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

Morning Transcript

Welcome & Opening Remarks

Susan C. Winckler, RPh, Esq., Reagan-Udall Foundation for the FDA
Patrizia Cavazzoni, MD, Center for Drug Evaluation and Research, FDA

Susan Winckler (00:00:28):

Hello, and welcome to those of you who are in the room and those of you who are joining us virtually. I am Susan Winckler, and I serve as chief executive officer at the Reagan-Udall Foundation for the FDA. We are so pleased to partner with FDA and NIH to host this important workshop on natural history studies and registries in the development of rare disease treatments.

(00:00:52):

We will get to the substance in just a moment, but I have to cover the housekeeping issues. So, most of our speakers and about 200 attendees are gathered here in person at the White Oak Campus, and we have over 3,000 registrants for the virtual attendee as well. So, welcome to our virtual participants. Because of the size of the meeting, our virtual participants will be muted and cameras will be off throughout the event. And our in-person engagement will be primarily what's happening here in the physical space.

(00:01:23):

But we want to hear from you, and here's how to make that happen. If you're joining us online, please share your questions using the Zoom Q&A function. And if you're joining us in person, please write your questions on the index cards provided, and you can hand them to a member of staff and I will feed those into our conversation. We do have reactor panelists for some of our sessions to help stimulate discussion, but we will also weave in additional questions as we have time.

(00:01:52):

Now, before we dive into the agenda for the day, I will note that I want to thank our co-hosts, the Rare Diseases Team in FDA's Center for Drug Evaluation and Research, and the Division of Rare Diseases Research as part of NIH's National Center for Advancing Translational Sciences. We appreciate your partnership and collaboration in planning this workshop.

(00:02:18):

A note also for the workshop, we are recording the entire event, and the recording, the slide deck and a transcript will be available on our website later this week. So, let's look at what we will cover today. Throughout the day, we are going to explore the importance, the role and the logistics of natural history studies and patient registries in rare disease research, which will just roll off my tongue by the second

time I say it today, because it's the 400th time we've said it in the last few weeks. And we're going to close with some case examples to help pull all of the messages together. As we noted, the full agenda is available on the website. Those of you in-person had access to a paper material, and there is a link in the chat for all of the slides that you will see today.

(00:03:15):

So, that gets it through all of the housekeeping that we needed to do. We're thrilled that you have joined us for the conversation. And I am thrilled to start the first substance of the day by turning the podium over to Dr. Patrizia Cavazzoni, who is the director of FDA's Center for Drug Evaluation and Research, providing strategic direction for all that happens in that center. I'm just thrilled that you could join us for a few moments this morning.

Dr. Patrizia Cavazzoni (00:03:43):

Good morning, everyone. I'm delighted to be here. Sound check. Good. All right, very good.

(00:03:50):

This is a very important workshop and I am really delighted that we're able to host it at FDA today. And thank you also for all the attendees who are joining us virtually today. Supporting the development and the evaluation of new treatments for rare diseases is a key priority for FDA and for CDER. Rare diseases affect both patients and their families. About 1 in 10 Americans have a rare disease affecting about 30 million people in the United States. Unfortunately, the vast majority of rare diseases do not have approved treatment.

(00:04:28):

Rare disease drug development presents some complexities, and I'll give you some examples. Natural history of rare diseases is often poorly understood. The diseases are progressive, serious, life-limiting, and very often with pediatric onset. Small populations often restrict the study design options. There is often phenotypic and genotypic diversity within a disorder, even in very rare diseases. Development programs often lack solid translational background or information that can be used as a confirmatory evidence in situations where we are dealing with only one small study. Drug development tools, such as outcome measures and biomarkers, are often poorly understood. And there is also often a paucity of clinically meaningful endpoints for drug development in some rare diseases.

(00:05:29):

So, while this workshop will focus on the use of natural history studies and registries in the development of rare disease therapies, the work that CDER does to support and address the challenges of rare disease drug development is much broader. Given the heterogeneity of rare diseases and the complexities of their drug development programs, we have a number of efforts on multiple fronts to solve the problems and make drug development for rare diseases easier and faster. About two years ago, CDER launched the Accelerating Rare disease Cures Program called or ARC Program. This is a CDER-wide effort, which I oversee personally in close collaboration with the two super offices where the review of programs and application takes place, the Office of New Drugs, and the Office of Translational Sciences. The ARC Program is designed to drive innovations and solve problems in the development and approval of safe and effective treatment options for people living with rare diseases.

(00:06:39):

Hearing from the rare disease community is very important to us. The CDER ARC Program have a number of initiatives that are really geared engaging the community. An example of this is the latest one, the Learning and Education to Advance and Empower Rare Disease Drug Developers. It's a

mouthful, also known as LEADER 3D. And we launched this initiative to better understand and address the unique challenges in bringing rare disease products regulated by CDER, to the market.

(00:07:13):

So, we worked with an independent third party to conduct interviews with the rare disease drug development community and performed a review of public docket comments to identify educational opportunities across many topics in rare disease drug development. In early 2024, we published a report summarizing the findings from the analysis of these interactions and providing recommendations to expand outreach and education to the rare disease drug development community. Based on the topics that are important to the community, such as the use of natural history and registry data, which we are discussing today. And I'm well aware that this is a very, very important topic for drug developers in the community.

(00:08:06):

In parallel with the LEADER 3D effort, CDER's patient-focused drug development program are working with the National Organization for Rare Disorders to develop an advanced drug development education series for patients and patient groups.

(00:08:21):

So, let's now turn to real-world data. So, real-world data and real-world evidence are playing an increasing role in healthcare decisions and in drug development. Real-world data are data that are routinely collected to provide information on individual's health, such as, electronic health records, billing claims, and increasingly, disease registries and patient-generated data, for example, using mobile technologies. Real-world evidence refers to the use of real-world data to study the potential benefits or the potential risks of a medical product. And real-world evidence can be generated by different study designs or analysis.

(00:09:05):

So, there is a long history of using real-world evidence to support regulatory decisions, but this history has been primarily confined to a post-market evaluation of safety. So, increasingly, we're turning our focus on the use of real-world evidence to demonstrate effectiveness. We at FDA, we have several categories of initiatives to explore the use of real-world evidence in regulatory decision-making. These efforts include guidance development, funding of demonstration projects, and engagement with sponsors and industry through public and private meetings.

(00:09:44):

Today, we will hear more about the use of natural history studies and registries to generate real-world data and evidence to support the rare disease drug development programs. Given the rare disease drug development challenges I mentioned earlier, natural history studies can be utilized to inform selection of patient population, identification of endpoints, as well as timing of their assessment and the duration of clinical trials.

(00:10:14):

But we need to go further. There is an increasing desire which we share at CEDA and FDA, to use natural history studies or registries as external controls, either as confirmatory evidence in conjunction with a single trial or as a direct comparison arm. The former approach led to approval of the first therapy for Friedreich's ataxia last year, for example. The latter approach is particularly relevant to smaller populations or ultra-rare diseases when it may not be possible to identify a sufficient number of patients for clinical trials.

(00:10:56):

When considering the use of natural history studies as an external control, there are a number of considerations to determine if the natural history study will be able to serve as a comparator to the investigational arm. We will hear more about this today, and in fact, most of the workshop today will be discussing these aspects.

(00:11:18):

So, to conclude, FDA's and CEDA's efforts have led to progress in the development of rare disease treatments. In 2023, 51% of the 55 novel drugs approved by CEDA were approved to treat rare or orphan diseases, but there is a lot more work to do. We hear loud and clear, and wholeheartedly share the sense of urgency from the patients, the parents, and the drug developers. In order to harness the full potential of real-world data and real-world evidence for the development of therapies for rare diseases, we need to work together to generate high-quality, fit-for-purpose natural history study or registry data. Once we have it, we need to use it in developing programs in ways that make clinical trials of smaller population rare disease therapies more realistic and more efficient.

(00:12:13):

Before wrapping up, I would like to thank the Reagan-Udall Foundation and our colleagues at NIH for their partnership in holding this workshop, and the rare disease community for your engagement. Thank you.

"What Are Registries and Natural History Studies?"

Dominique Pichard, MD, MS, National Center for Advancing Translational Sciences, NIH

Susan Winckler (00:12:30):

Thanks so much, Dr. Cavazzoni. What you underscored for us is all of the extraordinary work that's being done to try and advance the use of real-world evidence, but we can collaborate and do more in improving that. And I hope at the end of today, that we'll have a better understanding of some of those steps that we might take, that the community might pursue.

(00:12:53):

So, let's turn to our next session where we will hear from Dr. Dominique Pichard, who is director of NCATS' Division of Rare Disease Research Innovation. And she is going to join us to answer the question, what are registries and natural history studies? So, Dr. Pichard, I'll welcome you to the stage to provide that overview.

Dr. Dominique Pichard (00:13:19):

Thank you, Susan. All right. Thank you so much. So, as Susan said, I'm Dominique Pichard and I'm the director of the Division of Rare Diseases Research Innovation at NCATS, or the National Center for Advancing Translational Sciences.

(00:13:36):

So, really, my hope here is that over the next few minutes, this is just a short brief introduction, is to talk to you about really what are registries and what are natural history studies? Because this is part of laying the foundation for what is going to come the rest of the day.

(00:13:56):

So, we'll start with just definitions. So, what is the natural history of a disease? We can't talk about natural history studies if we don't actually know what the natural history is. So, the natural history of a

disease is just the course of a disease over a period of time, in absence of an intervention. So, from the disease onset all the way to disease resolution, or death.

(00:14:23):

And why is that natural history important? Well, when we talk about common diseases, let's say, high blood pressure, we know what happens, because it's been looked at for decades with millions of people affected by it. We know what to look for before hypertension starts, when hypertension starts, what should be screened for when you have high blood pressure. So, we understand the natural history and therefore, when we treat, we know that we are altering that course. We're altering that natural history.

(00:14:56):

In rare diseases, it's the same thing. We have to understand a disease from the start, or from even before we recognize that the disease has started, all the way through to the end. So, that we know, what are the goals of treatment, what body systems are affected, what symptoms exist for a particular disease? So, that we know what to treat. And that is what we look at in a natural history study.

(00:15:22):

So, a natural history study is a pre-planned observational study. So, there is no intervention. We're looking over the course of the disease, what is happening, again, in a pre-planned fashion, so that we can then have that data that we say, "We really know what this disease is." As Dr. Cavazzoni had mentioned, diseases have heterogeneity, both phenotypic and genotypic. And in rare diseases, that heterogeneity presents even more of a challenge because of the small numbers. When you have millions of individuals affected by a disease and there's heterogeneity, you can wash out that noise because of the number of individuals, and we don't have that luxury in rare diseases. So, it's really vital to have good natural history study, where you can understand the spectrum of the disease and all of the different manifestations that may occur in a given rare disease.

(00:16:19):

So, the other term that we're talking about today is registries. Now, registry, it's really a much bigger term. It is a collection of information about a specified group of individuals. A registry could be as simple as a contact registry. We know in rare diseases that is all some groups have. These diseases are newly identified or a small enough population that they have a contact registry, which just means it is a list of individuals who are affected by the condition and their contact information. And that has value because then when research studies come up, when clinical trials come up, you actually have a population that you can reach out to. But then, it also goes all the way to population registries. So, registry is just a broad term for a collection of information about a specified group of individuals.

(00:17:14):

And here, I'm just showing three examples of registries, just to demonstrate there is such a broad definition of this. These can be, the CDC has a National ALS Registry. The NCI has something called the SEER Registry, the Surveillance, Epidemiology, and End Results Program, which looks at all cancers and collects data on them. And then, something like a disease registry, the Rett Syndrome Registry. That is focused on collecting data about one particular rare disease.

(00:17:51):

So, I think, as we go through today, I think just keeping in mind what is a natural history study and what is a registry, so that when we talk about what the roles of these different, either registries or natural history are, we're all walking in with the same understanding of how they differ. And Dr. Lee will follow me and talk a little bit about how they can be used in ... She'll start off the conversation on how they can

be used in drug development. So, again, just, this is to provide that overview. And I will now hand it back over to Susan, to introduce our next speaker.

"Why Registries and Natural History Studies are Critical to Rare Disease Treatment Development"

Kerry Jo Lee, MD, Center for Drug Evaluation and Research, FDA

Susan Winckler (00:18:30):

That's great. Thank you so much, Dr. Pichard, in helping us with the what. And as you noted, we will turn it now to hear from FDA and particularly, Dr. Kerry Jo, who we've worked together so much that I am just jumping right straight to say-

Dr. Kerry Jo Lee (00:18:50):

Oh, wait.

Susan C. Winckler (00:18:51):

... let's hear from you directly, Dr. Lee, as you provide us more of the rare disease insight on why and how we might best use registries. So, I'll turn it to you, and then we'll get to the rest of our program.

Dr. Kerry Jo Lee (00:19:05):

Absolutely. Thanks so much, Susan. So, again, I'm Dr. Kerry Jo Lee, the associate director for rare diseases here. I am the lead of the Rare Diseases Team, which is a multidisciplinary programming and policy team that sits within the Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine here at the FDA. And in that role, our team is also the program management office for the Accelerating Rare disease Cures Program that you heard about from Dr. Cavazzoni.

(00:19:35):

So, I'm here to talk to you today, underscore a lot of what you've heard already, but really talk about how natural history studies and registries inform drug development. So, just to start off ... Let me make sure I can actually advance my slides. I had it. There we go. CDER has seen tremendous success in rare disease drug development in the years. You have a chart here that shows from 2010 on.

(00:20:01):

On this chart, you'll notice there are bar graphs, a bar for each year since 2010. We have our orphan new molecular entity in novel approvals in green. You have our non-orphan new molecular entity in novel approvals in blue. And at the top, you'll see a purple line that really designates and shows the percentage within each year of therapies that were orphan designated, that were approved.

(00:20:23):

And so, you can see by looking at this, that the number of orphan therapies has increased over years, as well as the percentage of therapies per year, which are orphan as opposed to non-orphan. 2023 was another wonderful year. We had 28 simply orphan novel or new molecular entity approvals. And so, these are therapies that are new and provide really important therapeutic options for patients.

(00:20:50):

However, as Dr. Cavazzoni said, we are well aware that 1 in 10 Americans are affected by rare diseases. We have 25 to 30 million Americans out there that are suffering from a rare disease or living with a rare

disease, and that there is a lot yet to do. There is significant need. So, looking at that, I'm going to go over some of the common challenges and talk about how natural history can be so important to them.

(00:21:16):

You'll see, we have common challenges in rare disease drug development. Right at the top there is that natural history is poorly understood. And this is important because one of the most informative things to developing your drug development trial or clinical study is good characterization of the natural history of a disease. Diseases are progressive, serious, life-limiting, and often lack approved therapy. So, there's an urgent need. This translates to an urgent need to jump into trials and clinical studies once you have a potential therapy. However, you really have to stop and think what you know about the natural history of a disease. Why is that important?

(00:21:54):

Well, you have small populations that restrict study design options. So, you really need to be informed about your patient population in order to try and design a trial that is going to lead to an answer as to whether or not the drug is safe and effective. And not only do small populations restrict study design options, they restrict your ability to go back and do over things that you may not have ... And utilize a patient population.

(00:22:23):

So, if you don't think and carefully plan duration of your study, selection of endpoints, the patient population within a rare disease that you are picking out, you're really not making the best of the design of the clinical trial that you are trying to do, in order to demonstrate whether or not a drug is safe and effective. You don't have the chance to do over in rare diseases.

(00:22:51):

Phenotypic and genotypic diversity are also incredibly important in rare diseases. And you can find these things out from natural history studies as well as from registries, and that can really inform what patient population you might want to select in order to demonstrate based on how your therapy works, whether or not the drug is safe and effective.

(00:23:15):

You'll see that drug development tools and outcome measures and biomarkers are also lacking. So, if you have a natural history study or a registry, you really might want to think about what are you collecting in these studies and in these registries. Are you collecting biomarkers? Are you collecting in conjunction with the biomarkers, clinical events, clinical manifestations? And are you doing that over time in order to demonstrate correlations?

(00:23:39):

There is also a lack of precedent, including clinically meaningful endpoints, for drug development in many rare diseases. We know that this is challenging in rare disease to select a novel endpoint for a condition that has not yet had an approved therapy. That's why there is a whole program, the Rare Disease Endpoint Advancement pilot program, that's dedicated to selection of an endpoint. However, this can be really, really important information to gather from your natural history study or your registry.

(00:24:08):

And when you're constructing these, you really have to start at the outset with the end in mind. What are the questions you are trying to answer? What are the aims of your study? Because if you're trying to select an endpoint, then you're going to want to think, which endpoint? Or, maybe there's many that you're selecting. Are you collecting those throughout all the patients over time? And are you collecting

the clinical course of the patients in relations with those endpoints? So, those types of collections can be really important to inform trial designs. So, not only would you have endpoint selection, but you're also ensuring that what is the timing at which you are going to be collecting those endpoints during a clinical trial, and what is the duration of your trial, that your trial needs to be in order to demonstrate the effect of a therapy that you're looking at. All of those are really critical components, as well as the patient population that you're selecting, that would work best with the therapy that you're investigating.

(00:25:11):

I just wanted to put forth a couple of guidances here at the FDA that are very important for rare disease topics and natural history study and registries. There is a website there that you can go to, on the Accelerating Rare disease Cures Program, we actually have a guidance tab that shows all of guidances and collated by topics, actually, rather than the name of the guidance. One of the things we realized when we were doing the LEADER 3D program, we often heard from people, "I wish you had this guidance." And we were like, "But we do." But people had no idea it existed. And if you don't know the name of it, it's very challenging to find it in your favorite search engine. So, that's one of the simple things we've done on the Accelerating Rare disease Cures Program that we're hoping is helpful.

(00:25:56):

So, the Rare Diseases: Natural History Studies for Drug Development is a very important guidance and it talks about some of those principles that I was talking about. How you can really utilize those to inform selection of your patient populations, to inform selection of your endpoints, and the information that you can get from natural history studies.

(00:26:12):

There is the Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence. One of the things that we've seen in rare disease drug development trials is that many, many rare diseases demonstrate effectiveness and safety through one adequate and well-controlled trial plus confirmatory evidence. Well, natural history data, registry data, real-world data, can be something that is utilized not only for informing the trial, but also as confirmatory evidence. And that guidance actually has a section in it that speaks specifically to that.

(00:26:47):

There's also the Rare Diseases: Considerations for the Development of Drugs and Biologic Products. So, this was a guidance that was revised just recently, came out in December of 2023. And that is not specifically only about natural history studies or registries, but really about all of the challenges and considerations that one really must think about in the outset, in order to inform the design of your rare disease clinical study. And so, that one is a good read for those of you stepping back to look at registries and natural history studies for what are the challenges, in order to sort of determine at the outset what is the question that you are trying to answer with your study. And then, Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drugs and Biologic Products. That is another one that is very helpful and timely for the topic today.

(00:27:36):

And with my last slide, I just wanted to put a plug out here for the Accelerating Rare disease Cures website. So, as I mentioned, we have that guidance tab there, where you can find guidances by topics. It's also a repository and a resource for conferences, such as these, that we are having. And those live on the ARC website, so that you can go back and read them. We have a number of conferences there. This one's natural history studies and registries, and will eventually be posted there. We have other ones related to innovative trial design in small populations, the utilization of real-world data. All types of clinical pharmacology, quantitative methodologies that they're using. So, there's a number of

conferences there that might really, really be helpful. Including a previous one that we also jointly did with our colleagues at NCATS at the NIH.

(00:28:28):

And so, in conclusion, I just wanted to note that we select these topics based on what we hear from the rare disease community in order to be most helpful. So, we really love hearing from you. We've done that through the LEADER 3D program. We do that through our engagement. And we look forward to many more of these. And I also just wanted to say, I think this is a great example of collaboration. We've enjoyed doing this with our colleagues at the NIH as well as the Reagan-Udall Foundation. In the rare disease community, we really do all have to work together in order for everyone to receive safe and effective therapies. So, thank you very much.

Getting Started: Developing Registries and Designing Natural History Studies

Leslie Gordon, MD, PhD, The Progeria Research Foundation
Elieen King, PhD, Cincinnati Children's Hospital Medical Center
Michael Wagner, PhD, Cincinnati Children's Hospital Medical Center
Kristen Wheeden, MBA, United Porphyrias Association

Susan Winckler (00:29:06):

Thank you so much, Dr. Lee. As we got from the what and the why. And now we will turn to our next session where we want to move from that very basic, it was just our baseline to establish what registries and natural history studies are, to now talk about how to start them up.

(00:29:27):

So, we will turn first to Dr. Leslie Gordon, who is the co-founder of the Progeria Research Foundation and serves as their volunteer medical director. She's also the mother of a child with progeria. So, Dr. Gordon, we will turn the slides over to you.

Dr. Leslie Gordon (00:29:48):

Thank you very much. Fantastic. It's already a great start to the day. Well, I first, of course, want to thank the Reagan-Udall organizers and the FDA and the NIH for inviting me to speak. I am thrilled to be here. And I think this is to advance ... There we are.

(00:30:12):

Yes. First and foremost, I'm the mom of Sam, who had progeria. This is just a note about using photographs of the children. You can get those within the Progeria Research Foundation. Today, my goal is to share highlights from building and using the Progeria Research Foundation's patient registry and natural history studies on our journey towards the cure for children with progeria. I think that through exchanging our lessons learned today, and many other days, we will all become better, faster, and stronger towards curing all of our patients. And since every minute of their time is precious, we know we have to help each other to succeed.

(00:31:15):

This is Rachel, and Rachel has progeria. You see her first as a newborn, and then, when she's a toddler. Then when she's seven years old, and then nine years old. And she passed away about a week before her 10th birthday, of heart failure. Rachel had progeria, an ultra-rare premature aging disease. Its prevalence is 1 in 20 million. There are 16 children today in the United States with progeria, and about 350 in the entire world.

(00:31:55):

We now know it's a genetic disease, autosomal dominant, so not passed down in families. And without treatment, children live, on average, about 14-and-a-half years, but there's a wide range. And they die of premature atherosclerosis. The same heart disease that can affect you and I in our 60s, 70s, and 80s, they get when they're 8, 9, and 10 years old.

(00:32:25):

When our son, Sam, was diagnosed when he was two years old in 1998, there was nothing known about progeria. I had been through medical school. I had never been taught anything. I'd never heard of it. This is not a new story for ultra-rare diseases, especially back then. There was no funding out there. There was no central source of clinical information. There were no physicians that knew much about it. It was poorly defined. Essentially, there were no treatment prospects and no place for families or their physicians to go for help. Like I said, not a new story. So, as with lots of ultra-rare diseases, my husband, my sister Audrey, and I got together and founded the Progeria Research Foundation just a few months after Sam's diagnosis. It's mission, to find the cause, treatments, and cure for progeria. So what I'd like to share with you now are just some milestones that PRF has experienced, and I want to use those to springboard and take a few of these to demonstrate just how critical registries and natural history studies can be.

(00:33:47):

In 2003, Dr. Francis Collins' lab, together in collaboration with us, we discovered the causal gene mutation for progeria. In 90% of cases, it's caused by a single same DNA-based change that produces a huge amount of the toxic protein we call progerin. From there, Francis' lab and Carlos López-Otin from Spain, went on to produce a couple of highly disease-faithful progerin-producing Mouse Models for the study of progeria. We never had that before. But when I say highly faithful, we only know that because now we understand so much more about the cardiovascular disease in children with progeria, and we can compare that to the mice.

(00:34:44):

We conducted a natural history study at the NIH Clinical Center in 2005 for a year, and followed that up with four sequential single-center open-label clinical treatment trials at Boston Children's Hospital. These were the first ever clinical trials for progeria. Those trials produced world's experts on progeria where none existed before and they all contributed to a clinical care handbook that every family and their physicians use to guide the children's medical care.

(00:35:27):

We've developed and are now validating a progerin assay in plasma to serve as our primary outcome for accelerated drug approval in future trials. This all culminated in our first FDA-approved medicine for children with progeria called lonafarnib in 2020. That was 21 years of using the patient registry. It took 13 years of continuous clinical trials with lonafarnib involved, but it showed us a life extension, that we're still analyzing now, of over four years or about 30% of the children's lifespans. But of course, that's not good enough. It's not nearly good enough.

(00:36:22):

We are working to develop new drugs that may be much more effective. We're working on, as you see here... I think I have a pointer. Here's lonafarnib. We've got small molecules in the works, antisense RNA therapeutics, and even DNA-based editing. You can see here, they're all better than lonafarnib alone. You've got a 25% increase in the mouse lifespan, and in our DNA editing project, 140%. The mice were living into old age. None of these accomplishments would be possible without the PRF International

Registry, an extension of that we call the Medical and Research Database, and natural history studies of progeria.

(00:37:19):

Here's how. When we first connect with a patient, our top priority is entry into the patient registry. We just want to gather the essential information to stay in contact with the patient families and their caretakers longitudinally. Continual two-way communication and education fosters trust, which is really important, program participation, and helps us to create better research studies for the children. We are now in touch with about 40% of the world's living population of children with progeria, now some of whom are young adults, in 51 countries because of this registry and all that we're able to do with it.

(00:38:17):

This type of contact allowed us to enroll all of the clinical trials I told you about, fully, within months of opening them. We have a program called the Medical and Research Database, and that is really an extension of the registry. It's where we collect copies of clinical charts, copies of people's scans and tests, and we use them to study the natural history of disease and develop trial outcomes. It's been used in about 30 peer-reviewed progeria studies, and it's been extremely helpful as both a bridge to our clinical trial types of natural history studies, and as stand-alones.

(00:39:14):

Oops. Pardon me. The graph you're looking at over on the left-hand side is showing you rate of weight gain for progeria. So you're looking at a pediatrician's chart here, and you are looking at that line, which is a bunch of children. What we discovered through the database was that children with progeria have a, they all fail to thrive their whole lives, linear and predictable rate of weight gain. So, we were able to use this as our primary outcome measure for our first two trials. Now, the children didn't gain a lot of weight in those trials, but this analysis was really our gateway to an era of progeria clinical trials. We would not have been able to conduct them without it.

(00:40:07):

This is a really cool slide. It's probably my favorite because it shows that lonafarnib, our only drug, was approved based on an extended survival on children taking the therapy. That survival data came from the registry and the database. Survival was not an outcome in the clinical trials. We developed an external control group that defined the untreated progeria survival curve, and you see that here on the left-hand side. Then we use that control group to assess survival effect in the treatment trials. What you're looking at on the right is a blue line, and that represents a control group. Every time you step down, a child has passed away. In two years, you step down nine times. But within the clinical treatment trial, you step down only once, only one child passed away.

(00:41:20):

Within the clinic... This was pretty exciting for us to be able to accomplish, but I think it's very doable, this real-world data, for others as well. Because progeria is so rare and we know so little about it, we decided to conduct the clinical trials at Boston Children's with a dual purpose, both drug testing and natural history studies. I think this is different from most commercial endeavors, but it's been absolutely critical. We studied every feature from head to toe, and we are still learning, even after all of these years.

(00:42:04):

In fact, now that we have a drug that's standard of care, we are going back to data mine all of our data on the trials to say, "Okay, everybody's on lonafarnib now, what's the new baseline? What's the new on monotherapy natural history?" Because, we have to know this. Otherwise, how are we going to tell if a

new drug, over and above what the children are all on, lonafarnib, is effective? We also went back to our registry and database and data mined again to support the progerin biomarker studies as that primary outcome for accelerated approval that I was talking about.

(00:42:52):

We not only had to show that progerin was teeming in these kids, and that it could be decreased with a medication, but that decrease correlated, related to survival. So what you're looking at here essentially is increase in life expectancy on the Y-axis and length on treatment on the X-axis. If you just follow the gray line, which is the line for children in the trial, the average amount of progerin that they decreased in the trial, you see that after 10 years on therapy, which a number of kids have been on therapy for over 10 years, they're gaining over six years of life. That we could only do because we had all of this fantastic data from the registry to data mine over and over again.

(00:43:49):

All in all, there are just a few take-home messages that I want to make sure, some overarching tips. Patient families, they are passionate partners. We can't do it without them. They can't do it without us. It is a partnership. Always assume your data will be used for drug approval, so use a REDCap or a similar database system. I have to, in all transparency, admit, we started 20 years ago, I was an academician and we used Excel for many, many years. That's a rough lesson. Great program, but just not for this. So now we're into REDCap. Your raw data will be used many times over and over again, at least that's what we've found, so safeguard that source data. Finally, patient registries and natural histories, as you can see, are critical foundational tools for the cure. So thank you again to the Reagan-Udall organizers, the FDA, and the NIH. I am thrilled again to be here, and thank you to my many, many talented collaborators.

Susan Winckler (00:45:07):

Thank you so much Dr. Gordon. If you want to take a seat on the stage, then we'll have you in place when we get to the question and answer session. Thank you for that great... Just bringing us from what I would call the telephone book of who to reach out to, and then the much deeper collection of information. I saw everyone note, " Not in Excel." So let's move... Our next set of presenters are joining us remotely. So we will hear now from Dr. Eileen King, who is a Research Professor within the division of Biostatistics and Epidemiology at Cincinnati Children's Hospital Medical Center, and her colleague Dr. Michael Wagner, who is Associate Professor of Pediatrics in the division of Biomedical Informatics at Cincinnati Children's Hospital Medical Center. So Doctors King and Wagner, if our audiovisual magic is working today, we should be able to hear you, and we look forward to your presentation.

Dr. Eileen King (00:46:09):

Great, thank you very much. Hopefully you can all hear us. Next slide, please. Dr. Wagner and I will be speaking about the Rare Disease Clinical Research Network, and I'm going to provide you with a very brief overview, and I'm going to talk about data collection, formatting, and quality assurance, and Dr. Wagner will talk about data storage, maintenance, and sharing. Next slide, please.

(00:46:40):

The RDCRN, as you could see, is made up of 20 research teams, and the NIH researchers of clinicians, patients, and patient advocacy groups, the data management coordinating staff, we all work together in great partnership in order to achieve faster diagnosis and better treatments for patients with rare diseases. This network is funded by a multitude of institutes and offices at NIH. The key component for

today is that each consortia is required to have a multi-center national natural history study, and each consortia studies at least three related rare diseases. Next slide.

(00:47:27):

This network is led by NCATS. It's in its fourth five-year funding cycle. Most importantly, it's established by Congress under the Rare Disease Act of 2002, and the RDCRN work has led to the approval of at least eight treatments for rare diseases. Next slide. Next slide. While we're moving to the slides, I'm going to talk about how we collect the data in the RDCRN. So it is important that you think about the platform you're going to collect the data in, and also how you're going to collect that data.

(00:48:19):

I don't know if you're seeing my REDCap slide, but we selected REDCap, which is the research electronic data capture system, to collect the natural history study data in REDCap. This system is designed and supported by Vanderbilt University. It's an intuitive interface. It has audit trails for tracking data manipulation and exporting procedures so you know who has touched the data, when they've touched the data, et cetera.

(00:48:58):

You can easily download your data for use in your common statistical packages like SAS, CSV files, Excel, if you so choose. Don't put it in Excel, but you can download it in Excel to do analyses. Then there's a lot of data integration across external sources via the APIs, which we use extensively. You could see that REDCap is widely available, well-supported by most academic health centers. It's used by over 7,000 institutions in 156 countries, over 2 million projects with over 3 million users. We [inaudible 00:49:39] most of our institutions are academic health centers, so their staff are familiar with REDCap. It's very intuitive for them.

(00:49:46):

The projects and data are very portable. So if a consortium leaves our network, we could package the data up for them, and they could very easily stand it up into their own REDCap system at their academic health center. Since Children's was an early adopter, we have deep expertise in REDCap, and we use many, many capabilities in REDCap. Especially, we use the capabilities of the data standards that are built into REDCap because they have available form libraries. Then also, there's great community support across the academic health center. Next slide.

(00:50:28):

You can see that REDCap is used for our studies, that we have sites across the US, and across the world in Europe, Australia, Asia, Africa, et cetera. Next slide. Let's talk now about data quality, integrity and data standards. So if you're going to build a REDCap data, or if you're going to build a registry, you really need to think about ensuring the quality of your data. So, you need to have policies and procedures in place.

(00:51:01):

For us, we have four key documents that we develop for every one of our protocols. One is a data management plan that we develop early in the development of the database. This indicates who is responsible for doing what with the data. For example, our staff at the DMCC will be continually monitoring the data and issuing data queries for data that we think are errant data, but the staff is responsible for responding to those queries in a timely manner. The data quality plan gets into more specific details about exactly what are the data quality checks that we're doing, what are built into REDCap.

(00:51:48):

For example, range checks, so that if someone enters a data value that is very extreme, they get a pop-up that says, "Are you sure this is the correct weight or the correct blood pressure?," and they have a chance to change it at the point of entry if it is errant. We will get data from other data sources that are sent to us as electronic files. When we get those files, we need to know the data transfer specifications, so we require data transfer specification documents so we know what is in the file, and exactly what the format of the file is.

(00:52:23):

Then we also have a database lock checklist that we use because, if a study is complete and we want to close out that study, we want to make sure we've completed all the steps, and that the data are as clean and accurate as we could possibly make it. We also use this database lock checklist for natural history studies. When investigators want to start writing manuscripts, or if they want to submit data to the FDA, we will do a freeze of that registry database, and we will complete this database lock checklist to make sure the data is of highest quality. Next slide.

(00:53:05):

A big focus for RDCRN, this funding cycle, is to develop data standards so that we can integrate data across our different protocols, and we can integrate data also with other data that is available through the private sector, or other academic areas as well. Knowing that our data from our natural history studies and our other studies may go to the FDA, the first thing that we do is we adopted the CDISC/CDASH standards where they were available and applicable.

(00:53:41):

We collect a lot of data in the different data types in the natural history studies, so there are some cases where these standards aren't available, so we reference the REDCap shared Library, which is a great help, the NIH/NDA Common Data Elements repository and the National Library of Medicine Library. We don't want to invent data standards if they're already available out there. Many of our data that we collect might be from neurodevelopmental testing, and these are instruments that are administered online. We'll work with the publishers to actually get downloads of those data, and so therefore there'll be standardized because everybody who gets a download would get them in the same format.

(00:54:28):

Then looking forward, we're going to also continue to use the direct REDCap links to the CDASH forums and common data elements. REDCap has now built this into their system so that when we want to build a data element, and there's a CDASH standard or a common data element, we could just click on that and it will automatically populate our database. I'm going to turn it over to Dr. Wagner, who will talk to you about data storage, maintenance, and sharing. Thank you.

Dr. Michael Wagner (00:55:03):

Thank you very much, Eileen. I appreciate being here and this opportunity. Eileen talked to you about REDCap. I'm going to zoom out and talk about the entire ecosystem that we are providing for the Rare Diseases Clinical Research Network, which of course has REDCap front and center, that's our workhorse, but also has a number of other tools that we integrate into this one cloud environment in close collaboration with the NCATS team. For example, we have a research pack system for images. We provide a genomic data management system. We provide an analysis tools such as R and SAS, also in the same cloud environment.

(00:55:46):

Then, of course, security is paramount, so we have a number of security tools that we use including secure text messaging so that patients can fill out patient reporting outcome forms in our REDCap system. I'll also be remiss to mention that we have a pilot project underway, which is showing a lot of promise to integrate multi-site EMR data, electronic medical records data, into REDCap. We're looking to expand that, and offer more consortia the same opportunity to enrich their natural history studies with EMR data.

(00:56:22):

Zooming out even further, what I just talked about is our operational environment, which is on the left-hand side of this slide. You can see that the audience there very much is the network itself and the consortia. The consortia are fundamentally responsible and own the data in this environment. On the right-hand side, you see the future data sharing environment for the RDCRN and the RDCRN Data Repository, which is currently under construction.

(00:56:48):

This is going to be an NIH-run/NIH-regulated data repository that takes in data from the RDCRN, the operational environment, and other data sources as well, and makes it available to the general public, including industry, patient advocacy groups, other investigators, and so on, and so on. Data sharing, obviously, is critical, and we are going to support it as best as we can to make sure that this data is reused many, many times as previous speakers have mentioned.

(00:57:22):

Data sharing is complex when you're dealing with 20 consortia with lots of sites, so the DMCC has put out a framework consisting of lots of template language for the various DUAs and data sharing agreements that need to be put in place to enable this, and we help the consortia document the participant-level data use limitations if there are any in REDCap directly as metadata, so that this metadata will travel with the data into the repository so that the data access committee can then adjudicate requests and make sure that the data is only used for the appropriate purposes.

(00:58:05):

Informed consent is critical to anything that we do. Again, the DMCC has assembled some template language that can be used by the consortia, which includes language about sharing with the admin core of the consortium, sharing with the DMCC, sharing with other researchers, and so on, and so on. If you're interested, I encourage you to navigate to our website rarediseasesnetwork.org, and find this language.

(00:58:36):

There's a lot of complexity here with lots of players involved in the research process. Starting from the left, the participant signs the consent with the site, the site has a contract, a contractual relationship with the consortium. The consortium, of course, has a grant from the NIH, and has a relationship with us. Then on the right-hand side, you have the data requester, which could be a scientist, a patient advocacy group, somebody from industry, or the general public, and they can either go to the consortium directly because all consortia have internal data sharing mechanisms, or you as a data requester will be able to go to the RDCRN Data Repository to request data and sign a data use agreement.

(00:59:28):

I'm trying to advance the slides. Okay, here we go. I went one too far. Let me go one back. Sorry about that. The joys of Zoom. So the data going into the Data Repository will come with metadata. We take that very seriously. Metadata is critical for truly understanding the contents of the data, and making

sure that any reuse is appropriate and doesn't lead to misunderstandings or false results. So, we have some hard requirements for metadata going into the repository, and this is information that will be made available fairly broadly since it's not as sensitive, but that includes the schedule of events, the protocol synopsis, data dictionaries, and so on, so on, and also some soft requirements, which we strongly encouraged the consortia to supply but don't necessarily make absolutely required.

(01:00:31):

We take QC very seriously, especially in the rare disease space. It is critical that the data be of the highest quality. Again, there's an extensive QC process that we operate to ingest data into the repository. Again, there are hard requirements and soft requirements, and you can read up on those on the slides. Then another slide on QC requirements, this has to do with doing QC checks across all the different data modalities that we have in the RDCRN, so not just the REDCap data, but all the other data as well.

(01:01:12):

In closing, I just wanted to reiterate that natural history data for patients is critical for advancing rare disease research to speed diagnosis and identify new treatments. The data must be collected using state-of-the-art systems, and we are so fortunate to collaborate with NCATS, and being able to provide all of these great tools to the Rare Diseases Network. Then lastly, data sharing is critical for us, so we are in the process again, in collaboration with NCATS, to build out this data sharing environment so that others can reanalyze and further analyze the data that is collected by the RDCRN.

(01:01:53):

Let me say a big thank you to NCATS, and to the great team that we've worked with over the last four and a half years, and also the great team at Cincinnati Children's that makes up the DMCC. Lastly, I invite everybody on this call to visit our website, subscribe to newsletters. Again, our engagement board does a great job of putting out information, and there's lots of information on the website which might be useful in general, not just for the RDCRN. Thank you very much.

Susan Winckler (01:02:23):

Great, thank you so much. Doctors King and Wagner, we will see you shortly. We'll bring you back virtually and put you on the screen here in the room to join our question and answer session. Speaking of questions and answer, those of you who are joining us virtually are doing a great of submitting questions that you'd like to see addressed. Those in the room, if you have questions, please write them out on the cards and we will do our best to get to them. Let's turn to our final speaker for this session. We are going to hear from Kristen Wheeden, who serves as President of the United Porphyrias Association. We've gone from a decades old registry to then hearing about a broader effort that is serving a number of different areas, and now we'll hear a very practical component here from Kristen. Dr. Wheeden, take it away.

Kristen Wheeden (01:03:15):

Oh, I wish I was Dr. Wheeden. You just gave me a title I haven't yet earned, but thank you.

Susan Winckler (01:03:21):

It's all good today.

Kristen Wheeden (01:03:23):

Excellent. I have to say that the presentation we just heard was so good. However, when I started in this, I probably wouldn't have understood that much of it. But this many years in, I can really say that I did, and I'm part of this, and it is possible for other patient groups to do this too. If there's no other takeaway from this and our day together, that this is all possible for groups to pull together a patient registry, if you have all the necessary components. So, thank you for that kind introduction.

(01:04:03):

Yes, my name is Kristen Wheeden, and I'm so happy to join my fellow panelists this morning. I serve as President of the United Porphyrias Association here in Bethesda, Maryland. Also, the UPA is our patient advocacy group for the Porphyrias Consortium. Dr. King, when she showed the graphic of all the consortia, the 20 currently funded consortia, the Porphyrias Consortium is one of them, and I'm really, really proud of our work together. So I'm going to take a few moments this morning to go through a little bit about porphyria. What is it? I'm going to share a little about our patient registry and then some considerations and best practices that have come from our work together.

(01:05:11):

So, a moment on the porphyrias. So the porphyrias are a group of eight ultra-rare diseases that are all based in the heme biosynthetic pathway. Essentially, there are eight steps to making fully formed heme in the body. Anytime there is a misstep in that, it equals a type of porphyria. There are two main categories of porphyria. The first is acute hepatic porphyria. The AHPs are triggered by neurotoxins. They are characterized by severe neurovisceral attacks that do attack multiple organ systems. If there's any takeaway from the AHPs, the acute porphyria, is that they are incredibly painful and overwhelmingly debilitating to our patient community.

(01:06:10):

The other type of porphyrias are the cutaneous porphyrias, and this is how I was introduced to this world. The cutaneous porphyrias are characterized by a phototoxic nature. Patients with this type of porphyria are susceptible to visible light, which triggers horrifically painful phototoxic reactions from either the sunlight or from artificial lighting.

(01:06:42):

Now, what you're looking at at this slide is four of my friends who have porphyria. On the left-hand side, that is my son. My youngest son, Brady, was diagnosed with erythropoietic protoporphyria when he was three. He's now 18, and that is him on the left-hand side under a blanket, you can see, and that is limo-tinted car. He had had a bit of a exposure that morning and he was doing everything he could to avoid sunlight. But the picture that's inset in there is him just free. That's his normal beautiful personality. And the three friends to his right, that is Jen and Sean and Morgan, and they are covered up in their protective gear, which they need to use to be able to navigate throughout their everyday life. And then in the inset, that is them just free, how they should be. So our patient registry, which I'm going to speak to, has helped them and others with porphyria to be free and to be able to navigate this world as they should be able to. So, when Brady was diagnosed, I got deeply involved in advocacy and ultimately launched United Porphyrias Association. We are focused on five main pillars, which are research, education, awareness, advocacy, and patient support. We are guided by a 22-member scientific advisory board. These are the principal investigators, researchers, clinicians, porphyria experts that are working really hard to make life better for people with porphyria, to help us understand it better. Those people also make up my president's council. It is a group of patients and caregivers that guide the work we do. It doesn't matter what we do if it doesn't matter to the patient community. I also have, we are governed by a six-member board of directors, and I have a staff of six. Most of all, I am very proud that we are

included as the patient advocacy group in every step of the way of the Porphyrias Consortium work. We feel like we are central to their role and that they value our work.

(01:09:28):

Now, onto our patient registry. So back in 2005 to 2007, led by a porphyria expert, and I would call him a visionary in this area, a champion of our group of rare diseases, he launched a needs assessment in our community. And what that needs assessment showed is that we didn't have guidelines for care. We had one FDA- approved treatment at that time, and it was actually Panhematin, which was the first FDA-approved treatment after the passing of the Orphan Drug Act, and that is among other needed components, but what we didn't have was a formal patient registry. We had no gathering or collection of information of our patient community to be able to better study these diseases.

(01:10:27):

So after a lot of work, we were successfully awarded our first round, first of three, grants by the Rare Disease Clinical Research Network. You just heard Doctors King and...

Susan Winckler (01:10:45):

Wagner.

Kristen Wheeden (01:10:45):

... Wagner, actual doctors compared to me. You just heard them sharing information about the RDCRN. But when the Porphyrias Consortium was funded by RDCRN, the Porphyrias Consortium was launched along with our patient registry.

(01:11:04):

So it was established in 2008, and our initial goal for this registry was to enroll 600 patients. We now have over 1,100 participants. They are all genetically and biochemically confirmed. We have 14 porphyria centers. They are geographically dispersed across 14 porphyria centers at academic institutions. We do have a separate contact database for further or alternate uses. And I think this is a really important point, that a contact database is simply how to contact people within your community, far different from a patient registry that collects information that's going to help you to analyze this community.

(01:11:58):

The data that we have uncovered has informed nine national natural history studies across all the porphyrias. It has been a part of over 230 publications from 2009 to now, present, 2024. It has supported the development of two additional FDA-approved drugs and we also have more that are currently in the drug development process. We have secured about four and a half million in industry support, knowing that we have this strong patient registry and collection of information. And we have also developed a novel patient reported outcome that has been used as an endpoint in those clinical trials.

(01:12:51):

So, a few considerations for a successful patient registry. First, the why. Why are you doing this in the first place? You have to have clear objectives. Do you want to collect or start a patient registry to focus on research only? Is it to guide clinical care? Is it for advocacy and funding? Likely all of the above, but you need to be very clear of why you are doing this in the first place, as you would with any project that you launch.

(01:13:24):

Next, who. Stakeholder engagement, and this is absolutely critical. You need to understand your key stakeholders and engage them all early and often throughout a patient registry process. Most likely, as with any project, you likely have a champion, someone who drove this in the first place. We certainly had that in the porphyrias, but there are a vast number, there's a myriad of folks that are engaged. Your team of researchers, absolutely critical. Your principal investigators who are signing on to do this and want to study your disease. Fill in the blank to disease; of course, for us, the porphyrias. A strong project manager makes all the difference in the world.

(01:14:11):

Besides your team of investigators, each of them have, in our case and like in most cases, a team of research coordinators that have the direct connection with the patient community. I often say the research coordinators make the world go round. These are the people who are contacting the patients, making sure that they stay engaged year over year for a longitudinal study. It's not just cross-sectional. You need to study these diseases over time, and it is the work of the research coordinators and an effective project manager who makes that happen.

(01:14:51):

Funders. Of course, to do this, you need funding. All the prior panelists, the clouds, and the people, and the platforms, and tools that are involved in a patient registry, unfortunately it is not free. It takes a lot of work to find the funding to be able to have a patient registry that is enduring. And then last of all, and, of course, I would say most important as a patient advocacy group leader, your patient community, both all the individuals that make up your patient community, but also how it funnels through a patient advocacy organization, a united voice for the patient community.

(01:15:39):

So that's the who, and then the how. The how is the big thing, and it really is possible for all levels of prevalence of patients of rare disease communities. You need to ensure inclusivity setting up a patient registry so participation is possible for anyone that you can get into it. You need to ensure data quality above all. The information you get out of a patient registry is only as good as the information that is put in a database. That is absolutely critical. And then, of course, the privacy and ethics. You need proper consent, proper approvals, and, of course, adequate and appropriate management of that data.

(01:16:36):

So wrapping up with a few best practices. Standardized data collection. Again, the last thing you want is to collect information, go through years of developing a patient registry, you get a researcher interested in studying it, in mining that data, they go to look at it, and there's gaps in that data. The data means nothing then. You need really full standardized process so that all data is input in the beginning and regularly. Follow-up is absolutely key. It is such a mistake to lose a patient to follow-up for whatever reason it may happen. So continuity in a patient registry is absolutely critical, and having that team that follows up with your patient community.

(01:17:33):

The use of technology, so the right tools and the right platforms ensure that a patient registry is efficient, that it is scalable. We started with 600 and we got over 1,100. We likely should have more, and we will have more as we continue our patient registry into the future. A database... The technology needs to be secure and capable of supporting a diverse... Both research needs as well as participants.

(01:18:06):

Collaboration, and this is one of my favorite ones. I'll say we just finished a publication within the RDCRN. It was the work of multiple stakeholders, and the focus was on collaboration of multiple

stakeholders and looking at best practices. And what we found from studying this is that there were four critical areas of collaboration and they impacted then four key areas in research.

(01:18:38):

The four key areas that factored into successful collaboration were defining clear roles and responsibilities, open communication, transparency among all key stakeholders, recognizing the value of the patient advocacy group, which doesn't happen everywhere, mutual respect as a foundation for all those groups. Am I getting the hook? Yeah, all right.

Susan Winckler (01:19:06):

You're good.

Kristen Wheeden (01:19:07):

And then that idea, those are in study design, planning and execution, funding, and engagement with external stakeholders.

(01:19:15):

So, to wrap it up, there are special considerations in rare disease. We all know this. And what I will say is that once my son was diagnosed, anyone with porphyria became part of my family. And because of our patient registry, we now have a validated PRO, we have guidelines for his care and for those in porphyria, and we are moving forward in furthering more FDA-approved treatments and greater knowledge of our rare disease.

(01:19:56):

So, thank you, and sorry if I went over time.

Susan Winckler (01:19:59):

That's all right, Kristen. Thank you so much. And if you would take a seat there, we do have Dr. King and Dr. Wagner with us remotely. Even if we don't see them in the room, everyone virtually is seeing them, and they're available to answer questions. So we have five minutes and I believe I have 27 questions. So we will not get through all of those, but I want to do a range of questions here. So some are going to be very tactical and some a bit more philosophical.

(01:20:34):

So, one just came in as I was stepping away from the Zoom that asked about patient and caregiver reluctance to participate in a natural history study or in a registry. Doctors King and Wagner, I'm going to have Dr. Gordon and Kristen pick this up here and they're each going to take less than a minute to answer that question.

Dr. Leslie Gordon (01:21:00):

Okay. Hello?

Susan Winckler (01:21:04):

Yes, you're good.

Dr. Leslie Gordon (01:21:06):

Okay. Okay. In less than a minute, I would say part of it has to do with patient communication among the community, which is very possible now with translators. And we have this fantastic thing called Progeria Connect and they can talk to each other, so that fosters a confidence among them. They share what they've experienced with us. And sometimes it's the home docs that help a lot. In certain countries, there just isn't a lot of trust. There's a huge language barrier and there's a trust barrier. We're in 51 countries, so think about the variety there, and sometimes the home docs championing can help a tremendous amount, because they see the value and they pass that along. And then, look, once we meet them and we establish a relationship and that relationship is longitudinal, you're off and running.

Kristen Wheeden (01:21:56):

Great comments. And it's so important to mitigate that distrust, but let's look at the other side of it is what I say, is that here's what I get from the patient community. I get the questions. Why, fill in the blank of this rare disease, why is this happening? Why does my stomach hurt? Why is there brain fog? Why? Why? Why? Why? You want to understand more about your disease? Participate in rare disease research so we can better understand it, so we can give your information in a secure, safe way to the researchers and experts who want to study you. We're not going to learn anything unless you participate in research.

Susan Winckler (01:22:39):

Excellent, both in content and timing. So let me turn, Dr. King and Dr. Wagner, to you. I've got two what I think will be quick hits, but important questions. It came from a couple of different folks to say, is the data set generated through REDCap FDA-compliant? Which may take 100 minutes to answer, but I'll give you one.

Dr. Eileen King (01:23:02):

Yes. Okay. So, REDCap is what is called Part-11-capable, so it has all of the features that is needed for it to be Part-11-compliant. The challenge is that, in order to dot all the I's and cross all the T's, every time you do an upgrade or a change to REDCap, you have to go through a very extensive process in order to validate that. And while we do go through a process to validate it, it's nearly impossible to do all that I-dotting and T-crossing. That said, the REDCap consortia is working on an automated system in order to make that possible for all the academic centers who are using REDCap.

Susan C. Winckler (01:23:49):

Excellent. So, capable.

Dr. Eileen King (01:23:52):

And I'm [inaudible 01:23:52] module that we have gone through the actual process of making sure that that is Part-11-compliant, that's E-Consent.

Susan Winckler (01:24:04):

Great. So, capable, and then, yes, to compliant, but with a lot of additional engagement. Dr. Wagner, one for you. There was a question about GDPR, so the Global Data Privacy Regulation, and is REDCap GDPR-compliant, recognizing that a lot of this activity would cross borders.

Dr. Michael Wagner (01:24:29):

Yeah, so it seems that I'm frozen [inaudible 01:24:33], but REDCap is GDPR-capable, and we at the DMCC for the RDCRN are absolutely supportive of GDPR, and we'll do what we can with our IT Compliance team to seek and request to be forgotten. Now, I will say that once data has been shared, and data sharing is important to us, obviously we cannot retract data from other groups or other repositories. So again, there's an asterisk there, but anything that comes into the RDCRN [inaudible 01:25:05] we will [inaudible 01:25:07].

Susan Winckler (01:25:08):

Excellent. So I have... Well, I will ask one more question, and this can be to any of you, but probably not all of you, so whoever jumps in first will get to answer. Have you thought about the application of artificial intelligence and machine learning to the data that you've collected?

Dr. Leslie Gordon (01:25:33):

Okay, you want me to jump? Well, I don't know if this applies exactly to what you're saying, but we've just moved into a space where artificial intelligence has changed our world, where somebody speaking Chinese can speak to somebody speaking Spanish and you don't use an interpreter. I feel like the world has opened up. So, anything is possible as long as you understand the capabilities and can work with them. You have to understand what you're doing and why you're doing it and what you're using in order to make the best of it.

Addressing Challenges in Registry and Natural History Data Collection

Benjamin Forred, MBA, ACRP-CP, Sanford Research
Zohreh Talebizadeh, PhD, Global Genes

Reactor Panel

Henry Kaminski, MD, George Washington University
Suzanne Pattee, Office of the Commissioner, FDA
Dominique Pichard, MD, MS, National Center for Advancing Translational Sciences, NIH

Susan Winckler (01:26:09):

So it might be back to good quality data and then thinking about the limitations in the application. All right, my job is to keep us on time, and so I have to thank Dr. Gordon, Dr. King, Dr. Wheeler, and Kristen for joining us in this session. We're going to move from that getting started to now talking about some of the challenges in registry and natural history data collection.

(01:26:36):

So I will note, we said that we are going to move to using reactor panels in our subsequent sessions. So I'm going to ask both our reactor panelists to come up to the table and our speaker to come up for this next session. Our reactor panelists have the role of asking clarifying questions, emphasizing some key points, and sharing additional information. So as they take their seats, I'll note quickly that our reactor panelists include Dr. Henry Kaminski from George Washington University, Suzanne Pettee from FDA, and Dr. Pichard, who we've already heard from.

(01:27:13):

So with our reactor panelists settled, let's turn to our first speaker, who's going to help us focus on addressing challenges in registry and natural history data collection. We heard a bit of that in the first session, but we'll dig more into that. So, to guide us in that discussion is Benjamin Forred, who is

Director of Translational Research and the CoRDS Registry at Sanford Research. You may have the microphone and control of the slides.

Benjamin Forred (01:27:41):

All right, thank you. Can everybody hear me okay? Awesome. Well, thank you so much to the organizers, for everybody who worked so hard to put this together. It's been a really great way to kick off this meeting, and I hope that you're noticing that there are some themes that come up no matter what the topic is. And so we'll kind of expound on some of those things in this talk, thinking in particular the great intro by Dr. Pichard to cover what is a natural history study, what's a registry, and what's the difference, because that's not always intuitive.

(01:28:10):

My name's Ben Forred. I have been the director of the Translational Research Group and the CoRDS Registry going on about 15 years or so. The registry has been in place for 10. And just by way of a really quick overview, this is a disease-agnostic registry, longitudinal study that's provided at no cost to patients, advocacy groups, researchers, and industries. And so this is something that's wholly subsidized by the hospital system that I work for based in the Dakotas. And we have about just over 20,000 participants representing about 2,500 of the rare conditions. And we're in around 100 countries. And then we also have worked with about 120 different advocacy organizations to create custom registries that we house, again, at no cost to anyone.

(01:29:05):

Let's see if I can...

(01:29:05):

There we go. So, I kind of went through some of this. I do just want to underpin that this is not a disease-specific registry. This is something that we have set up as a standard survey, and then we'll work with advocacy organizations to create a deeper-level disease-specific registry, the types of things that we've been talking about so far today.

(01:29:36):

Okay, so we're going to shift a little bit to just talk about how as a data provider we have worked to set up our system so that it can be effectively shared with other groups to meet a wide variety of different endpoints. And so I was asked to give a talk about, how do you prepare for a bioinformatics plan? How do you prepare for something that's down the road? How are we going to use this data? And I think that there are a couple different ways to approach that.

(01:30:03):

For folks that are in the audience or are joining online who have never heard the word bioinformatics, don't be intimidated. This is simply a word that means we're going to be using a computer, some computational tools to address a data set that's full of medical, biological types of information. So, nothing to be scared of. You can think of a whole bunch of different genetic elements being pulled together and analyzed.

(01:30:28):

So, in our case, the first thing that we have done with our questionnaires is based it on a set of common data elements that were published by the NIH around 2010, when we were getting started. And so every single person who joins the registry completes this questionnaire. And over the course of time, we've built up a rather large data set that's been covered across all of those different groups.

(01:30:57):

Interoperability is something that we've touched on today and in just about every one of the talks. And in that case, how are you collecting data now so that it's so-called fit for purpose down the road? How can it be translated into another format and then aggregated with other data sets? And so we talked about the CDISC standards. CDASH in particular was something that was mentioned as a way to collect those data elements that are more patient-reported too. And the OMOP I have up here is just a common data model that's really big in research, and so it's a standard way to collect and share data.

(01:31:39):

Another tactic that we try to employ is with discrete fields. So, when you're creating a survey, you can have a free text field, where people can enter in their answers, or you can choose to have that be more checkboxes, dropdowns, radio buttons, and those kinds of things so that a user can easily interface with it, but this also creates a cleaner data set from the beginning, because there is no need to go through that natural language processing step, and it can also lead to effective translation into other languages. So if you were to translate all of your surveys using those discrete elements, you can trace back to see exactly what choice was selected by that person.

(01:32:28):

And then, just having some sort of a systematic way to ingest large data sets from external sources. And so, if you were going to have a registry set up with patient-reported outcomes and you were going to take in raw genetic information or you were going to link to an EMR, something like that, making sure that from the start you have a good set of procedures and ways that you're going to go about doing that is going to be essential.

(01:32:54):

Ethics considerations. We talked about this a little bit in the last talk. The data needs to be collected in the right way from the start or else it's unable to be used downstream in research or other ways. We talked about contact registries, ways that advocacy groups can keep in touch with their membership and certainly know who and where they are. That's just part of running a good nonprofit organization. Collecting data for research has a different set of rules, and so there's an IRB, an institutional review board, that needs to review the protocol and the consent documents, and then adhering to Part-11, HIPAA, GDPR, and those kinds of things like we just talked about in the last Q and A.

(01:33:43):

For us as a hospital system, our databases, our servers, and all of those things are already HIPAA-compliant, and so it wasn't a big stretch or a big investment for us to set up this entire registry system on those servers and then maintain the Part-11 compliance and the HIPAA compliance that was there. But the GDPR rolling out was a little bit of a curveball in a way that you had to adhere to some new privacy regulations that extend to people, especially in the European Union, with additional privacy rights. The right to be forgotten was mentioned there. And so if a person says, "I want to withdraw from this study and I want you to pretend like we never met," then we have to comply with that. And so we've taken GDPR and extended that across the board just in a blanket privacy policy in anticipation that other states, other countries will be following suit with that down the road.

(01:34:43):

So those kinds of things are important to understand because you are collecting personal information from people. Participants have to know what they're agreeing to. Our privacy officer has this famous line whenever we bring up these kinds of things that a person can agree to anything they want as long as they know what they're agreeing to, and that's kind of this general theme to keep in mind. It's your job as the person who's curating that data set to know what rights that participants have and then taking the steps you need to take to protect them.

(01:35:18):

So, governance and procedures around governance. This is another thing we've talked about. We have an internal scientific advisory committee. This is something that we have. It's made up of physicians, genetic counselors, researchers at our research institute. We just review applications for access to the research on the back end. And so we want to make sure that all of the use cases and all of the requested needs for that data are based on a research inquiry. And we'll look through to make sure that materials are IRB-approved, that the proper channels have been followed, and then, if approved, then we'll work through the system to create the de-identified data set that they're requesting and send that out. Having that all mapped out ahead of time is exceedingly helpful in not having to try to adjust on the fly as you're going. And it should already be done in a certain sense, because you have to outline those kinds of things for the IRB when you're seeking approval.

(01:36:24):

I put a thing on here about identifiable versus de-identifiable data. This is something that groups should be aware of and understand. You could collect the identifiable data, but you have to make sure that what you're sharing adheres to what the patient agreed to. So again, they can consent to anything as long as they understand what they're consenting to. If you're going to be sharing that identifiable information, there are other documents and other things that you have to make sure are taken care of to remain compliant with the things that you've worked so hard to become compliant with. Sharing de-identified data is a different story, and there are 18 elements of protected health information that have to be scrubbed out of the data set, and there are some really great online resources for that sort of thing.

(01:37:15):

The security measures are basically, how are you going to share the data and then how are you going to keep that secure? What we've done in the past is set up S... They're secure file transport sites. You can imagine it being like a login screen where we can dump files and then people can remotely access those in a secure way. We get very clear answers from people before we're going to commit to a new tool or a new add-on for the registry. And then the person who is receiving the data, the principal investigator of whatever study it is that we're working with, needs to sign, basically it's a legal document that just says, "I am going to comply with the terms that are listed out in this study and we're going make sure that we do everything that we can to protect this data in the same way that we would protect our own."

(01:38:20):

There we go. So this is my cue to wrap this up. To summarize, I probably didn't say a whole lot that hasn't already been said today, but the thing that I want folks to take away from this particular presentation is that building a registry is complex, that there's a lot that goes into it, and there are a lot of things that you have to kind of think about and figure out before you begin. There are awesome resources out there. You can think of us as a resource. We'll answer questions, we'll make sure that we can set you up on the right path, and, if desired, like I said, we will build the registry and host and maintain that ourselves at no cost to you. However, there are great tools that are out there. The Radar program from the Office of Rare Disease Research is an excellent tool that advocacy groups, individuals can use to kind of steer their ship and basically help them in a really process wise manner, and get to the point where they need to be. And essentially protecting all of that information on the back end too. So again, thank you to everyone for inviting us to speak today. And, yeah.

Susan Winckler (01:39:42):

All right, thank you so much, Ben. Really practical information and you may take one of the purple chairs and we'll get ready for our Q&A session after our next presentation. But really helpful just to hear the experience that you have at the health system and with a number of different activities in this space. So now we'll turn to our second speaker and we are going to be hearing from Dr. Zohreh Talebizadeh and she is the leader of the RARE-X Research Program at Global Genes and serves as the senior director and principal investigator. So Dr.Talebizadeh, go ahead.

Dr. Zohreh Talebizadeh (01:40:25):

Thank you. Okay, it's a pleasure to be here. Thank you so much for the invitation. Let me make sure I know how to move my slides. That's number one. So I am going to talk about RARE-X Research Program, which is a research program at Global Genes. Global Genes was founded as a non-profit organization in 2008 to provide support and connections to rare disease patients and families. As we know, and we heard throughout this wonderful workshop, data silos and lack of data on rare and ultra-rare diseases are one of the main roadblocks in promoting research in this space.

(01:41:29):

Global Genes' data collection research program called RARE-X was launched in 2021 to address this critical need by facilitating virtual patient-owned data collection, including patient-reported outcomes or PROs. And I joined Global Genes about six months ago as a new principal investigator and senior director of this research program. To enroll in RARE-X, participant begin by signing up, logging in and providing consent and data sharing preferences as shown in this slide. We use a branching logic starting with the general medical health and development survey, which is called Head to Toe survey that follows the clean gene standards. RARE-X survey assignments relies on symptom-based reporting, which has two main advantages. One is that it could facilitate data collection on symptoms, symptom domains that may be under or even unreported, and also accelerate collecting data for new diseases and undiagnosed cases. And the second advantage of this approach could be that it could enable cross disease comparison, which we think that it's very essential and important, particularly in case of rare diseases.

(01:43:14):

As shown in this slide we have several, I mean the branching logic follows several layers, as Layer 2 or Level 2 surveys map symptoms using HPO terms and almost all surveys are assigned on a 12-month basis. But in addition to that, participants are also able to manually trigger a new version of the survey at any point if they feel that it needs to be updated. And this allows for longitudinal data collection.

(01:43:52):

Also similar to other groups, we use expert working groups for domain development and the process involves steps such as scoping, prioritization, landscaping, selecting measures, and finally licensing and implementing those measures on the data collection platform that we call it DCP. And domain implemented today include neurodevelopmental, neurodegenerative and also neuromuscular and implementation of additional domains is in progress. This slide, I just wanted to highlight that how RARE-X has created, as we call it integrated ecosystem to support patients as partners in research and has also developed a service model to support biopharma and researchers. For example, it enables patients to participate in a patient owned data collection platform at no cost, as well as covering the requirement for data governance and governance and informed consent.

(01:45:10):

Furthermore, it provides education and support to facilitate retention and engagement efforts for patient communities, communities, as we just heard from our previous speakers, is also another essential element in this type of efforts. And data on this platform is structured and made available to

researchers across academia, industry and advocacy. It can be utilized for sponsored studies, consortia and natural history studies, as well as patient identification for recruitment for clinical trials.

(01:45:59):

And I just wanted to provide a very brief overview of the data that we currently have on RARE-X platform. To date, RARE-X has attracted 7,700 participants, representing 67 disease communities and 106 patient advocacy groups or PAGs from almost about 90 countries. The compilation rate averages around 50% across participants, which 78% of participants expressing concern about development in various areas. Additionally, 615 reports including genetic testing information have been uploaded for curation.

(01:46:56):

And this graph generated from the Level 1 general survey provides a comprehensive overview of the symptoms symptom domain reported by a patient or participant in this platform. The most frequently reported domains as shown in this graph, are the brain and nervous system and developmental issues. And the next slide. This graph highlights the most commonly reported symptoms across the second level, Level 2 in-depth domain surveys, which as you can see again, the top reported symptoms include cognitive impairment, coordination issues and hypotonia.

(01:47:46):

And quickly I wanted to also review a few elements about data access, which as we heard also from other speakers, like other programs, we also, participants, I mean we follow some workflow for data access and data requests and participants basically always have access to and control of their own data. And RARE-X consent process enables the RARE-X program to assign data use ontologies and allows a different level of data access for requesters, as shown here, it could be in a aggregate form or patient level. So requesters basically need to submit request, which will be reviewed and for approval by the committee. And RARE-X maintains robust compliance program including GPDR.

(01:48:52):

One of the core missions of RARE-X is to facilitate data sharing and with input from our stakeholders, we have generated a number of easy to understand templates for sharing aggregate data with patient advocacy organizations for their engagement and dissemination efforts. And here are a few examples of some of those templates and aggregate data will be shared as a PDF or PowerPoint and it may be also shared as Excel format for data visualization and also to meet their needs and for their customization.

(01:49:36):

As noted earlier, RARE-X was launched three years ago and now we just started to see longitudinal data for the first group of participants. While we obviously need more data to conduct a meaningful analysis, but this slide I wanted to show, this slide basically shows a snapshot of data points collected over three time points for three different patients with the same rare disease. And this example demonstrated the potential of capturing individualized phenotypic changes over time using a platform like RARE-X.

(01:50:26):

And as far as applications of this platform, based on our experience and pilot studies that we have initiated, I would like to highlight four applications. RARE-X can be utilized for or contribute to validating PRO Surveys. For example, it can implement established surveys in larger and more diverse rare disease populations and develop new surveys to address unmet needs. And all of these can be validated against established measures already on the platform.

(01:51:09):

And second application is to contribute to national history studies and RARE-X currently collaborates with multiple academic medical centers to reduce study burden and enable a subset of study data to be collected in a decentralized manner on the RARE-X platform instead of, or in addition to a clinical site.

(01:51:36):

The third application that I wanted to briefly mention is to facilitate formation of research consortium around certain domains, symptoms or diseases by bringing together diverse stakeholders to create collaborative data collection programs with specific aims. And lastly, RARE-X categorizes rare disease database on shared symptoms. And this approach along with HPO ontology alignment, forms the basis for cross disorder comparative research and data linkage with other researchers resources.

(01:52:23):

So here is an example of an ongoing partnership facilitated by RARE-X. In collaboration with the Commission for Noble technologies for Neurodevelopmental CNVs and Illumina, rich genomic data have been generated and are being mapped to phenotypic data that has been collected on the RARE-X platform on three ultra-rare disorders. And as also mentioned briefly, another impact of or potential use of contribution of this type of PROs could be to contribute in natural history studies. And this type of partnership will enable participant enroll in both RARE-X and a natural history study to complete the necessary PRO data just for one time for both studies. And additionally, participants can update their symptoms on RARE-X, which facilitate capturing symptoms or patterns as well as previously unseen patterns or reported phenotypes.

(01:53:42):

Finally, in the last three slides I wanted to summarize past, present and future directions. We have successfully launched RARE-X and incorporated several key features as shown in this slide, which include established active engagement with the stakeholders for PRO data collection, developed symptom-based data collection, implemented genetic data curation from reports, enabled patient-preferred data sharing, provided both aggregate and also individual-level reports, collected data from multiple time points, as I showed one example. And I wanted to highlight that despite the fact that there has not been any concrete or focus campaign I would call it, among the research community during the initial launch phase of this program, I'm pleased to also share that we have seen a growing interest among the research community to use this type of data bases. And here I wanted to say that this program also holds significant promises with several key applications already underway. We have piloted efforts to assess feasibility in areas such as data mapping and natural history, as I briefly mentioned. And to facilitate secondary data analysis, we have launched Open Science Data Challenge and additionally to enhance accessibility and promote inclusion and diversity, we have initiated a translation workflow for, in select languages.

(01:55:37):

In the brief presentation that I provided, I tried to highlight the achievement of patient-led data collection initiatives such as our platform and despite the resource constraints they face moving forward, I believe that the success of these unique and complementary initiatives relies on addressing various challenges. These include coordinated efforts to facilitate data aggregation, establish standard protocols for PRO data collection, developing standard evaluation matrix, enhancing analytical capabilities, as we also heard from previous talks, and implementing a standardized workflow for longitudinal data collection. And to address these needs effectively, a national workforce could play a crucial role. And this would involve conducting a comprehensive assessment of current protocols and identifying dedicated funding resources to support the future direction of PRO collections, harmonization, and sustainability. So thank you so much and I wanted to thank our team. Thank you.

Susan Winckler (01:57:04):

Fabulous. Thank you, Dr. Talebizadeh. And if you would take a seat next to Director Forred, we will start our reaction. So as a reminder, our reactor panelists for this session include Dr. Henry Kaminski, professor of Neurology at George Washington University, Suzanne Pattee, who's a regulatory counsel here at the office of the Commissioner and FDA. And we are welcoming you back, Dr. Pichard, to the stage to react to what you've just heard. So for our three folks here, I think you do have to push to talk to get your microphone to work, but does anyone, what do you think? Do you have questions? Who's going to jump in, lean in first? All right, Dr. Kaminski, you win.

Dr. Henry Kaminski (01:57:49):

Excellent. So a question for RARE-X. So in particular your outreach to socially disadvantaged communities. And just to give you kind of context of that, the Myasthenia Gravis Foundation of America established a patient registry probably now 10, 15 years ago. And we started some surveys and 90% of the respondents were white and actually over 50. And so how do you actually try to reach those communities? And one other comment there, I attended a lecture from somebody who's a leader in the rare disease community and the claim was in this rare disease, a 100% of the population is Caucasian. Clearly not the case. And often, you learn from diversity than uniformity. So how do you reach those communities? Which is very difficult question to ask.

Dr. Zohreh Talebizadeh (01:58:58):

Yes, thank you so much for asking a wonderful question, actually. And one way that we have tried to address that need is that this program is global. So as a result of that, and we are working very hard to also enroll and engage participants from a wide range of countries, which obviously then bringing much richer diversity. But another element which very briefly in one of my slides I mentioned, is that to facilitate that we started actually translation workflow because that's another barrier, right? You want to reach out different countries, then it cannot happen in an inclusive way if you just provide your resources in English language. So I'm proud to say that our team started that and soon we are going to launch recruitment materials in select languages to address that need. So that's one effort that we are doing to address that.

Susan Winckler (02:00:22):

Ben, do you want to add anything?

Benjamin Forred (02:00:22):

I just want to underscore the importance of that. A statement like, "A 100% of patients are Caucasian," really limits the research that's out there. We know that rare disease doesn't respect geographical borders. It certainly doesn't respect racial borders either or socioeconomic borders. The one thing that we do and that we have, we didn't anticipate this being a challenge, but we have had to address it and overcome it, is even very affluent families may have a rare diagnosis within the family or multiple diagnoses in the family and the costs that incur can push them into a much lower socioeconomic bracket.

(02:01:05):

And this is an online platform and the assumption is it's 2024, everybody's got the internet in their pocket and that's not the case. There are a lot of people who need access to these surveys in paper so that they can fill them out and mail them in. And there are systemic issues that contribute to that group being predisposed and comprised of marginalized communities. And that's where you wind up missing a

giant segment of the patient population and losing out on all of the information that you would glean from having a diverse group of people.

Susan Winckler (02:01:47):

Helpful, Suzanne or Dominique, who's going to lean in? All right.

Suzanne Pattee (02:01:53):

Thank you, Susan. I'm Suzanne Pattee and what I'm hearing today is gratifying, but I also wanted to bring a real-world perspective, not a [inaudible 02:02:06] word, but I am a lawyer at FDA, but I actually am a rare disease survivor. I have cystic fibrosis. I was born with this disease and diagnosed at about six months of age and I was fortunate to have a rare disease that has an amazing patient advocacy group and I worked for them for about 18 years. You probably think of them as mostly Caucasian, but I have at my physician appointment last week, he reminded me that they are looking at people of other genetic backgrounds who actually have the main mutation and can take the new modulators that were approved in 2019 by FDA, which has enabled 90% of the patients to be much healthier. The number of people who are on lung transplant lists have dramatically dropped.

(02:02:51):

Just for background, the disease actually affects the lungs and the digestive system. It is a thick mucus that clogs both of these. When I was born in the sixties, my parents were told that I had a 50% chance to live to be five years old. Fortunately, I've certainly surpassed that and I actually started participating in clinical trials as a teenager at NIH. Fortunately with these new modulators that are really changing the basic cellular defect, the life expectancy now is in the mid-fifties. I have fortunately surpassed that as well and I hope to keep going. So it's really important. The other thing for this panel today is there is a registry for this disease and it was actually started in 1955. And it really, I have participated because all of the care centers that care for people with disease provide information to this registry. It's not based so much for the patients, but I do have to sign a consent every year or so to say, "Yes, I agree to continue to have my data in this registry." And it's been very helpful to see how we might develop new therapies as well as how the newer therapies might impact the continuation of older therapies. For example, now they're trying to see if some of the therapies people like myself have been doing for years, like Pulmozyme, I guess I shouldn't talk names or a therapy, that's a therapy that helps to loosen the mucus in my lungs and help me cough it up. Is that still sustainable and necessary for people who don't actually have the mucus in their lungs these days? So it's really incredible and important to have this kind of really basic tool that is essential. Thank you.

Susan Winckler (02:04:35):

Suzanne, I want to follow up on that a little bit because a number of the questions that have been coming in are about, and we heard it on the first panel, choosing to participate in a registry and kind of that thought process. Can you give us just a little bit of the window into how you thought about that?

Suzanne Pattee (02:04:54):

Thank you, Susan. I think as a patient with a rare disease who knew early on that I needed to be aggressive and my parents needed to get, be aggressive to make sure we had good caregivers, I realized it was also important to be participating in the data collection. So it's almost like why not participate in this data collection? It's the idea too with tissue samples, if I'm going to go through the pain sometimes of giving a tissue sample, I want it to be used. I don't want it sitting on a shelf. I want it to give us new information to benefit future populations as well.

Susan Winckler (02:05:31):

So it was helpful for you in that context of then how the information might be used and the results that you might see? Okay. Do Pichard, do you want to, all right, go ahead.

Dr. Dominique Pichard (02:05:44):

Thanks so much. And really, going off of that point of if I'm going to give tissue or a specimen or even data, I want it to be used. You made a comment saying, I wrote it down, "The right way to consent." And that consent really is what allows the researcher to use that specimen or the data for the purpose that was outlined for that particular study, but potentially for more. So can you talk about what does it mean the right way to consent?

Benjamin Forred (02:06:18):

Yeah, that's an awesome question. There's certainly global standards for consents and how IRBs work and everything. There's ICH guidelines and things that govern this, but I think that the main things that you have to worry about with the consent is making sure that it's really approachable, that a lay person can read and understand what's going on with it. And depending on the study, you want to make it such that they know what they're agreeing to now and then they have the option to have that data used in other ways down the road. Or if they've contributed a biospecimen, can other researchers with different studies approach them for participation in their studies using that biospecimen?

(02:07:03):

And so there are a lot of different situations you kind of have to think through ahead of time and cover those bases. Some studies take the approach of just being so vague that it all falls under that, but I think that begs an ethical question about how wide of a net can you cast and are those people really understanding what they're consenting to?

Dr. Zohreh Talebizadeh (02:07:27):

Yeah, the comment on that, another approach that actually we are taking to address that type of need is by incorporating data sharing preference for the participant. And it is not just a one-time selection. So at any time, participants can log in and change their preferences. For example, if they have new information and they don't want to participate in certain type of, or they don't want their data to be included in certain type of research, for example, design, then they have the option to do so. So I think it gives them more freedom again, to make an informed decision at any time. And that flexibility be based on the feedback that we have received from our participants, they appreciate that additional added level of flexibility to honor their choices.

Dr. Dominique Pichard (02:08:29):

Can I just make a comment about that?

Susan Winckler (02:08:31):

Sure.

Dr. Dominique Pichard (02:08:31):

I think these are really excellent points and it is important to talk about how the consent is actually a process. I mean, we end up getting a form with a signature, which is the consent form, but that is not the end all be all, as has been mentioned here, it's the process of making sure the individual signing it is

understanding what they are signing away. And it can be challenging, especially in an online world where you may not have that face-to-face interaction. Going back to the comments earlier of the entire population, do they understand? And even if they're given the opportunity to change their data use or data sharing commitments, do they know what that means? Are they informed enough? And what are some ways that those individuals that are either encouraging their community to contribute data or they themselves are running a registry, how can they handle this?

Dr. Zohreh Talebizadeh (02:09:37):

That's a very good point. Of course, we cannot say that for sure we cover everything. But also another sources that we use is community engagement team that constantly, they basically, they receive sometimes questions if there are areas that participant either before consenting or even after, that if they have any questions. So they have the option to reach out to us and get answer to their questions.

Benjamin Forred (02:10:11):

I think from the perspective of CoRDS, this is a clinical study, I'm the principal investigator, we're on clinicaltrials.gov is like a 100-year study or something like that. So it's out there. We have to abide by all of those rules. But all of that said, the consent form and the consent process is nothing if it's not approachable. And those types of documents and those kinds of conversations have to take place in the vernacular language that people speak. And so translation and those kinds of things become difficult because they're the different parts of the world. Especially thinking about the African continent where there are so many languages and there's so many different dialects of different languages. Are we making sure that we're communicating as a study team with that individual in the right way and in a way that they fully understand what's going on here? And so those are challenges that are very real and very hard to face, but we do our best to make sure that we're able to be accessible to them.

Susan Winckler (02:11:12):

I am struck in the approachable consent process is probably the key takeaway there, that it's a multi-component. Yeah, Suzanne?

Suzanne Pattee (02:11:25):

Thank you. I wanted to add that FDA has recently published a new guidance in March that adds a new tool to the toolbox and it's a guidance called Key Information and Facilitating Understanding and Informed Consent, and I was the main person on this for many years, shall we say. This actually does address the fact that how informed are people if we can't really explain the consent. So we actually have come out with some tools on this, including an example in the guidance of how you might want to use things like plain language in white space and chunks of information. For example, one of my providers talked about if somebody gives you a pineapple and you are going to eat it and you're like, "What do I do with this?" I'm not as much of a cook, but if you cut it up and put it into bite-sized chunks and then you can understand it and eat it. It's a great analogy. That's part of what this guidance tries to do, to help you both write it out more appropriately in a two-page, key information, that's the term, and then also help you guide you through the process with the oral consent discussion, so I encourage you to look at this.

(02:12:47):

But part of this also is communicating with the patients and the communities ahead of time when you're developing this kind of approach. It's not a one-size-fits-all. It is helpful to look for each different study of what really do the participants need to know for registries? What is it that they need to know about

data sharing? We do encourage you to take a look at this guidance. I think it was going to be mentioned in the slide somewhere, but thank you.

Benjamin Forred (02:13:14):

That's an awesome resource. That's an incredible thing to put together to help educate people on what's exactly the right way to approach some of these stuff. I think that there's, don't quote me on this, I think in the ICH guidelines, it basically says when you're writing a consent, it should be understandable to a seventh grader. You can't exceed that kind of language in the writing. Some of the things that we do to ensure that we're interacting, it's a clinical study, so it's a one-to-one interaction. We work with patient groups and their scientific boards, their physicians, their scientists to create these questionnaires and these surveys that really drill down into a given disease. But when they're engaging the community and they're working with the individuals who would ultimately enroll in the registry, we don't want to just say, "Nice working with you," and let them explain our study to their communities. So when they have a family meeting or they have a Zoom call or something or board meetings, we'll join those and we'll make sure that we're available for the people in those communities that have ready access to ask questions and make sure that we're able to help them out. We've had to become creative in ways that we address those kinds of concerns.

Susan Winckler (02:14:37):

I'm going to, if I could, because since we've talked a bit about needing to broaden the recruitment and make sure that we are getting a representative population and then challenges in the recruitment, I'm sure there are other challenges that folks are thinking of. Yes, Dr. Kaminski.

Dr. Henry Kaminski (02:14:53):

Yeah, so kind of dovetailing on the consent process. In these ultra-rare diseases, right, there's the potential for exposure of the individual and also now with obviously genetic testing and such. How do you kind of approach those things if you have one person in North Dakota with a certain disease?

Benjamin Forred (02:15:15):

Yeah, that's an excellent question. It's something that we've worked through a billion times with IRB because we share de-identified data. When you look at the list of 18 elements from the legislation that talk about these are the identifiable things that need to be scrubbed, location is a component of that. I can't say that so-and-so is from Cincinnati but I can say they're from Ohio and I can share that state-level data and be in compliance with everything. But if there's only one child in Ohio that has a pediatric illness, whoever is getting that data set is presumably savvy enough with the community to know who that individual is. That goes into the conversation we have with folks about consenting and about understanding what they're agreeing to is that we're going to do our absolute best to make sure that this is a de-identified situation. But given the data that's being requested, we might have to say what state different individuals are from to establish some sort of geographical distribution. In that case, it might be more or less easy to identify you.

Dr. Zohreh Talebizadeh (02:16:37):

Yeah, similarly for rare [inaudible 02:16:40], we follow similar guidelines to do our best not to enable identification of subjects. For that reason, even for de-identify aggregate data when it comes to location, which a lot of time we get requests particularly for location. So our standard is that if there is less than three, for example, in one geographical region, we don't disclose that. We put it into a bigger map like

East Coast or North ... Something to make it, again, combine several states as opposed to specifically highlighting the region.

Dr. Henry Kaminski (02:17:29):

Yeah, just a little bit of a follow-up on this and I think this is going to have to be figured out by people at higher levels than me. But there's also very important to know the location of the person, right? Because then there's the environmental factors, the social deprivation index or not socially deprived. That intricate environmental data is going to be needed, but I have no answer to that.

Dr. Dominique Pichard (02:17:55):

And I think to add to that, it's not only geographic distribution, some of those data elements may include the date of their visit. Well, if you have a developmental disorder where it matters if a child is three months old versus 12 months old or 12 months versus 18 months because developmentally there are differences, you lose a little bit of that data integrity and part of that natural history.

Benjamin Forred (02:18:24):

We've been able to take an interesting approach to that with regard to the dates of events, their birth dates, the dates of a doctor's visit or something like that where we'll share the data and shift the data by a certain number of days. Then basically the researcher understands that any dates you see in this report are plus or minus 10 days or something like that. That way they don't know the date of the person's birth or the date of the encounter, but they have a window that's tight enough that it doesn't really make that big of a difference.

Susan Winckler (02:19:01):

It gives you the temporality. You can ...

Benjamin Forred (02:19:04):

You can say, "This is a 12-month visit, this is an 18-month visit," but I don't know what day it happened.

Susan Winckler (02:19:10):

Intriguing. Other challenges or components that the reactor panel wants to raise? Yes, Dr. Pichard.

Dr. Dominique Pichard (02:19:19):

We talked a little bit about data interoperability or you both presented on data interoperability and how important it is, especially when you are getting data from different sources as well as data standards, so using common data elements. One of the comments that I've heard from the rare disease community is, "But we're different. We're special, we're unique. This particular common element is irrelevant or doesn't quite capture the specifics of my condition." Can you talk a little bit about how you navigate in rare diseases getting data that is useful, interoperable, but also specific enough to provide data-specific information?

Benjamin Forred (02:20:15):

Do you want me to take that?

Dr. Zohreh Talebizadeh (02:20:16):

Yes, please, and then I add one comment. Thank you for helping me, but it's a teamwork. Yeah, collaboration.

Benjamin Forred (02:20:23):

I think that the setup for interoperability comes from making sure that there are some kind of standards that you're following there. I think that what you saw in both the case of rare X and in courts is that there's this layered approach to how these surveys are deployed. Our architecture is based on a diagnosis and we use the Orphanet list to make sure we're covering all the synonyms and we're mapping people to the right questionnaires and stuff.

(02:20:58):

But a person always fills out our standard questionnaire that includes these common data elements from the NIH. Then we'll work with that advocacy group to create a more specific questionnaire that is much more in line with whatever that condition is. Within that condition, there might be clinical tests, there might be validated instruments that we want to use that are a part of that. Almost everybody includes the PHQ-9 and GAD-7 because mental health is such an extremely important topic in rare disease across the board. There are ways to use standard instruments and standard elements to help bolster some of that patient-reported data.

Dr. Zohreh Talebizadeh (02:21:48):

I also wanted to add, as you also mentioned and very well aware that another challenge, particularly in this space, even though even in common diseases, we see that too, we don't yet know full phenotypic picture of events a lot of very well-studied common diseases. So then what can we say about rare diseases that a lot of them, we haven't even had the chance to even know what is the scope of basically phenotype? Then adding or implementing standardization based on what we know today, obviously. But are we going to miss a lot of important information just because of the fact that we didn't have any common data elements or a standardization in place, so as a result of that it was missed? I think it requires maybe thinking a little bit more holistic way in my opinion, and also considering maybe different version of defining a standardization, at least in this space. Maybe it requires a little bit of mix and iterative process. Meaning that okay, using some of the standards, so there is some rigorousness, but also have some protocol in place to have a pause, take a look at it, map it to additional information available in the literature, and revisit that standardization. So it's not really a written in the stone just because it happened to came from this toolbox or another toolbox. It doesn't make it something that we should not teach it and touch it for 10 years.

(02:23:32):

I think it requires little bit of flexibility and again, knowing that it is evolving a standardization and do we have a accepted process for that to practice it? I think that's something that I would like to see that in future direction we would have more dialogue and resources to do that.

Susan Winckler (02:23:59):

We have 45 seconds left. Any final thoughts, observations? Oh, Ben raised his hand. You win.

Benjamin Forred (02:24:05):

I'm sorry.

Susan Winckler (02:24:06):

For first part, yes.

Benjamin Forred (02:24:07):

Yes. I went to first grade, so I know.

(02:24:12):

We would be doing a massive disservice, I think, if we were going to have a panel, a discussion about setting yourself up for success and collecting data in the right way without mentioning survey fatigue. One of the biggest things that we do when we're creating these questionnaires is that we implement a brevity check. The way that we have this submitted to IRB is in a Word document with all the track changes and everything. If that document is more than 10 pages, we go back to the drawing board because there's no way that people are going to fill out the 11th page. So many, so many well-intentioned groups put together surveys that are phenomenal instruments to collect all of these different data sets that don't wind up going anywhere because nobody gets to the end.

Funding Opportunities

Tiina Urv, PhD, National Center for Advancing Translational Sciences, NIH
Katherine Needleman, PhD, RAC, Office of Orphan Products Development, FDA

Susan Winckler (02:24:59):

Yeah. That is a great way to end this discussion. Ben, thank you so much. To our panelists, Drs. Kaminski, Pichard, and Suzanne for joining us. Dr. Talebizadeh and Director Forred, thank you so much.

(02:25:19):

All right, we have one more session before we take a break. We're deep into talking about registries and studies and in fact some of the questions that came in while we were doing that panel said, "And how do we think about funding?" We're going to hear before lunch, two different opportunities there. First we are going to hear from Dr. Tiina Urv who is joining us as program director for the Rare Disease Clinical Research Network at NCATS at NIH.

(02:25:50):

Dr. Urv, thank you for pinch hitting today and take it away.

Dr. Tiina Urv (02:25:55):

Thank you very much for having me.

Susan Winckler (02:26:02):

Large green-

Dr. Tiina Urv (02:26:02):

Yep.

Susan Winckler (02:26:02):

Large green button. There you go.

Dr. Tiina Urv (02:26:03):

There we go. So you've heard a little bit about the RDCRN and what some of you might not know that this is part of the Rare Disease Act that was established in 2002. The RDCRN has been around, well last year, for 20 years. It's an RFA that's re-competed every five years. I work on this along with my colleague Joanne Lumsden at NIH in the office of, well, no longer the Office of Rare Disease, the Division of Rare Disease Research Innovation. Some habits die so hard.

(02:26:43):

You saw this earlier. We like presenting this and we present it over and over and over to drill it into people's heads that this is what the RDCRN looks like and this is our purpose. We work with 10 different NIH institutes to fund this program. Again, it's a network of 20 research teams studying over 100 different rare diseases. Each of the individual honeycombs there is a different consortium studying at least three different diseases. It's a U54 mechanism, which means that it involves more involvement than usual from the NIH. It involves the researchers and clinicians. One of the most important things of this program is that we've embedded the patients and patient advocacy groups into the network. They're written in, you must work with them, you will work with them, and you will treat them as wonderful partners that they are. Study at least three different rare diseases. There's administrative core, clinical research projects. They have to do two to four studies. One of them has to be natural history study, which is why I am addressing you here today.

(02:27:50):

They also have a career enhancement core that works on developing the next generation of rare disease researchers. That's an important thing to bring up, especially when you're doing natural history studies or longitudinal studies. These may go on for quite some time so you need to bring on the next team of investigators. There's also pilot feasibility core, and it was managed by the DMCC that you heard from earlier. The DMCC provides administrative support, data management, clinical research support, and engagement and dissemination.

(02:28:26):

What kind of impact has a program like this that has been going on for 20 years had? One of the focuses of the RDCRN is clinical trial readiness, how to be prepared. That's one of the things I haven't really heard yet today, that these natural history studies and these registries are really taking some of the risk out of clinical trials in that you're preparing the information that you're going to need when you go into a clinical trial. I often tell investigators that your first point of data is as important as the data you turn into the FDA. It should be as clean and as high-quality as you can possibly make it.

(02:29:08):

The RDCRN, the way the program is designed, we don't have enough money to pay for large clinical trials, but what we do support is establishing a foundation. The clinical trials in the past that were directly funded by the U54 are predominantly small phase I and phase II studies and currently 18 trials funded by the RDCRN program. They primarily, the studies they've done have repurposed drugs, they've looked at diets, diet supplements, procedures, devices, and some novel devices. But where the real strength of the program is a foundation that they've established. The RDCRN associated clinical trials, which are predominantly phase II or III, and these are the studies that are funded by IC-specific, NIH-specific grants, have been funded by patient advocacy groups, have been funded by industry. They've taken the data that's been established by the RDCRN, the foundational work, and they've leveraged this information, the phenotypes of patient population, having the clinical sites, having the investigators already working together, having a team that have experience together. They've identified biomarkers and have done some early-phase safety and efficacy data. They've not had any NCATS dollars involved.

They've helped provide for 12 FDA-approved treatments for 11 different rare diseases. You're like, "20 years? That's not enough." But if you really look at the numbers, they they're doing quite well.

(02:30:44):

One of the things when you're doing rare disease research, people are like, "Well, we need these giant grants." But what you really need are smaller grants and understanding the bigger picture of what needs to be done and finding funding from different places and cobbling together. We're going to hear from our colleagues from FDA about the funding opportunities they have. I'm telling you about this one specific funding opportunity. If you look at your document you have here or the people online, if you look at the web page and you scroll down, you will see what the NIH opportunities are and you'll see a lot listed from NCATS. But many of the NIH different institutes have opportunities for rare diseases and we can help you find them.

(02:31:36):

One that's near and dear to my heart is a Rare Disease Clinical Research Network and right now we are in that five-year cycle of where these funding awards are going to be awarded. In this NOFO, we're asking for single-site clinical trials, no phase II clinical trials. They have to study rare diseases, at least three of them. One of the studies has to be natural history study. I see these are in the negative, but I'm spinning them around to be positive. You need to have between two and four different projects and you have to have the patient advocacy group involved. There's no basic science. This is all clinical research work and the applications that propose any type of in vitro model must use relevant clinical endpoints.

(02:32:29):

Right now, this is the thing that's active. Henry over here is probably preparing his application, so I'm wondering why he's sitting here and not writing. They're due on August 13th and the awards will come out in July 2025. If you have any interest, you can contact me. We have the QR code there, so if you just take a picture of the QR code or the link to the website is listed there. Myself and my colleagues at other NIH institutes, we have 12 other NIH institutes this cycle that are participating, we will be happy to answer any questions you might have. Thank you for listening. I pass on to my FDA colleagues.

Susan Winckler (02:33:18):

Fabulous, thanks Dr. Urv. As you were finishing up there, you answered a question where we had a question come in on the Zoom chat saying, "If I have questions, what do I do?" Email. Please do that. Then I guess also know that if you're supposed to be working on something, the office will be aware and expecting you to submit things.

(02:33:41):

But let's hear now from the FDA component. Dr. Katherine Needleman, who is director of the Orphan Products Grants Program in the office of Orphan Products Development at FDA.

(02:33:52):

Dr. Needleman, what should we know about the FDA component here?

Dr. Katherine Needleman (02:33:56):

Hi, thanks for having me. Happy to be here. I'm Katherine Needleman. I am the director of the Orphan Products Grants Program in FDA. A lot of folks do not realize the FDA has some grant opportunities, so I'm going to talk to you about a few of them. I know I am the only person standing between you and lunch, so it will be brief. The Office of Orphan Products Development is in the FDA and it provides incentives for sponsors to develop products for rare diseases. Our mission is to promote the

development of drugs, devices, biologics, as well as medical foods for patients with rare diseases and special populations. We have several programs within our office to help in our mission. We have three designation programs that provides various incentives for the types of products you may be exploring. We actually have four grant programs that help move this mission along as well. I'm going to be speaking about the clinical trials, the natural history, and the Rare Neurodegenerative Disease Grants Program, but we have a Pediatric Device Consortium Grants Program as well. Our website will list all these opportunities for you as well. Our Orphan Products Grants Program is our oldest program in the office. It was established back in 1983. We have an annual overall budget of $19 million. The goal is to advance the development of orphan products that demonstrate promise for the diagnosis and treatment of rare diseases and conditions. Under this umbrella program, we can fund either clinical trials or natural history grants. The Clinical Trial Grants Program, again, that's our oldest standing program funds phase I, II, or III clinical trials. We have at any one time about 75 ongoing studies. The focus really is on efficiency as well as innovation of these trials of trial designs. These grants have helped lead to over 85 product approvals, so we do see that we have great success within this program and fostering the funding for helping at least de-risk some of these important studies to move along to product development.

(02:36:04):

We also have led to numerous publications as well as impact in the field. Our Natural History Grants Program is our newer program. It was actually launched in 2016. We currently have about 14 ongoing grants there. This is an every two-year cycle, so every about two years, we'll have an RFA out. We've seen it has the potential to impact future clinical development and future trial designs as well as support regulatory decisions. Through this program, there has been multiple collaborations between patients, industry, patient advocacy groups, as well as multiple publications.

(02:36:43):

Our Rare Neurodegenerative Disease Grant Program actually is our newest program within the office. It was established in 2021 after the enactment of the ACT for ALS. The '24 budget is $5 million. The purpose of these grants is to help either private or private entities to cover costs of research on or development of interventions for diagnosing, preventing, mitigating, treating, or curing either ALS or other rare neurodegenerative diseases. To learn more about this program or any of our programs, you can look on our website as well.

(02:37:17):

A little bit about the details of each of these. They're all slightly different, but generally their eligibility is the same. We accept foreign as well as domestic applications, private and public for-profit, as well as non-profit entities. Pretty much anybody outside the federal agencies can apply. To be applicable, obviously you need to have a disease that is rare and that's of which affecting less than 200,000 people in the United States. The budget will depend on the type of FOA you're going to be applying for. Again, looking at that particular RFA is important. They will depend, if it's a clinical trial, natural history study, etc.

(02:37:56):

How to apply. We do utilize NIH's grants program platform so we will go through grants.gov. We utilize the year 424 application guide unless it's otherwise noted in our RFAs. We do always post a helpful hints document on our website, so please do, if you are going to submit, check that out because that has specific details about each of the RFAs and just to acknowledge that there are several registrations that would be required to apply. Some of that takes a lot of time, so please do start early. In terms of how our awards are either reviewed or awarded, we do formalize ad hoc committees of experts to look at

these indications, usually mostly with external rare disease experts, but we also utilize our internal colleagues to help provide that regulatory background when needed and applicable. The number of each particular grants that we award will be dependent on what we get as well as the sufficiency of those applications. Of course it will always be dependent on federal funds.

(02:39:05):

These are our three opportunities that we currently have available. The Clinical Trials Grants Program is the one that has a receipt date coming up in June. That's a resubmission date, so that's for folks who have come into us prior and want to try to do a little bit better. If they have a very large resubmission, meaning they're changing their study design greatly and/or if they have a new application that's going to be in October. So October 22, 2024 will be when that funding opportunity is due. Those are for next fiscal year, so that would be for Fiscal Year 25.

(02:39:38):

We just had our Natural History receipt date in February, so we are under a cycle for that and we are looking at that RFA and going to evaluate that and hopefully repost something shortly.

(02:39:50):

Then the Natural History Biomarker for Rare Neurodegenerative Diseases actually just had its receipt date last week, so we are actually under review for that as well. If you're interested in any of these particular grant application opportunities, please look at our website over time. We do update that regularly as well as grants.gov. That's my contact information and thank you for your time.

Susan Winckler (02:40:14):

Excellent. All right, so we've closed out our morning session in hearing about those funding opportunities. We are now going to take a break until 1:35 Eastern Time, so you have 55 minutes. I want to thank everyone who spoke or reacted this morning. I'll note there is a kiosk outside of the room where lunch can be purchased. If you were looking for slides, those of you who are here in the room, there's a QR code that you can scan in the back of the room. With that, we'll see you at 1:35. Thank you.