor panelists, and then joining us as new faces, Dr. Donna Rivera from FDA's Oncology Center of Excellence and Dr. Kimberly Smith from FDA's Center for Drug Evaluation and Research. So I'm going to change microphones. There we go. All right. Reactor panelists, are you ready? Who wants to ... Oh, Donna's got the first. Donna, you're first, push to talk. Go ahead.

Dr. Donna Rivera (00:36:06):

Well, I think the first thing I want to say is that I thought the optimism of the last talk by Dr. Farmer really, really highlights what we're hoping for, that we can bring safe and effective medications to the market, especially in rare diseases. And one of the things I think that was highlighted through the talk was this concept of early and often, and I would like to echo that. I think that we're here because we want to try to support drug development and provide the tools. And my colleague Dr. Smith might get into the guidances a little bit more, but I'll talk about other options and pathways and ways we think about this, including ways in which, at least in oncology, which is where I am, we have, actually, in partnership with the Reagan Udall Foundation, the Oncology Q-Card, which is really working around standardizing ways to come in to start talking with us, to come in and submit these materials.

(00:37:07):

And as you think about coming in and whether or not natural history study, the use of real-world data, the use of a registry is something that makes sense. I think, again, it's that engagement with the clinical division to say, is there a justification for the use of real-world data in this clinical setting? Is it a rare disease? What is the best possible evidence and how do you generate that evidence? And I thought one slide, in particular, around data evolution was particularly good because I think we really do think about that pragmatic drug development, how data evolves, and even in the other talk about doing your homework.

(00:37:48):

And so I think we've seen the use of registry data be successful. It's been successful in oncology for the approval of a BATASET for acute graft versus host disease using CIDMTR data, and it has also been successful in the approval of Alpelisib for PIK3CA related overgrowth spectrum. And that was in the context of a rare disease and was done using data from an expanded access program, and was very carefully thought through predefined statistical analysis plan really in a high area of high unmet medical need and had objective endpoint with image reviewed BICR.

(00:38:32):

So I think thinking about endpoints, all of the things you've woven through your conversations, which gets me to the last point of auditing, and I think that's a really important aspect as you think about, with the end in mind, if the data are going to come in for regulatory submission, then there is going to be this process of auditing in order to potentially establish substantial evidence of effectiveness. So being able to make sure that the data are carefully collected with the provenance, reliability, and relevance necessary through the auditing process. I think all of these things are really important and we really want to hear from you within the community, so come talk to us.

Susan Winckler (00:39:17):

Thanks so much, Donna. I am struck on the, as you underscored and others have, the early and often, but also, then, with questions. Is that fair? So that it is bringing something in. All right, who's going to reach in next and ask a question or, yes, go ahead.

Dr. Kimberly Smith (00:39:36):

Yeah, and I think Donna covered all of the key points pretty well there. So I think what I wanted to highlight is natural history data, registry data, all of these data contribute an infinite amount to drug development programs. In the earliest stages, you don't even know what events are key to patients, on what timeframe are they developing it, what are the predictors of patients who are likely to have an event in the time of your trial, or there are just so many ways a number of patients are out there, where are they located? So these data just contribute in numerous ways, even in advance of being used to support a regulatory decision. So even if you never get to the point of omaveloxolone, this work is so important. So I think that's the first thing that I wanted to say.

(00:40:27):

If you then want to layer on using these data for regulatory decision-making, it gets more complex, requires more, probably, engagement with the agency, more planning, more rigor, but that's feasible, as well, with the thought and the engagement. And so I think one question that I actually had for you and those of you who presented today is, what were your different engagements with the agency and how did you navigate if you had different sponsors in an area who may want to take the data collection in different directions or a different advice for different types of drugs being developed, how did you navigate that? How did you engage and feed that back into your data collection with the idea, if the end goal was to have a drug approval and have your data be used beyond the trial planning, but in more of a regulatory decision-making role, how did that process look and do you have any lessons learned for folks who want to do that?

Jennifer Farmer (00:41:30):

Well, I think most of our discussion with regulatory agency was really more around the trial planning, so making sure that the clinical outcome assessments could be registration quality endpoints. So a lot of our early conversations with FDA, or getting feedback from FDA, was to get feedback on that data as it was coming in, and dialogue back and forth around, and ours is called the Modified Friedreich's Ataxia Rating Scale because it's modified based on FDA feedback around certain elements of the assessment that were not contributory, really. And so changing that, the way the items that are included in that was part of regulatory feedback.

(00:42:28):

In terms of the being used for a treatment decision, that was not the original plan. So I'm having a tough time, but I think part of my answer to your question is once we had a lot of data, we worked with the Critical Path Institute and we had the data mapped to CDISC Standard and in a repository where it could

be shared with anyone in the FA community. So the data set was not siloed at FARA or within an academic institution, it was at the Critical Path Institute where any drug developer could access it, as well as the FDA could access it. And so I think that's part of the answer to your question, is having the data accessible in a format that everybody can use it and not making it available to some partners and not others, or making the data set based on what one group may need and others may not.

Dr. Collin Hovinga (00:43:51):

Yes. Is it on?

Susan Winckler (00:43:53):

Yep, you're good.

Dr. Collin Hovinga (00:43:55):

One of the things I think that happens that early often is that in previous discussions with the agency in past roles, generally there's under a formal FDA, regular type B or type C meeting where the outlining what your proposed control group, for example, might be, and then providing supportive evidence to why that's important is what's done.

(00:44:19):

In general, I think there can be subtle differences to interpretability by different sponsors, but oftentimes, I think in particularly with [inaudible 00:44:28] controls in rare diseases, in particular, it's so new to them. So there's not a ton of experience where the sponsors have had these type of negotiations. So it's good to consult with people that have, as well as consulting with the agency as you prepare to go in, but be prepared to demonstrate why this is a meaningful difference, why it's meaningful change, what's the quality of the data, those types of things. But I suspect that that will be increasing because I think with accelerated approval, there's been a lot of interest in using external controls as supporting every evidence.

Susan Winckler (00:45:06):

Go ahead, Tiina.

Dr. Tiina Urv (00:45:07):

I was going to say, the question you asked was a question I was asked just last week by patient advocacy groups and researchers and they said, "Is there a way that we can get advice when we're just starting out and setting up these natural history studies and these registries when we don't even know if there's a treatment down the pike somewhere soon?" Is there a way to reach out to the FDA at that early point to make sure that what they're setting up so early is going to be useful? Because these patient advocacy groups and investigators are investing large amounts of money that are rare resources and you don't want to leave them astray. You want to make sure that they know that what they're doing is right early on.

Susan Winckler (00:45:55):

Right. Donna, do you want to jump in on that?

Dr. Donna Rivera (00:45:58):

Sure. I think the answer is, certainly, yes. There are, I think, opportunities to come in early and interact with us and understand. I think the importance of forums just like this where it's not necessarily commercial sponsors, but there's a lot of advocacy groups, as well as non-profits that are interested in the drug development space. So I would say there's a variety of mechanisms.

(00:46:22):

There's also the opportunity to come in through research INDs, so not necessarily tied to a specific development program, but I would encourage those of you to reach out to across FDA to the various development programs within oncology. As far as registries go, the oncology Role Evidence program has a website, the FDA CBER CDER Rule of Evidence program has a website. You can reach out to our email inboxes and there will be individuals able to meet with you to discuss, even early, just some of the conceptual ideas. And then also, I think as stated by our colleagues, including Carrie Jo, there's a host of guidances that do also point out to how you can start outlining the important elements.

Susan Winckler (00:47:14):

Because it can be challenging to think through, and even obviously, the agency, you know really well what you have available, but that, just navigating the FDA website can be a labyrinth. But you can find the information there, and I think you're saying go ahead and particularly to reach out to the rare disease offices, as well, with questions.

Dr. Donna Rivera (00:47:37):

Yeah, absolutely. And our colleagues are here. I know that all of us are open to really facilitating these questions.

Susan Winckler (00:47:45):

That's great. Tina, did you want to follow up with a question and then Ben, we're going to turn it to you.

Dr. Tiina Urv (00:47:50):

Oh, I have an actual question, too. I was just bouncing off of them. I'm like, oh, that's funny, I was going to ask that. So this is for Colin from Critical Path. You're developing this wonderful resource, and actually, Ben could actually comment on this, too, is you're developing these wonderful resources and you're giving people access to the data. How are you making sure that people are finding this information and that people are using it and they know it's there? If you build it, they will come. Does that always happen?

Dr. Collin Hovinga (00:48:22):

Lots of outreach. You think about the seven to 10,000 rare diseases, it's a lot of outreach, but disproportionately, it's probably never enough. We do regular meetings, we're constantly reaching out to different communities, and then we hold a lot of different webinars to help incubate ideas around the data, but also how to access and use the data. We have a rare disease meeting, we present at NORD, but there's lots of opportunities. And we do a lot of one-on-one conversations with the community and different advocacy groups all the way from helping them decide some of the things that we're talking about today, as well as how to share data as well as how to use their data type of conversation. So there's a plethora of things that we undertake. So same thing as what was said about the conversations with the FDA is that come to us if you have questions, we're happy to help or point you in the right

direction. If we don't do it, we're networked with an extremely large community of just wonderful people. So we can definitely make those connections. And I'm good with you.

Benjamin Forred (00:49:33):

And I can echo what Colin was saying, too, about making sure that the resources that are out there are made available to people and that they understand they're there. So in the terms of our program, it's a cost free option that's out there for people to use to build their registry and start. I look at as a starting point. And we've shared data with C-Path from a couple of our different groups, and I think that it's important to note that maybe 20% of the time we spend with the group is actually building the questionnaire. The 80% is spent educating and talking through problems, and talking through logistics, and just making sure that we're on the same page, in terms of what are our goals here. And once we hit those goals, what's the next set of goals? And trying to be as visionary as we can all be. Otherwise, you either wind up with a questionnaire that is so narrow in scope that it's not going to be very long-lived, or something that's so broad that it can't be applied.

(00:50:36):

And there's this Goldilocks zone that we try to hit in the middle. And I guess maybe it went a little bit off topic, but that's a big part of what we do is making sure that people know C-Path is there and the radar tool is there.

Dr. Collin Hovinga (00:50:55):

I think the other thing we do, and we try to, when we talk to have conversations because obviously we have a lens that's focused on a lot of drug development. Correct, right? So one of the things we do is we try to work with communities to define a regulatory question based on an unmet need they've expressed to us so that there is a solution that can be produced to address that specific unmet need that's in a regulatory framework. So is there something under a particular context of use that is a tool that can be used to solve regulatory question? That's generally not how most of us think. I could say as an academic researcher, I wouldn't have even known what a drug development tool was, let alone any of the ones that C-Path would have works on.

(00:51:37):

So we spent a lot of time working through that because I think at the end when people are doing their design of their natural history study, they think by collecting data and understanding what the outcome is, that's it. And it's actually a lot more complicated question and it could be refined a lot better and can actually give you more impact with low effort.

Susan Winckler (00:52:00):

Yeah, Colin, I was struck that DDT has a very different recognition outside of drug development. Yeah, Ben.

Benjamin Forred (00:52:09):

Yeah. I've worked with, in this registry space, for eight or nine years and seen it take this gradual change with AI and all these different things that have come along where at the beginning, we used to tell folks that it's important to have a physician champion or researcher champion to help spearhead your efforts. And now I find myself telling people you need that and a data scientist, because there's going to be so much going on here that if you don't have that team and that input right away, it's going to cause problems down the road.

(00:52:46):

And leads into my question, one of the things that we talked about, especially Colin, in your talk, was taking different groups of data and aggregating them into one. In the rare disease space, this is so common. Everybody's disparate in the around the world, global unique identifiers were brought up as something that can be used to harmonize that data. And that's something that we use in the past. And if you're not familiar, they're sometimes called GUIDs, but they're just a way that you can generate a unique code for an individual based on some factors that aren't going to change.

(00:53:19):

And one of the problems we ran into is there's multiple GUIDs. So how do you make sure that you're using the same one or that different groups have had the same one, or as C-Path, if you are using GUIDs, do you just tell the data contributor that they need to use this GUID when they send in this dataset?

Dr. Collin Hovinga (00:53:39):

Actually, we, at C-Path, don't advocate for specific GUID. Yeah, it sounds like something you could scrape off the bottom of your shoe or something. But no, we don't advocate for that, but we encourage it because 90, we work with different groups. We encourage them to adopt that and to adopt one that's patient friendly because I've had, we can offline talk about lot of horror stories about them, but it's essential because utilizing data across different diseases.

(00:54:09):

I'll give you an example. There's a disease state that I'm working on right now where I can say the average participant goes through probably about five different research programs where they collect bio specimens, they get data, and they travel to do this, but tracking them is nearly impossible without that GUID. And so there are a lot of different types, and some of them are better based on the disease, but I just highly recommend them and they're a sensitive topic when you talk about them because people do have their preferences.

Susan Winckler (00:54:44):

So helpful, and I think particularly, Colin, that example of the multiple when you're getting care in the multiple different places, how to collect and compile. Other thoughts from the reactor panel? We probably have time for two or three more questions. Yes, Dr. Smith.

Dr. Kimberly Smith (00:55:00):

Yeah. So I think a key challenge with use of these data for regulatory purposes, at times, is just the completeness of the data. So patients come in, but then they're lost at some point, and there's always that question in your mind of, well, were they lost for a reason that would impact the answer to this question you're trying to answer here. And so I think it's impressive for Jen, for the registry and the study, how many patients you've accrued over time and just how long the study has been going on for. So do you have any advice or lessons learned in terms of both your ability to recruit a representative group of patients? You mentioned, for instance, realizing that you were not as successful, initially, in recruiting pediatric patients, so broadening there, but then also retaining patients over time and just making sure that you have that complete data over time.

Jennifer Farmer (00:55:51):

Yeah, this was one of the topics I'd hoped the previous panel was going to discuss because it is, it's a real challenge. Families are significantly burdened and traveling. We only have eight centers in the U.S.

where people with Friedreich's Taxia can go to participate in a natural history study. And so we know that travel's a huge burden for cost and time and the physical energy that it takes, and so we try and supplement some of our funding to help provide families with some travel support. We can't fully fund all the travel, but we try and give a little support. The investigators have worked really hard with their coordinators to be really mindful about consolidating visits. So if they can combine a clinical care visit with a natural history study visit, or with a screening for a trial, or another biomarker study, but just making sure that, that person's really, when they come, they can come for multiple studies or multiple reasons, has helped a lot.

(00:57:10):

We did add virtual visits to our natural history study, as well, so that if a family can't come back in person, there's at least a minimal data set that we can collect through a virtual visit. Certainly all the PROs can be collected that way. You can get an updated medical history, medication history, there's quite a lot you can get from a virtual visit in addition to getting their medical records in the intervening year, which might have important adverse events that you're going to want to include in your data set.

(00:57:46):

So those are the big ones that we've tried to add over time to boost our retention. And I think it's important leaving that door open for people, too. That they understand that if they miss a year, it doesn't mean they're out, they're welcome back the next year or the third year.

Dr. Collin Hovinga (00:58:12):

I'd just add one of the other things that we used to do because the lost to follow-up problem is huge. So we took a page out of the rule book from Pharma, in that there's an end-of-study visit where if they wanted no longer to participate, there was an option where they could do an end-of-study visit that gave us feedback on why they left the natural history study. So if they decided not to because their disease was getting worse, they would knock that, or they just didn't want to go to the doctor as much, etc. It allowed us to just not guess, and to minimize the bias.

Susan Winckler (00:58:47):

And then that type of explanation I think would be helpful from the regulator perspective. Okay. All right. Donna's, she's got the trigger finger there. Go ahead.

Dr. Donna Rivera (00:58:59):

Well I bet both of you have examples of ways in which you've been successful and creating efforts in developing rare disease registries, and I was wondering, you mentioned expertise and the need for collaboration. These efforts, I think, at least on the regulatory side, our teams are very multidisciplinary when it comes to review. So I was wondering for people that are thinking about starting beginning a registry effort, what's your wisdom? What's your advice to these groups and what are your take-home points?

Jennifer Farmer (00:59:34):

I think that the first piece of advice I have is don't try and do it all. Start small, start focused, even if it's with that contact registry. You heard earlier, there's a lot you can do with a good contact registry. You understand the prevalence of your disease, maybe, that you didn't previously understand, or you have an ability to enroll a clinical trial. Start with something that you can do well and you can sustain. And I think if you get success, you'll be able to expand upon that and expand upon that.

(01:00:13):

And the other thing to understand is whatever you start with won't be what you're doing five years from now, 10 years from now, 20 years from now. You're going to keep evolving as you go forward. So just don't get stuck by, it's too overwhelming, I don't know what to do. Start small and start with something you can do well.

Susan Winckler (01:00:38):

Jen, I want to, because I think some people might hear that and say, well how does that fit with, begin with the end in mind. But the end in mind, I think if I hear you correctly, is learning more, and so it's that continuous learning cycle, and so you've got to have good enough information to continue to learn.

Jennifer Farmer (01:01:01):

Exactly. And when we got started, it wasn't that we were going to use our natural history as an external control.

Susan Winckler (01:01:08):

Right.

Jennifer Farmer (01:01:09):

That wasn't the end that we had in mind. The end that we had in mind was we want to be able to do a trial.

Susan Winckler (01:01:15):

Yeah, okay.

Jennifer Farmer (01:01:15):

And so the end, unfortunately, keeps moving, which is kind of annoying, but it's a reality.

Susan Winckler (01:01:22):

But the end is to continue to learn, so there isn't really an end there. All right, Colin, you've got 47 seconds.

Dr. Collin Hovinga (01:01:29):

I'm Just going to add, echo all what Jen said. That's fully founded. The only other thing I would add is I know this is a pain because as you're figuring things out, is providing structure because somebody else that's not in the room isn't going to understand what your data collection strategy looks like, they're not going to be able to extrapolate what you're thinking. If you're doing things like imaging and other assessments that could be read differently by different individuals. You've got to have a rule book. And without that rule book, it becomes less reliable and that creates more variability and it's subject to interpretation. So with that handbook and whatever that question is, expect you're going to revise it. And I think that's the biggest thing is you're probably not going, to Jen's point, you're not going to be done with the first reiteration and just accept that. You're going to come up with more hypotheses and more things you need to about. But get started, get moving, have well thought. Good documentation.

Natural History Studies and Registries that Informed Regulatory Decision Making
Example: Nulibry for molybdenum cofactor deficiency
Ronen Spiegel, MD, Emek Medical Center
Liza Squires, MD, Sentynl Therapeutics
Example: Lumasiran and Nedosiran for Primary Hyperoxaluria
John Lieske, MD, Mayo Clinic Hospital – Rochester
Reactor Panel
Catherine Lerro, PhD, MPH, Oncology Center for Excellence, FDA
Kirtida Mistry, MBBCh, DCH, MRCPCH, Center for Drug Evaluation and Research, FDA
Jill Morris, PhD, National Institute of Neurological Disorders and Stroke, NIH
Catherine Pilgrim-Grayson, MD, MPH, Center for Drug Evaluation and Research, FDA

Susan Winckler (01:02:25):

Excellent last point there. So let's thank our reactor panelists and our speakers for another informative session, which takes us to the part of the day in reading the chat and talking with you at break and the cards that are coming up, there's been a bit of, let's hear more about where this has worked, where there has been regulatory decision making. And so we're going to come, now we're going to talk about case studies. So this is pulling a lot of it together. We, for this session, also have reactor panelists and so let's bring our reactor panelists up to the stage for this session. They will include Dr. Kathy Laro from FDA's Oncology Center for Excellence, Dr. Kirtida Mistry from FDA's Center for Drug Evaluation and Research, Dr. Pilgrim-Grayson, also from CDER, and then Dr. Jill Morris from the NIH National Institute of Neurological Disorders and Stroke.

(01:03:26):

Now we are going to have our first case study has a virtual presenter and an in-person presenter. So we are joined by Dr. Ronen Spiegel of the Emek Medical Center. He is more than just a few hours ahead of us, so we thank him for investing his evening with us. And then Dr. Liza Squires from Sentinel Therapeutics. You're both going to walk us through the journey of Nulibry for molybdenum cofactor deficiency. So Dr. Spiegel and Squires, we'll turn it to you.

Dr. Liza Squires (01:03:58):

Thank you.

Susan Winckler (01:04:07):

Dr. Spiegel, do we have you?

Dr. Ronen Spiegel (01:04:12):

Hello? Can you hear me?

Susan Winckler (01:04:15):

Yes, we can.

Dr. Ronen Spiegel (01:04:17):

Thank you. Thank you and thank you for the kind introduction and Dr. Squires will assist me in moving forward presentation. So the title of our presentation is the Leveraging Natural History Data for Rare Diseases Drug Development and Approval. And we will use Molybdenum cofactor deficiency type A and

Ultra-Rare Disease as an example of the utility of natural history studies to demonstrate drug efficacy, and in this case, increased survival of treated patients with Fosdenopterin and novel treatment for molybdenum cofactor deficiency, which we will term here, MOCD. And next slide please. Next slide please, Liza. Thank you.

(01:05:18):

Thank you. So molybdenum cofactor deficiency is an ultra-rare autosomal-recessive disease. It was first describing a human patient in 1978, and the causative gene MOCS1 was identified 20 years later, in 1998. Patients typically present within the first days of life with intractable seizures, feeding difficulties, and rapidly progressive encephalopathy that results from the extremely neurotoxic sulfite accumulation in the brain. The disease further progresses with loss of all developmental abilities and the inability to acquire new ones and early lethality within the first years of life. All patients have characteristic biochemical abnormalities with decreased urinary and plasma uric acid and elevated xanthine and S-sulfocysteine. Next slide, please.

(01:06:25):

So here you can see the de novo three-step synthetic pathway of molybdenum cofactor. It serves as a cofactor in four separate enzymatic reactions, including sulfite oxidase, which converts the highly neurotoxic sulfite into the non-toxic sulfate that is excreted in the urine. There are three types of MOCD in agreement with the defected enzyme. As seen on the right panel, the [inaudible 01:06:57] mutations in the first enzyme MOCS1 prevent the formation of cyclic PMP and the subsequent deficiency of molybdenum cofactor and accumulation of S-sulfocysteine. Next slide.

(01:07:16):

So MOCD is a pan-ethnic disease. Collectively, all three types of MOCD result in a very similar clinical and biochemical phenotype and are differentiated exclusively by genetic testing, with MOCD type A being the more common, comprising more than half of the patients. All together, more than 100 MOCD cases have been reported so far, but the disease is probably under-diagnosed and, in specific, the later onset attenuated cases. Next slide.

(01:07:59):

So the story of developing a novel treatment for MOCD Type A started more than 20 years ago with this brilliant researcher, Dr. Guenter Schwarz, in the picture. In these Studies, Dr. Schwarz showed already, in 2002, that the lethal MOCD type A mouse model, was rescued following replacement treatment with cyclic PMP that was stably produced from E. Coli strains. In 2008, baby Z, from Melbourne, Australia, was the first MOCD type A human patient to receive daily intravenous cyclic PMP treatment. Although the clinical outcome of this patient was only partially successful due to the relatively late initiation of treatment, the proof of concept was confirmed with complete normalization of the typical biomarkers. Next slide.

(01:09:08):

Since the first treatment in human patient, several other named patients were treated with the recombinant cyclic PMP that was produced at Orphatec/Colborne. However, given the extreme rarity of the disease, the challenges in early diagnosis and the very narrow optimal therapeutic window, it was clear that randomized double-blind placebo-controlled clinical trial is unethical, and therefore, a different strategy was needed. Next slide.

(01:09:48):

So the strategy that was chosen was to establish a comprehensive natural history cohort that will serve for comparison with the treated patients. In brief, the study design was observational, multinational

with both retrospective and prospective arms. In the retrospective arm, clinical, biochemical, neuroradiological and genetic data of diseased and living patients were collected. In the prospective arm, clinical data and characteristic biomarkers were collected and analyzed in a central lab. The primary outcome was to characterize the natural history of patients with particular emphasis on age and symptoms at presentation, survival data, disease progression, and biomarker levels. I will now hand over the presentation to Dr. Squires.

Dr. Liza Squires (01:10:55):

Thank you Ronen. We'll continue with the development program of Fosdenopterin. Several companies were involved in this development program. Colbourne Therapeutics, founded by Guenter Schwarz, who you just heard about, was the company that established the named-patient use, which allowed for the demonstration of early efficacy in the initially treated patients. The named-patient program actually was continued to be run by Colbourne Therapeutics until it was assumed by Origin and Origin continued the named patient program through the acquisition of the drug by Sentynl Therapeutics and Sentynl still has a named patient program for patients outside of the approved regions to receive treatment. Alexion Pharmaceuticals acquired Cyclic PMP from Colbourne, and at that point, the first thing that they did was actually to reformulate to simplify the drug manufacture and to also provide drug that was consistent and in a scalable manner so that we could meet clinical supply requirements.

(01:12:21):

The other thing that Alexion did that we've talked a lot about is that they had to set up a clinical development program and they very honestly did begin with the end in mind. Now, unlike many of the other natural history programs you've heard about today where there's been an active and engaged patient advocacy group, because of the severity of this disorder and the fact that children often don't survive past early childhood, no patient advocacy group existed. So it fell upon Alexion to design a natural history study, and really I think the motivation was to utilize all available data in this ultra-rare, mostly fatal condition.

(01:13:09):

So as Ronan mentioned, the natural history study looked at both deceased patients and living patients and collected retrospective data on all patients as well as prospective data on those living patients who consented to participate in the prospective portion of the trial. In addition, Alexion ran a chart review retrospective observational trial of those children who had been treated with recombinant cPMP where their families were able to give consent. Alexion also ran two prospective Phase 2 open, open-label studies, one of which was a switch study in which children who'd been treated with the recombinant drug were switched to the newer synthetic formulation. And a second study, which was also a prospective open-label study of treatment-naive patients.

(01:14:22):

There we go. The development program utilized really centered around the natural history data. So because many of the patients were deceased and we were leveraging data from a retrospective portion, it was critical to think about variables that could be ascertained through medical charts. And so many of the variables you see on the right-hand side of this screen are things that you would typically see in a healthcare chart of a child, either in general pediatrics or obviously children with more serious disease, including documentation of baseline characteristics, growth parameters, neurologic examinations, and developmental assessments. The objective of the study was to summarize all data for the treated patients and compare it to the data in the natural history study, specifically looking at the survival rate of those children who were treated compared to the natural history trial, as well as to assess the other variables.

(01:15:37):

The full analysis set for the NDA included 13 treated patients and 37 patients from the natural history study. The demographics show that there's a slight imbalance between males and females in the natural history study. We believe this is merely due to small sample size. The region of birth is well-represented across both the treated and the natural history patients with North America, Europe, and rest of world, largely focusing in the MENA region being represented in both the treated and natural history patients.

(01:16:25):

The age of first MoCD symptom for the treated patients is all less than 28 days, and that's because the protocol was specifically focusing on neonates who have the most severe disease. In the natural history study, you can see that this was the vast majority of patients. However, four patients had the later onset disease, which does have a milder phenotype. The presenting symptoms, again, are seen across both the treated patients as well as the natural history patients and include seizures, feeding difficulties, high-pitched cry and exaggerated startle response.

(01:17:17):

This is a Kaplan-Meier curve of the overall survival comparing the treated patients in orange to the untreated control patients in black. The treated patients had a one-year survival of 92% compared to 75% of the natural history controls. Two-year survival was 84% for treated patients, and 70% for the historical controls. The mean age of survival of the untreated patients was 50.7 months, and this overall survival cannot be estimated for the treated group due to the low number of events.

(01:17:59):

A genotyped matched analysis was also performed. In this analysis, treated patients were matched with natural history patients who had the identical pathogenic variant or, where that did not exist, a variant that was felt to have a similar impact on protein expression. Here, the treated patients had an overall survival at one year of 92% compared to 67% of the control group. And at three years, the survival for the treated patients was 84% compared to 55% in the natural history study.

(01:18:47):

The program also looked at the neurotoxic biomarker, S-sulfocysteine, as it was excreted in the urine corrected for creatinine. You'll see that at the baseline values, the treated and untreated groups both have significantly elevated values of S-sulfocysteine. At the last visit, treated patients have a much lower value, actually well below what's considered pathological, and the untreated controls actually have a value that's a bit higher than that that was seen at the baseline visit. Sitting unassisted was evaluated both by medical records and in the prospective study. And in this group you see that sitting unassisted by 12 months was achieved by 43% of the treated patients compared to 11% of the untreated controls. Unassisted sitting by the end of study, meaning at any time to the end point of the study, was seen in 63% of treated patients compared to 11% of the untreated controls.

(01:20:08):

The gross motor function classification system is a scale that was originally developed for the use of physical therapists to assess the motor function of children with cerebral palsy. A child with a gross motor function score of one is considered age-appropriate motor development. So for a child at 12 months, that includes being able to move in and out of the sitting position independently, to crawl on all fours, to pull to stand, and to cruise along furniture. In the treated group, 29% of treated patients were able to reach the milestone by one year of age, compared to 14% of the untreated controls. By the last visit... And just for context, at age two, a gross motor function scale of one would be a child who's walking independently, and by age six it would be a child who's able to perform some higher level gross

motor skills such as running, jumping, and climbing stairs. 38% of the treated patients were able to achieve a gross motor function scale of one by their last visit compared to 9% of controls. Oral feeding is an important neurologic function that also has meaningful impact on social interaction and quality of life. And at the last visit, 54% of treated patients were feeding orally compared to 30% of the controls. On the right-hand side of the screen is the Kaplan-Meier, and this shows that the time to sustained non-oral feeding was 75 months for the treated patients compared to ten-and-a-half months for the untreated controls.

(01:22:14):

As part of fair balance, we'll quickly discuss the safety of cPMP. Most of the adverse events were mild to moderate in nature and were not related to the study drug. The most common side effect of fosdenopterin was infusion catheter-related complications. This drug is given intravenously once a day by central catheter. And the other adverse events such as viral infection, pneumonia, and vomiting are those typically seen in a pediatric population. And this was a very long-term study. There were no discontinuations or dose modifications due to adverse events. There were two deaths in the retrospective data. One patient died due to necrotizing enterocolitis and another patient died due to RSV pneumonia.

(01:23:03):

Because fosdenopterin or cyclic PMP is a terin, it does make patients oversensitive to sunlight. Parents and their caregivers are advised to avoid or minimize exposure to sunlight and artificial UV light and to adopt precautionary measures when exposed to the sun. This includes wearing protective clothing and sunglasses, and in children older than six months of age, to apply a broad- spectrum sunscreen. If photosensitivity occurs, caregivers and patients are advised to seek medical attention immediately and consider a dermatologic evaluation.

(01:23:41):

In conclusion, approval of fosdenopterin would not have been possible without this novel natural history study. It allowed for the demonstration of improved survival and for the demonstration of improvement in the urine SSC biomarker levels. Additional confirmatory evidence was provided by the animal model, and in closing, the drug was safe and well tolerated. In summary, this natural history study provided an opportunity to better characterize this ultra-rare or disorder, to develop appropriate disease biomarkers and to ethically study potentially life-saving treatments and to facilitate the development of therapeutics in ultra-rare and rare disorders. Thank you for your attention.

Susan Winckler (01:24:37):

Thank you so much. Dr. Spiegel and Squires. Dr. Spiegel. We will bring you back on camera when we get to the Q&A session. And Dr. Squires, thank you for taking a seat there. I can assure you there's already double-digit questions in the chat, and I expect those from our reactor panelists as well.

(01:24:55):

So we have a second case study and then we will turn to our discussion. Our second case study will be presented by Dr. John Lieske, who's a nephrologist and professor of medicine at Mayo Clinic in Rochester, Minnesota. And Dr. Lieske will walk us through Lumiceurin and nidoserine for primary hyperoxaluria. Dr. Lieske, the stage is yours.

Dr. John Lieske (01:25:17):

Great, thank you. I think all these rare diseases are a mouthful.

Susan Winckler (01:25:21):

They are, and I practiced half of them and you can't tell, but that's all right.

Dr. John Lieske (01:25:25):

Right. Thank you very much. See if I get to slides one here. But I had like to thank the organizers for the chance to be here, present on our rare disease. It's been for me personally and for everyone a long road. Here we go. There we go. So I included my disclosures. I was going to take this out because it probably wasn't so relevant, but just to make the point that, and if you're working in these rare diseases, that our approach has been to be very inclusive because lots and lots, especially as you build these registries and you have the patients and a lot of companies will come to you and I think you have to be ready to talk to them because I can tell you that the first company that came to us was not the one that ultimately was the one that developed something that was useful for our patients.

(01:26:19):

So I'm talking a little bit about primary hyperoxaluria, the key role of our patient advocacy group as well as the American Society of Nephrology for developing our registry and our interactions, the key natural history features that informed the treatment efficacy measures. And then finally what the ultimate outcome of these efforts were.

(01:26:37):

So for those that don't know, I'm not going to go through these pathways in great detail, but primary hyperoxaluria is a disease that involves the liver. There are several genetic defects that lead to blockways and pathways that then lead to overproduction of oxalate. Oxalate, I have another slide, is an end product of metabolism that we can't metabolize. So in each of these three known genetic diseases, you increase production of oxalate coming from the liver, and then this leads to problems because we don't have a way to deal with it as humans. High concentrations of this molecule, oxalate, in the urine, lead to kidney stones, nephrocalcinosis, chronic kidney disease, and often kidney failure. And then when you have kidney failure, it actually can deposit throughout the body and lead to bed outcomes as well.

(01:27:21):

There are two types, basically the primary hyperoxaluria, which is the genetic form, which was on the last slide there, which is due to things going on in the liver. It's a rare disease with one to three per million in the population. And then enteric hyperoxaluria can be due to over absorption of oxalate from your gut, which we're not talking about today.

(01:27:41):

So what is oxalate? It's this small molecule here, two carbons, four oxygens. It is two negative charges, likes to combine with calcium in the urine. We have lots of calcium around, so it makes these nice calcium oxalate crystals, can make these kidney stones, but we also can get some of it from our diet, and that's important especially for enteric. So some things are high in oxalate, some plants you might eat. If you absorb enough of this, then that also goes out in your urine and can lead to kidney stones, and then in patients with fat malabsorption, to enteric hyperoxaluria.

(01:28:11):

So with that little bit of a background, if we go back about eight years or so, the group that we were working with, the Oxalosis and Hyperoxaluria Foundation recognized that there was an increasing possibility for clinical trials in oxalate-related diseases. There were approaches out there to try to manipulate the gastrointestinal microbiome to either delay absorption of oxalate or to actually break down oxalate, and there are enzymes that we know that can do this. So there were people working at

trying to use the actual enzyme or these bacteria manipulations to do that. And then there were also approaches to either block these pathways in the liver that were overproducing oxalate with siRNA, with small molecules or with chaperones.

(01:28:54):

At our advisory board meeting in 2016, we recognized that primary and enteric hyperoxaluria were both rare diseases. The clinical trials looking at kidney function, chronic kidney disease, kidney failure or even kidney stones were probably not feasible because of the long lag time for these things to happen and the relatively small number of patients that were available for these sorts of studies. It was recognized that the FDA was increasingly receptive to alternative approaches to looking at these hard clinical endpoints. And there were certain case examples out there like Duchenne muscular dystrophy. We had the idea that we could put together some sort of an informative white paper on oxalate diseases. And in general, the scientific advisory board was very enthusiastically supportive of this. We really didn't have funding in particular to do this, so it was an unfunded mandate, but we had a dedicated group that was going to be willing to work on this.

(01:29:52):

So at that point, we went off to Washington to meet with folks. Our first stop there was at the American Society of Nephrology, and then that was where we really learned most about the Kidney Health Initiative, which was a unique resource that we had available to us in the nephrology space. The Kidney Health Initiative was actually formed to bring together patient advocacy groups in this industry, the ASN and the FDA, to try to do collaborative projects to try to basically develop products that would be useful for patients in a rigorous sort of way.

(01:30:25):

So the collaborators are just listed here, but it included things like patient advocacy groups as well as researchers, foundations, et cetera. And then we did notice that on the list of projects that were funded at the time we were looking at this was one identifying surrogate endpoints for clinical trials in IgF nephropathy, which we thought was perhaps analogous to what we were trying to do.

(01:30:47):

So at that same initial visit in 2016, we had set up a visit here at the FDA and that was mentioned that the FDA is very open to collaboration and talking. I don't think people often appreciate this, but it was true. We met here for an hour. They in general agreed with our general concept that probably these long-term hard outcome trials were not going to be particularly feasible. We talked a little bit about the mechanisms for a surrogate endpoint and our candidate surrogate here would be oxalate as the endpoint for our rare disease. There are ways to validate these things, but there are certain long-term obstacles to doing that. As mentioned, that might not be the very best approach, but there was really no firm advice about what we should do. But it was a very informative and helpful meeting.

(01:31:34):

We did submit a proposal to the Kidney Health Initiative to try to develop a project. It was well received, we got some constructive feedback, wasn't funded on this very first cycle, but the plan was to resubmit this the following year, which would be our next opportunity. The next year at our patient advocacy group meeting, we went ahead with trying to put together our white paper to look through what the outcome data was for primary hyperoxaluria and try to put together some sort of a scientific document to describe this. We tried to be very organized. We had eight different areas we were looking at, including the biology of oxalate there at the top. We had a group of researchers and physicians that were willing to work on this without really any funding for it. And we divided into groups and put together these documents. At the same time, we put in our reapplication to the Kidney Health Initiative

and that was ultimately funded and we continue work on this document as well as getting data from the registry, which we had funded for years prior to that.

(01:32:43):

So again, we had this funding in 2017. Then we had a bigger group outcome. One of the things that the Kidney Health Initiative did provide for us was an administrative framework, which we did not have as the patient advocacy group. So there were people that had contacts with FDA and they also helped to organize our group, organize meetings, organize these working groups, and we systematically worked through what was known about the natural history of primary hyperoxaluria, what the scientific data was, the literature, and what data sources might or might not be available.

(01:33:17):

One of the key concepts that we got from the FDA was the endpoint markers for clinical trials, what was required for a surrogate endpoint, that there had to be biological plausibility, there had to be epidemiologic or other data showing consistent association between this biochemical marker and the clinical outcomes. There had to be data from clinical trials showing that the effects of treatment on the candidate marker largely accounted for their effects. And then an assessment of the quantity of effect, the M marker that needed to be clinically significant.

(01:33:50):

So that was where the registry came in. So we had had a primary hyperoxaluria registry that had been around for about 20 years or so prior to this. It initially had been funded by a supplemental grant from the NIH tied to another grant on the primary hyperoxaluria, and then we'd had it as part of a RDCRN funded consortium, the Rare Kidney Stone Consortium as well. And so about the time when we were putting together these data that was needed for these documents and for this project looking at endpoints for primary hyperoxaluria, we had about 600 patients with primary hyperoxaluria. This is just showing some of the demographics here. Being a severe rare disease, there were a significant number of people that were deceased in this case, about 11% of people were deceased at the time that we were doing this.

(01:34:41):

And then kidney failure was quite common. So you can see that kidney failure at the top two rows there, almost half of the people had kidney failure at the time we were putting together this data. And then this was a medical record-derived registry, so that we did have a lot of laboratory data including serum labs, urine labs, and then a lot of years of follow-up as well.

(01:35:02):

And I think this was one of the key findings that we had from this registry. So all the legwork we had put in getting this data over many years in many hundreds of patients, the normal level of urinary oxide excretion in millimoles, which is what this graph is showing, is going to be about 0.3 or so millimoles per day. And in primary hyperoxaluria, it tends to be quite high between one to three millimoles per day. So it can be up to even 10 times what you might expect to see in the urine.

(01:35:32):

And when we looked at though the outcomes as far as kidney failure, which is one of the key outcomes in primary hyperoxaluria, it wasn't just any elevation was bad, but indeed it was pretty severe. Elevations were bad. So this is divided by quartiles of our data. And the patients that had over 2.4 millimoles per day, at 30 years, only 20% of them were free of kidney failure. And then if you go up to the intermediate zone, 1.6 to 2.4, it was about a 50/50 proposition. And then if you were less than 1.1 millimole per day, your renal outcomes, on average at least, are pretty good.

(01:36:08):

And if you look at the types of PH, they're also probably not created equal. And PH1, which is one of the specific genetic defects, their risk of kidney failure out to age 60 is almost uniform, at least historically. Whereas PH2, one of the other genetic outcomes is indeterminate and intermediate. And then for PH3, they do somewhat better. There are cases of kidney failure, but it's relatively less common. And indeed that parallels with their urinary oxalate excretion in general. The urinary oxalate excretion is the highest for PH1 and the lowest for PH type three.

(01:36:46):

On the other hand, if you looked at kidney stone events, that actually is quite common for all the types of PH. So starting at very young ages zero to nine, they're on the bottom there, between PH1, PH2, PH3, that the number of stone events per year is about 0.2 to 0.3 in all the types of PH. So that's a lot of stone. So one kidney stone every two or three years. And that is persistent throughout lifetimes. So even though PH3, maybe they don't get as much kidney failure as the PH1 patients, but they get tons and tons of kidney stones.

(01:37:21):

The eGFR trend for primary hyperoxaluria is a little bit different than it might be for other kind of kidney diseases that we as nephrologists study, that in general we think of there being a slope of decline that it's linear over the years in people. But indeed that's not really what we've seen clinically in PH is that in general the GFR does go down down over some period of time. But when patients reach about CKD stage 3b, which is an eGFR less than about 45, it seems like people often will then just plummet off a cliff. And that's indeed what we were able to show from our registry data, that the loss of eGFR shown here as their annualized change in eGFR over time was about -5 or so in CKD stages 2 and 3. But then suddenly when you got to 3B, it was about -10 to -20. And then when you're in stage 4 getting closer, they just really go down very quickly there, 20 or so. So basically going from 20 to zero over the course of a year or so.

(01:38:27):

The other thing that we see with primary hyperoxaluria, so kidney failure is obviously not a good thing, but it's a particularly bad thing if you have primary hyperoxaluria because the oxalate tends to deposit throughout the body. So when you can no longer get rid of it through the kidneys and dialysis doesn't really remove it all that efficiently, suddenly you're getting oxalate deposits throughout the body. This is showing what happens with oxalate, that there is this increase with declining eGFR, that it's going up curvilinear or so that when your eGFR gets down below about 15, your plasma oxalate on average is up there over 30. And indeed this is above the saturation point where we would predict that oxalate should be depositing throughout the body, and that's what we see.

(01:39:09):

Clinically on the other hand, if you look at people on dialysis with primary hyperoxaluria type 1 the most severe, the plasma oxalate does not really go up with time over dialysis. It's really flat. And that's not because their oxalosis is not getting worse, but it's because the oxalate's going into their bones and tissues and everywhere and it's not staying out in the bloodstream. So they've crossed this point of supersaturation. And so really plasma oxalates is not the greatest biomarker for efficacy for dialysis of somebody with hyperoxaluria. And if we follow these people over time, this is a difficult graph to get your head around, but in general, if we go out to five years or so, the brown, which shows evidence of oxalosis in the various organ systems. Almost all patients have oxalosis in all organ systems if you go out to four or five years on dialysis. And in general, they die a relatively unpleasant death.

(01:40:04):

So based on the data, and this is just the highlights of the things that we were able to glean out of the registry, we identified several viable candidates for endpoints and trials in hyperoxaluria, plasma oxalate, urine oxalate change in eGFR and kidney stone events.

(01:40:23):

This was summarized in several publications, the most important one, the first one there, the endpoints for clinical trials in primary hyperoxaluria. We also had a patient advocacies, two parents here that led the efforts for a patient caregiver perspective article that accompanied this, Jennifer Lawrence and Debra Wattenberg. And then we described this as well in this AJKD editorial talking about the process of developing our endpoints.

(01:40:53):

So to then get into the trial. So based on all this work, there were two companies that were fairly far along at the time we were putting together these endpoints documents. And they had two small inhibitory RNA strategies for treating primary hyperoxaluria type 1. Lumasiran targets glycolate oxidase, which is a key precursor for oxalate production that's upstream of the AGTG protein. And if you starve that of glyoxylate, then you would expect that you would have less oxalate generated. And then nedosiran targets LDHa, which is a more final step that glyoxylate transferring to oxalate would get blocked theoretically with nedosiran. The thought and hope was that perhaps this would be effective for all three types of PH, whereas the lumasiran would be useful only for type I.

(01:41:52):

And this was the key pivotal study for the nedosiran, which was the glycolate oxidase study. And the patients, and you'll see that it was a relatively short study and a relatively small number of patients based on all the data that we had and that went into the design of the study. But it was three months, patients were randomized two to one to get lumasiran, and then after three months, those that were on placebo were then transitioned over to active agent. And then there was an open label extension, everybody on lumasiran for the next 36 months.

(01:42:22):

And the key finding in this first study in the first six months was that patients that were on lumasiran had a fairly dramatic drop in their 24-hour urinary oxalate excretion, down close to the upper limit of normal there, which is about 0.5 millimoles per day. Whereas the placebo, there was really no effect on urinary oxalate excretion out to six months. And really largely based on this study, which was ultimately only 39 patients, this was approved as an orphan drug in November of 2020.

(01:42:54):

There were companion studies in other populations, including those with chronic kidney disease that showed changes in plasma oxalate, both in patients that were near but not on dialysis, and as well as patients that were already on dialysis. Nedosiran was the LDHa targeted small inhibitory RNA. They also had multiple studies looking at different sorts of patient populations. The key study though was their PHYOX2, which the design I would say was fairly similar, if not fairly identical really to the study with the lumasiran looking at over six months the effect of their agent on urinary oxalate excretion versus placebo. And I would say the effects were more or less interchangeable. It seemed like both of these things worked pretty well, that they dropped the urinary oxalate excretion close to the upper limit of normal when they were on the agent. And placebo really did very little.

(01:43:50):

Companion efforts to this included patient voice of the patient activities where we had a conference with the FDA to get the input of the patients, what they were willing to endorse as far as a treatment. As

part of that, we did quality of life efforts. And I would shout out that REDCap is not only useful for organizing sort of hard data, but it's also very good for these sort of quality of life exercises. And we were able actually to use REDCap to do this study in concert with Novo Nordisk to help with their program with nedosiran.

(01:44:27):

And we incorporated into this validated tools. There was one PH specific survey that we developed, but also things like the Wisconsin stone Quality of Life and the Work Productivity and Activity Impairment Questionnaire. And some of the key things that the patients told us were they had lots of kidney stones and they worried a lot about decreased kidney function. And because of all of this, they had a lot of anxiety or depression. And what outcomes would they deem as most important were stopping the formation of kidney stones, decreasing their need for super hydration. Really, these patients are told to drink tons and tons of water, and they apparently find this quite burdensome. And then stopping disease progression, meaning they were very worried about kidney failure. Because everyone in this disease space knows the consequences of kidney failure are relatively severe.

(01:45:13):

So the current treatment landscape, based upon all this, that we have two agents that seem to be equally effective for type 1 PH. There are still some unanswered questions regarding the optimum dosing, even though we thought that nedosiran might work for PH 2 and 3, the data on that are fairly unclear at this point. So there's clearly some things about the pathways we don't understand. It seems that maybe not all patients with these genetic diseases respond equally to these agents. So there may be some genotype phenotype things we need to work out.

(01:45:46):

There are still other approaches being looked at, including gene therapy, small molecules, perhaps using multiple agents to target different targets at once. There may be opportunities to use these agents instead of the liver transplant, which was the traditional therapy for these diseases. And thus, given all these unanswered questions, there's still a key role for the registries going forward.

(01:46:11):

So in conclusion, I can say that this project worked as we had envisioned. We were ripe for success, really having the patients, the registry, really once this small RNA technology became ripe, this was one of the diseases that showed up on the development pipeline for these two companies as well as others. Pulling this data and retrospective registry is crucial for understanding monogenic diseases like this. And because of all this, we have two approved therapies in 2024. With that I can conclude. Thank you.

Susan Winckler (01:46:42):

All right, thanks so much, Dr. Litsky. So let's turn to our reactor panelists and have some conversation about the case studies that you just heard. I mentioned your names before, but to remind everyone, we are joined by Dr. Katherine Laro from the FDA's Oncology Center of Excellence, by Dr. Kirtida Mistry from FDA's Center for Drug Evaluation and Research, Dr. Jill Morris from NIH, and particularly the National Institute of Neurological Disorders in stroke. And finally, Dr. Catherine Pilgrim-Grayson also from CDER. Oh, Dr. Pilgrim-Grayson's got it.

Dr. Catherine Pilgrim-Grayson (01:47:25):

I want to.

Susan Winckler (01:47:25):

Yes, go ahead.

Dr. Catherine Pilgrim-Grayson (01:47:25):

Yes. So as the acting director in the division of Rare Diseases and Medical Genetics, I just want to take a moment to reiterate what you've heard from many of us in CDER. So we acknowledge that there's a significant unmet need for patients with rare diseases and for their families. And many of the conditions have devastating outcomes and most of them don't have available treatments. So I just want to reiterate our commitment to working with you to bringing safe and effective treatments to patients and their families. And I think fora like this are perfect opportunities for sharing learning as we move that work forward. So I just want to put that out there.

(01:48:11):

Next I have a comment and a question. So I think we've established that rare diseases are complex and each disease has unique considerations. And these two case examples highlight very nicely how development programs have to be tailored to those unique considerations and natural history studies and registries can really help fill those knowledge gaps as we move the work forward. So speaking specifically to natural history studies and to [inaudible 01:48:45], which was reviewed in my division, you have heard that the applicant was able to provide substantial evidence of effectiveness using one adequate and well-controlled trial and confirmatory evidence. And in that trial they used the natural history study as the control arm.

(01:49:09):

I think it provides a really elegant example of how the planning that went into that natural history study and the planning that went into that trial allowed them to address all of the things that we need to be able to evaluate when we're looking at the science. So I just want to highlight some important things that Drs. Spiegel and Squires pointed out in their talk. So one thing is that they selected a primary endpoint that was clinically meaningful for patients, mortality. It's also reliable and it's objective. That's really, really important. They were also able to demonstrate a large treatment effect on that endpoint.

(01:49:53):

Also, in design of their study and in the statistical analyses, they're able to address many of the biases that we would be concerned about when you're using external control. So you were able to address selection bias through numerous things, but some things you pointed out were the genotype matching and matching patients in the treatment group and in the natural history study on age of onset of symptoms, you also were able to adjust detection bias.

(01:50:22):

And then another thing we're concerned about, of course, is the post hoc nature of the analyses. So in the natural history study, the mortality outcome was already known for many of the subjects in that arm. But with all of the points that I've mentioned before, plus the fact that there was mechanistic and confirmatory evidence, we were able to really feel that in spite of those concerns, the evidence was there for approval. So it's a really elegant example.

(01:50:51):

Now, your story, barring the long timeline, could almost make it sound like, oh, this natural history study came in a nice box with a bow around it, but that's actually not the case. And then a morning we discuss the challenges that can happen or that you can encounter. So I just was wondering maybe if Dr. Spiegel and Dr. Squires could maybe point out one key challenge that you encountered in developing and executing the natural history study. And maybe there's a learning there in how you address that

challenge that could be applicable more broadly, even though your disease is ultra-rare and has its own distinct considerations.

Dr. Liza Squires (01:51:38):

I'll go ahead and start and then hand over to Ronen. So I think that one of the challenges, particularly in the rare disease we were studying is that because it was an ultra-rare disease and that the treatment was relatively new and under investigation, there's not a lot of time for intervention. So as it turned out, this was one of the challenges of identifying patients for both the active and the natural history study because often patients were not diagnosed until a second affected sibling had been born. So that was challenging and unfortunate, obviously for the families and for their community. But what it did was it did allow for the potential that some children could go into the treatment arm and sometimes their affected siblings were in the deceased arm. Ronen, do you have anything to add?

Dr. Ronen Spiegel (01:52:45):

Yes, and I also want to address Dr. Squires, Liza already mentioned the emergency in starting treatment very early because the disease is rapidly progressive. And one other point is that you're practically unable to do a double-blind placebo-controlled clinical trial in this disease because you have to put a central line and to treat daily intravenous treatment with the patients. And it's clearly unethical to put a central line and to put a placebo in the central lines. So the natural history arm is highly important in this setup. So this is the point I wanted to raise.

Dr. Catherine Pilgrim-Grayson (01:54:05):

I think what I'm hearing from both of you is that the challenge that you encountered in this ultra-rare disease that's rapidly progressive and has fatal outcomes is that the time constraint was a big challenge in terms of enrolling patients in both arms. Thanks.

Susan Winckler (01:54:22):

All right. Who's next on our reactor? Yes, go ahead, Dr. Morris.

Dr. Jill Morris (01:54:26):

So one thing I haven't heard yet today and I think is really important to emphasize is that once a therapy is developed or approved by the FDA, the continued follow-up of those patients and those clinical outcome assessments. So being at the Neurology Institute at NIH, we have a lot of complex diseases and I'm in charge of the lysosomal storage disorders, the leukodystrophies. And what we've seen is, for example, enzyme replacement therapy has been developed for a systemic disorder that includes a neurology phenotype. But as the children are treated, the cognitive deficits, all of us suddenly became apparent where normally they didn't live long enough to assess that. Or in a disorder that has ex vivo gene therapy that treated the CNS dysfunction, now we have peripheral neuropathy that becomes one of the major problems. So I think it's a continuous process even after a therapy has been identified.

Susan Winckler (01:55:31):

Yeah. Dr. Litsky, do you want to comment on that at all? Because it strikes me as consistent with our last panel discussion of it's really a continuous learning system and the natural history study is a way to facilitate that.

Dr. John Lieske (01:55:46):

No, I agree that's very important. And now since we have two different agents and we think they're similar, but we don't really know that. So I think that that kind of data is going to be important. And we also think there may be some genotype-phenotype issues there as well. So we need to follow that up. And then there are also some other approaches on the horizon, people looking at gene therapy and other small molecules. And I think the need to compare these treatments over time is going to be important. And I think quite frankly with the small inhibitory RNAs, they've not been around very long. So we really don't know if there is or isn't any long-term issues with that. So for lots of reasons I agree 100% with what you said.

Susan Winckler (01:56:26):

Very helpful. All right, who's next? Dr. Mistry, go ahead.

Dr. Kirtida Mistry (01:56:32):

Yeah, just want to follow up on that. I think this is a hard, difficult space. This is not easy to conduct trials showing safety and efficacy of new drug products in a population with rare disease in whom data are sparse and there are lots of knowledge gaps. That said, I think the examples that were presented are great examples. Our division was involved in the approval of the two products that Dr. Litsky presented. And I think it goes to show how when the community gets together includes multiple stakeholders that we really can do this.

(01:57:35):

I think for primary hyperoxaluria type 1 for which that's the disease for which both of these products are now approved, at least nedosiran is approved for a reduction of urinary oxalate in children down to nine years of age with relatively preserved kidney function. And lumasarin, which was approved first was, is now approved for all patients down to birth with PH1. But I think what was important is that we heard from patients, from the externally led patient from the PFDD meeting that what was important to patients was the stones and all the morbidities associated with that as well as the progression of their disease to kidney failure and addressing that.

(01:58:43):

But I think it was clear that given the rarity of the population that it was not going to be feasible to conduct studies using those endpoints. And so really the community then came together to figure out, based on the natural history data, epidemiologic data and registry data, what evidence is there to support surrogate endpoints that could give you an indication of the clinical benefit. And in PH, I think one of the things that was maybe important is that we understand the pathophysiology of the disease. And we understand, as Dr. Litsky presented, is that the urinary oxalate in patients with relatively preserved kidney function plays a causal role in the manifestations of the disease in the kidney stones, the nephrocalcinosis and the kidney injury that leads to the loss of kidney function.

(01:59:59):

And then there were also the epidemiologic data that put together the relationship between changes in urinary oxalate and those outcomes of kidney failure. And then additionally, there were data to suggest that if you reduced urinary oxalate in patients with relatively preserved kidney function, for example, patients who had a liver transplant, in whom the genetic abnormality affects the liver, which causes then overproduction of oxalate, and if you transplant the liver, that's gone. And so you expect urinary oxalate to come down. And there were data to suggest that if that happens, that patients do better and their outcomes are better.

(02:00:54):

There are also other treatments, for example, patients with certain genetic mutations will respond to pyridoxine. And again, supportive data that other treatments that reduce urinary oxalate affect outcomes. And so even though we didn't know the quantitative relationship between if you reduce urinary oxalate by this percentage, you could reduce kidney failure by this percentage. But we knew that a substantial reduction in high baseline levels of urinary oxalate were likely to have a relationship to the clinical outcomes. And so that's how the development programs were designed. Is that ...

Susan Winckler (02:01:45):

I'm glad you underscored that having the information from the natural history study then allowed the patient population to reflect on and share what was important in the treatment. So it's, I guess another way of looking at that learning tool that patients provided their information and then could provide their input based on what was learned in this study. Dr. Lerro.

Dr. Catherine Lerro (02:02:17):

I just want to echo what a lot of my colleagues I think have said today. I think it was a really interesting presentation from both of you to hear about the very distinct but elegant ways that you used real world data and natural history studies to forward your clinical development programs. And as an epidemiologist at the FDA, it's really always encouraging to see innovative uses of real world data, especially in these rare disease spaces where I think it's maybe the most needed. And I guess one question I had for you both, and it specifically came I think from the second presentation, was talking about the registry studies and kind of gleaning data from multiple different data sources and sort of maybe how you thought about harmonizing this data across multiple data sources and how you think that maybe strengthened your research or how it may be presented specific challenges.

Dr. John Lieske (02:03:14):

Well, for the primary hyperoxaluria, the registry, it was done kind of the old-fashioned way. So we were getting the medical records from the providers. So patients would sign the appropriate consent so we get the records and we try to update that every year. So we were actually getting ... almost everything that's in the registry is from a medical record, and so that makes it pretty easy to harmonize it. And then the data fields were built so that there were issues with the unit, so we kind of knew what the unit should be or we knew how to convert them. And there were range checks and things like that.

Dr. Catherine Lerro (02:03:51):

Actually, and similarly, I think for the first presentation as well, I noticed you had from multiple countries, I assume multiple languages, different continents, just harmonizing data across those spaces as well.

Dr. Liza Squires (02:04:03):

Obviously one of the challenges was that in the retrospective data, it was important that the data was collected in a similar fashion. So we actually had investigators who were trained on the appropriate collection of retrospective data and what retrospective data would count. What does it really mean to sit independently for 30 seconds? How do you know that that's really what the child did? That was one aspect, especially for retrospective.

(02:04:34):

For the prospective piece, which included the interventional trials, the prospective interventional, as well as the natural history. I think it's important to note that again, the investigators received similar, if not identical training on how to collect not only endpoints that included validated scales in the appropriate administration of the scale, but also for things like collecting height and weight. There's a good way to collect length or height in children and a not so good way. And the same is true with weight. It needs to be standardized. So I think that these were things that were considered and leveraged. They were challenges, but again, that whole beginning with the end in mind I think was really critical to say both the retrospective and the prospective data needs to meet a regulatory standard.

Susan Winckler (02:05:37):

Yes, Dr. Morris.

Dr. Jill Morris (02:05:39):

I'd just like to emphasize that point too about the harmonization of data because that occurred to me as well. And we've actually had funding opportunities for groups to come in and take retrospective data from multiple sites and do harmonization, and I think it was mentioned earlier today, but the expertise in data science, but in the expertise in statistics is so critical. I always tell grantees when they're submitting a grant, you live and die by your statistics. So when reviewers review, we always have that one statistician on the panel. You have to make sure your statistics and as well as the harmonization, and it can be really complex, especially when, in my experience, when it comes to things like imaging. So brain imaging, what type of imager did you use? How were the measurements done? So I think there has to be a lot of thought that goes into data harmonization.

Susan Winckler (02:06:37):

One of the Zoom questions we got related to part of what you were talking about, the complexity of data sources, but it was actually a bit more about the complexity of the handoffs from different companies as molecules might've moved through or the engagement of different advocacy groups. Any of the three of you want to talk a little bit about the, I would say complexities, but maybe we should talk about it on a flip side and say collaboration? But certainly there's some movement there.

Dr. Liza Squires (02:07:13):

Sure. Why don't we ask Dr. Spiegel to start because he was involved from the very beginning of the development plan, and then I'll finish up. Ronen, would you like to address that question?

Dr. Ronen Spiegel (02:07:27):

Can you repeat the question? I have some problems with the voice. Can you repeat this question please?

Susan Winckler (02:07:38):

It was about whether there were any complexities introduced in the different organizations involved, whether it was different companies, product sponsors, or different ... Well, I think that would probably be most true in your case example. So some of those where there might've been handoffs.

Dr. Ronen Spiegel (02:08:01):

You mean the transition between different companies?

Susan Winckler (02:08:05):

Correct.

Dr. Ronen Spiegel (02:08:08):

Okay. So yes, I was in fact involved in both studies, in the natural history, both retrospective and prospective, and in the phase two clinical trial then, the open label. And in my experience, it moved smoothly because although there was several companies involved, the data and the procedures and the study protocols were handled smoothly. And I did not see any obstacles. And I am speaking as a PI in both studies. So in my opinion, it was not a disadvantage. It just happened.

Susan Winckler (02:09:36):

Okay. Yes, go ahead.

Dr. Liza Squires (02:09:37):

And really from a sponsor standpoint, and I think a plug for rare disease, I think companies that get involved in rare disease have big hearts, and when the drug moves on, it's like passing on a child. And we still have deep involvement with Gunter Schwarz from Colburn, but when I was at Origin taking over the program from Alexion, I can tell you that they were very good partners. They were available, they provided what we needed and good perspective. And then I was also involved in the passover to Sentinel. And I think that it's always critical that when the business development part of your organization is looking to move a molecule on to a new sponsor, that they find someone who's going to be a good steward for the disease and that they have their own team being available and willing to assure a successful transition.

Susan Winckler (02:10:46):

Great. So it can be done and be collaboration. I'll turn it back to the reactor panelists, what other things would you want to highlight or questions do you want to ask of our speakers?

Dr. Jill Morris (02:11:02):

I acknowledged in Dr. Lieske's presentation how he did a survey of what was most important to the patients. And I think that's so critical to have that strong collaboration with the patient community. And the areas I'm responsible for, they're mostly pediatric. So if you're in a room of parents whose children have a rare neurologic disorder, and you mention sleep, sleep is a big one. That being able to have a good night's sleep affects both the child and the parent. I think it's a real positive that you did that survey to look at what the patients found to be most important.

Susan Winckler (02:11:50):

Yeah. Dr. Lerro, go ahead.

Dr. Catherine Lerro (02:11:52):

Sure. I had kind of similar question or I guess follow-up question on your comment, but I was curious if you have mechanisms for kind of returning results to the patients in the way I think you published, Dr. Litsky, you mentioned a lot of publications that came out of the registry that were obviously really influential in a lot of ways, but I'm curious if this is in any way communicated to the participants of the study or just kind of more broadly the advocacy community.

Dr. John Lieske (02:12:19):

So we do a couple things. We work with the PEG and so they publish things on their website. So we do have that. And then we send out newsletters at least once a year, if not a couple times a year. So we send out some key things and then we have a lot of patient meetings, so it's communicated as well. So about once a year. They kind of had a pause during COVID, but we have those and those tend to be pretty well attended. So I think in multiple ways we're doing that.

Dr. Catherine Lerro (02:12:50):

And do you find that that encourages continued participation in the registry or perhaps encourages new participants to join?

Dr. John Lieske (02:12:56):

Yeah, definitely. I would say both. And I have more than new participants, I would say. So I think the more you do to highlight things, the better.

Susan Winckler (02:13:06):

Do you want to add anything, Dr. Squires?

Dr. Liza Squires (02:13:08):

We don't have an advocacy group, so we're in a different situation.

Susan Winckler (02:13:13):

So there the feedback is more in those than use of the product?

Dr. Liza Squires (02:13:19):

Correct.

Susan Winckler (02:13:20):

Okay. But I'm glad you asked that. That came up a couple of times in the Zoom as well and saying how do you share the information back? Because particularly in the natural history studies, the patients have contributed the information and so what might they learn? All right, we have time for one more question or two more observations. Anything that you want to ... Yep, go ahead, Dr. Pilgrim-Grayson.

Dr. Catherine Pilgrim-Grayson (02:13:45):

I just want to add on a little bit to what we've heard about engaging the patient. So when there's so little known about the natural history of a disease, it's just really, really important for us to hear the voice of the patient, to hear what's meaningful to you, what changes you would like to see, and that can help companies and the FDA together as we work to figure out what sort of endpoints would be important in a trial. There are lots of avenues for patients to work with us and there can be patient listening sessions, drug development sessions, if a drug is at the IND stage, working with pharma so that we hear your voices in those situations. So just want to stress, we've heard this a lot early and often involvement, but we really want to stress that we want those opportunities to interact with you.

Closing Remarks

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

Susan Winckler (02:14:46):

Really helpful in saying let's structure this well so that we can continue to learn and gather the information. All right, any other final thought? All right, we will let it go there. Let's thank our reactor panelists and our speakers for this session, and we can go ahead and extend that and say let's thank all of our speakers and reactor panelists for the day. So helpful. I was struck, I'll note we heard everything from the what and why and the potential power of registries and natural history studies to the rigor and discipline of getting started in that data collection.

(02:15:38):

I don't know if you all wrote down, but I heard in the one panel about having the approachable informed consent process, which is how you think about that in the pineapple. That you have to make it approachable and then bite-size. Then also beginning with the end in mind, but recognizing that it's not about an end, but rather that we'll have a continuous learning cycle from these pieces, to our last case study exploration and thinking about the importance of the endpoint choice and then not only gathering patient data, but gathering insight from patients about what's important to them.

(02:16:19):

So just an extraordinary sharing of information today that we just have to thank you for everyone contributing, whether you stood at a podium and spoke or were contributing insightful questions on cards or in the Q&A. So I'll note the meeting recording and the transcript will be posted later this week at ReaganUdall.org. We hope that you have found this helpful and that it advances all efforts to support the development and use of natural histories and registries in rare disease product development. With that, have a great rest of your Monday and have a productive week. Take care.