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Annual Patient Engagement & Regenerative Medicine Meeting 2022: An FDA CBER Workshop for Patient Advocates

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DR. ANNE ROWZEE: Good morning for those of us on the East Coast, probably a very early morning for those on the West Coast. And hopefully, we have some folks joining from overseas.

I want to thank you all for joining us for our second Annual Patient Engagement & Regenerative Medicine Meeting. Today's workshop is hosted by the Office of Tissues and Advanced Therapies, or, as we usually say, OTAT, within the Center for Biologics Evaluation and Research at the U.S. Food And Drug Administration.

My name is Anne Rowzee, and I am the Associate Director for Policy at OTAT. I will also be your host for today's event.

Some of you may have joined us last year for our first patient engagement workshop. And if that is you, welcome back, and thank you for being here. And if today is your first time attending one of our events, we welcome you and are happy that you have joined us today.

Our goal today is to bring together patients, patient advocates, caregivers, and other key stakeholders to discuss natural history studies and why they are important for advancing drug development. We designed this workshop to be both educational and interactive, with the hope that we will all leave with more knowledge and understanding of what natural history studies are and the role they play in the development of regenerative medicine therapies like cell and gene therapy.

We have an exciting agenda planned today. We'll kick off the workshop with a brief introduction about natural history studies and how they contribute to the foundation of product development. Then we will move into a panel discussion featuring patients, caregivers, and patient advocates. We will get to hear about their experiences participating in natural history studies and discuss additional opportunities for patients to help advance clinical research. After our lunch break, we will move into our third session, which will feature experts from the FDA

and from NIH to talk about natural history study initiatives, programs, and some resources.

So before we get started, I'd just like to share a few notes about today's workshop. The workshop is being recorded. The recording and the slides will be posted on the FDA's website in the next few weeks. Closed captioning for this event is available directly within Zoom, and we will have some time during each of our sessions for questions.

If you have a question for one of our speakers or panelists, please type your question directly in the Q&A box in your Zoom window. The Q&A box can be found in the bottom of your screen. Regarding your questions, please note we are unable to answer questions about specific medical conditions and diagnoses. But we encourage you to discuss those questions directly with your health care team.

We also understand that people may have some questions about the status of specific investigational products or drug applications; however, there are laws that FDA must follow that limit the information we can provide about investigational products. We do appreciate questions and comments, and we will do our best to address as many as we can today.

Finally, there is a chat box within Zoom, and if you would like to share a general comment with the audience or with folks presenting today, or if you are experiencing technical difficulties, please use the chat box for those issues.

I would also like to mention that today's workshop is part of a series of virtual events which we call RegenMedEd. The RegenMedEd event series includes educational webinars and workshops where we invite patients, caregivers, and advocates, to learn about different topics related to regenerative medicine. Our previous RegenMedEd events can be found on FDA's website, and I invite you to use the hashtag #RegenMedEd on your social media channels if you would like to share your thoughts on today's workshop.

Let us go ahead and get started. Our first session today is an overview of natural history studies. And at this point,

you might be wondering: What exactly is a natural history study? Why is it important? And why have we dedicated an entire workshop to natural history studies? Well, our first speaker of the day, Dr. Wilson Bryan, who is OTAT's Director, will help to explain just that. Thanks so much for joining us today, Wilson. I am going to turn it over to you.

DR. WILSON W. BRYAN: Thank you, Anne. And good morning, everyone. I am Wilson Bryan, and I am Director of the Office of Tissues and Advanced Therapies, or OTAT, as Anne said. Welcome to this first session of today's Annual Patient Engagement & Regenerative Medicine Workshop. As Dr. Rowzee mentioned, we are so glad that you have joined us today.

Today we are going to give you an overview of natural history studies, and that includes what they are, why they are important, why we need patients and caregivers to participate in these studies, and the critical role that natural history studies play in developing new treatments for all types of diseases and conditions, including rare diseases. And because my office is in charge of regulating cell and gene therapies, we are also going to spend some time talking about this exciting field of medicine and ways that all of you can get involved to help advance research for and development of cell and gene therapies.

First, I guess I should put things in into context. The FDA probably seems like a big organization, and that is because it is a big organization. We have various centers and offices throughout the agency working hard to review data to ensure that drugs and therapies meet high standards for safety and effectiveness.

The FDA has highly trained scientists and doctors, pharmacists, public health experts, health communicators, and many others. And all of these folks are committed to making science-based decisions to help patients and their families.

The Office of Tissues and Advanced Therapies is one of the program offices responsible for regulatory oversight of biological products. And OTAT is located within the Center for Biologics Evaluation and Research, which we call CBER.

Now, OTAT's mission is to promote public health through a data-driven process to provide regulatory oversight that helps ensure that medical products are safe and effective. And in doing so (and this is from our mission statement), we want to be sure that we make all of our regulatory decisions based on data and that we do that with impartiality, but also with compassion.

At OTAT, one of our primary responsibilities is to regulate regenerative medicine therapies, such as cell and gene therapies, to make sure they are safe and effective for patients. A simple definition of regenerative medicine — and there are many different definitions out there, but one definition is that a regenerative medicine is a medicine or treatment that replaces or regenerates human tissues, cells, or organs to restore or establish normal function. Regenerative medicine can involve using stem cells, engineered biomaterials, gene editing, and other scientific technologies to repair or replace damaged cells, tissues, or organs.

Now, as you can imagine, regenerative medicine is complex, and it is important to note that while regenerative medicine has been around for decades, it continues to evolve and progress through scientific advancements. That is one reason why we are here today: to talk about some of those advancements that have occurred in regenerative medicine. Here are a few different types of regenerative medicine therapies, or RMTs. These include gene therapies, which includes, of course, gene editing; cell therapies; therapeutic tissue engineering products; and xenogeneic cell products.

Let me say a little bit more about cell therapies. There are so many different types of cell therapies: There are stem cells and embryonic stem cells and mesenchymal stem cells and induced pluripotent stem cells and all different types of a cell therapies. And when we — gene therapies, including gene editing — there are many different types of gene editing, too. What gets most attention recently has been a CRISPR-Cas9 system, a very exciting method for gene editing.

Part of OTAT's responsibility is to provide regulatory oversight for regenerative medicine therapies. The FDA has several roles, and I am going to describe a few of them.

As I am sure most of you know, FDA approves drugs and therapies to ensure they are safe and effective for patients. We — at the FDA, we have got a rigorous analysis process to review data and ensure the decisions are based on scientific evidence. Regenerative medicine therapies also go through this same rigorous review process before they are approved for patient use. We monitor products before and after they come to market to ensure their quality over their entire life cycle.

In addition, FDA provides oversight of clinical trials of products when they are in development. This is to help ensure that people participating in clinical trials are protected. While FDA does not conduct clinical trials, we do work with researchers and scientists to provide guidance on clinical trial designs, and we oversee clinical trials to verify the quality and the integrity of the data.

Another key role that we at the FDA play is in regulating regenerative therapies, and the goal there is to advance the state of the science by providing advice and education to product developers.

Finally, stakeholder and patient engagement is a critical aspect of our work. We collaborate and communicate with patients, caregivers, and advocates and with product and technology developers. And today is one of the opportunities to engage directly with you.

Before we talk about natural history studies, I want to spend a few minutes sharing some information about the drug development process. This figure provides an overview of the product development process and the major stages of bringing medical products to market. So the steps — you know, starting from early on in development on the left, going all the way through preclinical animal studies and then to phase 1 initial studies based on focusing on safety and tolerability, phase 2 studies to gather additional information about the population and outcomes that are most relevant for a product, and then phase 3 studies to gather definitive information to support a biologics license

application. And a biologics license application, or BLA, is what sponsors submit or a drug company submits to us to try to get their product on the market. And I should mention there that in phases 1, 2, and 3, the drug developer has to have an investigational new drug application in place, or an IND.

What is important to note is that FDA and OTAT are involved in each stage from early on in development through the clinical trial phases and after products are approved in the marketplace. Because of various considerations, this process is often modified for cellular and gene therapy products, as well as therapies for rare diseases. And each product is different; each development program is different. We have to be prepared to be adaptive and open to new ideas in drug development, and we like innovative trial designs and innovative drug development programs.

Talking about rare diseases, I want to mention the connection between gene and cell therapies, particularly gene therapies, and rare diseases. One of the problems with rare diseases is that we do not know much about them, and so there is still a lot to be learned. But one thing we do know is that around 80 percent of rare diseases are caused by a single-gene defect. This is what makes the field of regenerative medicine and gene therapy, in particular, so promising for the treatment of rare diseases.

Gene therapies to treat rare diseases that are caused by single-gene defects could mean improvements in health outcomes, quality of life, and disease management for patients and their families. Right now, we have only two FDA-approved gene therapies for single-gene disorders. But we expect that there are going to be many more approvals in the coming years. And right now, we have more than 1,200 investigational new drug applications (INDs) in effect for ongoing clinical studies with gene therapy treatments — over 1,200. So again, I am optimistic that we are going to, over the years ahead, have many more gene therapies making [it] to the marketplace to help patients.

I need to emphasize that none of this scientific progress — none of it would be possible without the patients who participate in clinical research. Patients are a precious resource for advancing clinical research in their

particular disease area, and they deserve high-quality research programs that produce high-quality medical products. Because of that, FDA and OTAT conduct a wide variety of activities to gather input from patients to help advance research. As you can see, there are many ways that patients can get involved in disease research and development. That includes clinical trials, patient registries, listening sessions, and meetings, such as today's workshop, and of course natural history studies, which is what we are talking about today.

So let us begin with what we mean by "natural history study." A natural history study is an observational study of a disease. It follows a group of patients over time. It involves collecting data like the patient's age, information about the diagnosis, their symptoms, impact of the disease on the patient's quality of life, and more information. Natural history studies can include people with a disease but sometimes also people who are at risk of developing a disease but do not have [the] disease. For instance, a patient may have a genetic mutation that makes them at risk of developing a disease, but they do not yet have that disease, and they could be enrolled in a natural history study.

Natural history studies are valuable tools for advancing understanding of a disease, research, and product development. These natural history studies — they can help to identify demographic, genetic, environmental, and other variables that correlate with disease development and outcomes. The natural history studies help us to better characterize the disease and the patient population.

This is particularly important for rare diseases, for which we have much less data. Natural history studies help to clarify the impact of a disease on the lives of patients and their families. They collect patient-reported outcomes and other disease specific clinical outcomes. And ultimately, what these natural history studies do is, they inform clinical drug development processes by providing crucial diagnostic information and guidelines for disease management. We learn many things from natural history studies that determine what the drug development process is going to look like.

There are four types of natural history studies, and the first two types rely on data collected from patient records. First of all: retrospective studies. And these retrospective studies look into the past, and they use data collected from existing medical records. And these studies are often done as a first step in describing a disease and the progression of that disease. In contrast, prospective studies are an ongoing collection of data as patients come in. So these studies establish definitions and data to be collected ahead of time. So you have a protocol, and then you gather data going forward.

The second two types of natural history studies collect data from cohorts or groups of patients. And cross-sectional studies collect data over a specified, limited time period. In contrast, longitudinal studies collect data at various time points over a long period. Cross-sectional and longitudinal natural history studies can be either retrospective or prospective, so you can have a prospective cross-sectional study or a prospective longitudinal study. And each type of a natural history study has value. The ones that are most useful tend to be the prospective cross-sectional and longitudinal natural history studies. But they take more of an investment and more effort than retrospective studies do.

The FDA has recommendations regarding natural history studies, and we have thoughts of a lot of things, including who should be included in the study, and those are known as inclusion and exclusion criteria — who gets included and who gets excluded from the study. In general, for natural history studies, we like the eligibility criteria and the inclusion criteria to be very broad — include as many patients as possible. We also may give advice on the types of information to be collected and how that data will be collected and analyzed.

Strict protocols: Strict protocols for natural history studies are crucial to ensure that the studies provide reliable data with scientific credibility. Now, I think most people that are involved in drug development understand that protocols for prospective natural history studies need to be strict and written out. There have to be good, strict protocols for retrospective natural history

studies too. So either retrospective or prospective natural history studies — rigorous protocols are important.

It is important to note that although natural history studies can be extremely beneficial, we — at the FDA, we do not require natural history studies in drug development programs. If you are thinking of including a natural history study in a drug development program, please, please start early. These studies take time. They take years, particularly prospective studies. And I've seen many drug development programs stall because they did not do their natural history studies in advance. By the time you get into clinics and in doing clinical trials, the natural history studies should have already been started years before.

Natural history studies provide a wide variety of benefits to rare disease research. Ultimately, these serve as the foundation for the eventual treatment of a disease. They inform important aspects of a drug development by refining the target patient population, helping us to understand which patients are going to be most informative if they are enrolled in clinical trials.

Identifying and developing clinical outcome assessments — which outcome assessments are going to be most reliable, which ones are going to be most sensitive, how quickly those outcome measures are going to change over time — identifying and developing biomarkers — and this says "biomarkers." And biomarkers are useful, particularly in identified populations to be studied in clinical trials, but sometimes these biomarkers can serve ultimately as eligibility criteria and serve, in some rare cases, as surrogate endpoints for a clinical trial, so they can make clinical trials go faster.

These natural history studies inform the design of future clinical trials. Understanding the rate of progression of the disease — understanding which patients are going to develop which outcome measures, over what time period, helps us to know what the clinical trials' inclusion and exclusion criteria should be, helps us to know which outcome measures to use, and helps us to know whether we are going to need a 6-month trial or a 2-year trial in order to see changes in the patients.

And in limited circumstances (and these circumstances are very limited), the natural history studies can serve as an external control in clinical trials. Most clinical trials have comparison between some group of patients who received the investigational product and another group of patients who do not receive the investigational product. They may receive standard care of treatment, or they may have been receiving placebo. But in some cases, you can have just patients who received the investigational product, and they are compared to the natural history control rather than having a concurrent control in the trial.

Natural history studies play a critical role in rare disease research. This is especially true when the progression of a particular disease is poorly documented or described. Designing an efficient drug development program for the treatment of a rare disease often depends on these observational studies that gather data on patient diagnosis, treatment, symptoms, and outcomes.

When knowledge about the disease is insufficient to guide clinical development — and then again, this is particularly true about rare diseases. With some rare diseases, there are maybe only a few hundred, maybe a few dozen patients in this country that have the disease, and then there is no physician that has seen hundreds of patients with the disease or maybe even seen dozens. And so, knowing how to design a clinical trial can be extremely difficult, because no one has enough experience with the disease. In these situations, a natural history study can provide valuable information to researchers as an aim to develop effective therapies.

There are many ways that stakeholders can work together, and working together is the key here to advance regenerative medicine. This includes designing and conducting your own natural history studies, finding opportunities to work together. We need patients, advocacy groups, scientists, industry, regulators — everyone working together and collaborating with one another early on in drug development, long before the clinical trials start.

As mentioned before, none of this is doable without the patients and their families and caregivers who participate in natural history studies and other types of research.

Patients are heroes, and we owe them a great debt for choosing to participate in research. Please remember that we cannot hope to cure and treat rare diseases without patients and families. OTAT is committed to finding opportunities to work together.

During the next session, you will have a chance to hear directly from patients, caregivers, and researchers about their own experiences and their expertise as it relates to natural history studies. We think you are going to find their stories inspiring.

Here is my contact information if you have questions or feedback you would like to share. Now, if we may, over the course of the day, hopefully we will have some time for questions, but usually there is not enough time for questions, and often you think of the question the next day or the next week after the workshop is over. And my email address is pretty straightforward: wilson.bryan@fda.hhs.gov. And as Dr. Rowzee said, I think these slides will be available and our contact information will be available.

This slide includes more points of contact for OTAT and CBER in case, because you are going to realize that there are people at CBER and OTAT who have answers and better answers than I do. With that, I am going to say thank you for you attention today. And Dr. Rowzee, I am going to pass it back to you.

DR. ROWZEE: Yeah. Thanks. Thanks, Wilson. You know, that was fantastic. And thank you so much for setting the stage for our workshop today. And we have had a few questions submitted ahead of time. But I just want to take a moment to remind folks that if they have a question — please feel free to submit it within the Q&A box in your Zoom window. We're going to try to get to as many of those as we can today, and again, if you have some general comments that you would like to share, please feel free to use the chat window.

So, like I said, we had a couple of questions submitted ahead of time, and we have a few minutes for questions, Wilson. So I am going to start with one, and it is a little bit about terminology, and I get these concepts and these

terms confused. So I was wondering if you would help me understand if there is a difference between a patient registry and a natural history study. And maybe — do they work together? Do they inform each other? And if you could, help us sort of tease those apart.

DR. BRYAN: Well, I guess I should start to say I have struggled with this distinction as well. And that is because the terms are used in different ways. I think natural history studies are probably better defined, in that natural history studies are done with a protocol, and that describes the gathering of data. And they are done to characterize the patients with the disease and characterize the disease itself. As we mentioned, talk about the symptoms of the disease, the diagnosis of the disease, the clinical cause, the outcomes. And the purpose of natural history studies — usually, it is to inform doctors regarding the usual course of the disease and often to inform drug development to help us in designing clinical trials. And so, natural history studies have a very particular purpose.

Now, registries — there are so many different types of registries out there, and they have a variety of different purposes that often goes beyond just characterizing the disease and the patients. Now, they can serve that purpose too, but they are often done for other purposes. For example, after a product goes on the market, we often have registries to gather information about the safety of that investigational product when it is on the market. And that can be done through a registry. During drug development, for instance, a drug development often does not enroll patients who are pregnant. And then in post-marketing, we need to know whether that drug is safe for people who are pregnant, and so we will have a patient registry to see how the drug — if it has any adverse effects for newborns.

And so, registries are often used as sort of a preliminary to clinical trials to enroll people to see if they are good candidates for clinical trials. So registries have a lot of different purposes, sometimes looking at safety, sometimes looking at patients' behavior: Which drugs do they take? Which interventions do they use? And that is a little bit different than the sort of limited scope but extremely important scope of natural history studies.

DR. ROWZEE: Great. All right. Thank you. Thank you for that. I think that is really helpful, at least for me. I think that more folks besides me probably have that question; they probably are hearing these terms from folks.

You know, I know we have got a little bit of time left, and I was wondering — you know, I know you probably didn't get enough time allotted to you for your talk today to go into everything that you would want to, but I was wondering if you could maybe share an example with us — an example of when a natural history study was used for an FDA-approved gene therapy product.

DR. BRYAN: Okay. So, as I mentioned, we only have two gene therapies so far that are for single-gene defects. One of these gene therapies — it is a product called Zolgensma — is a treatment for spinal muscular atrophy. And for those of you who are not familiar with spinal muscular atrophy, or SMA, it is a rare disease. There are many different forms, and the most severe form, called infantile spinal muscular atrophy, usually presents by age 6 months. And these kids — this is a bad disease. They get weak. They are floppy. They can't sit up independently. And they never walk. These kids are going to be dead by age 2. This is a bad disease. And Zolgensma is a gene therapy, and it was studied in a phase 3 trial, and that phase 3 trial, I think, had 21 subjects in it. And I want to make that point: that these trials in rare diseases do not have to be huge trials. Sometimes a small trial can gather the evidence needed. And the phase 3 trial for Zolgensma had only 21 patients in it. And the control was an external control. They had done a natural history study 10 to 15 years earlier, and that natural history study had only — it was 22 or 23 patients. So natural history studies do not have to be huge.

But from the natural history study, we learned about the survival of these patients, and we learned that they are not going to be able to sit up independently. And in the phase 3 trial, we were able to compare the patients who got Zolgensma to the natural history study, and it was just obvious that this was a lifesaving treatment that allowed patients to sit up independently.

And fortunately, now, there are patients who received Zolgensma who — you know, you look at them; they are 6 or 7 years old, and it looks like a normal kid. They are running, and they are laughing, and it is just wonderful. And natural history studies allowed us to bring that product to the market faster. And that is what we want to do. We want to speed drug development.

DR. ROWZEE: That is — yeah, that is a really amazing story. And I know it is one that, you know, can help folks — a lot of hope, particularly for some of the diseases and conditions for a lot of the products that we are seeing coming into our office.

So I think we are at time. I want to thank folks who did submit questions. We are going to take these questions back and take a look at them and try to see if there are other ways that maybe we can answer these questions in the future, maybe with future webinars or workshops. So stay tuned for that.

This is going to help set the scene for our next panel discussion, which will take place in 5 minutes, maybe 4 minutes. I will stop talking. So, folks, let us just go ahead and go to a break, and we will see everybody back here at 11:45. Thanks so much.

[BREAK]

So, welcome back, everyone. Thanks again for joining us today. Now that you got a little more information about what a natural study is and why these studies are important, we are going to move into our first panel discussion: perspectives from patients and advocates.

During this discussion, you are going to hear from patients and patient advocates about their experiences as they relate to natural history studies. Our panelists today have participated in natural history studies in one way or another and have sometimes played multiple roles. And we are very appreciative that they are here today to share more with us. I am going to now pass things over to my colleague Karen Jackler, and she is the Patient Engagement Program Manager for CBER, and she is going to moderate today's session. Thanks, Karen. Over to you.

MS. KAREN JACKLER: Thanks, Anne. And welcome, everyone. As Anne mentioned, my name is Karen Jackler, and I am the Patient Engagement Program Manager at the Center for Biologics Evaluation and Research, also known as CBER, here at FDA. And I am excited to be the moderator for our first panel discussion, where you will hear directly from patients and advocates about their firsthand experiences participating in natural history studies.

And with that, I will introduce our panelists. Great. So, our first panelist is Leah Schust Myers. Leah is the founder and Executive Director at FamilieSCN2A Foundation. Leah has spent her career working in health care administration. She never imagined she would find use for her skills in an entirely different way. When her son was diagnosed with an *SCN2A*-related disorder in 2012, it became clear that Leah could leverage her experience to not only help her family but countless others.

Our next panelists are a mother and daughter pair: Amanda and Bailey Regalado. Amanda and her daughter Bailey live in Texas. Bailey has Gaucher's disease type 3. They are both involved in the Gaucher community to help spread awareness and serve as a pillar of support for newly diagnosed families.

Our third panelist is Brad Williams. Brad is the Director of Research and Diagnostic Innovation at the Jain Foundation. Brad lives with dysferlinopathy, limb-girdle muscular dystrophy type 2B/R2. Having a scientific background in physics, Brad decided to change his career path and work on identifying treatment for muscular dystrophy.

And lastly, I would like to introduce Dr. Bruce Marshall, who is the Executive Vice President and Chief Medical Officer at the Cystic Fibrosis Foundation. Dr. Marshall has been with the Cystic Fibrosis Foundation for 20 years and is here today to tell us about the foundation's robust patient registry. Dr. Marshall earned a Bachelor of Arts degree at Johns Hopkins University and his medical degree at the University of Maryland School of Medicine. He earned a master's degree in medical management from Carnegie Mellon University.

Thank you all for joining us today. Before I pass it over to Leah to kick off our panelist presentations, I do want to encourage everyone in the audience to submit their questions for panelists in the Q&A box on Zoom. We will have some time at the end of the presentation for our discussion. For general comments, please add those in the chat box on Zoom. And now, I'll pass it over to Leah to tell her story.

MS. LEAH MYERS: Great. Thank you so much. Hi, everyone; my name is Leah Myers, and I am the founder and Executive Director for the FamilieSCN2A Foundation. I have a little boy named Ben, who was diagnosed with an *SCN2A*-related disorder in 2013. He is 11 years old now.

And a huge shout-out for the FDA team for prioritizing this type of workshop, highlighting the importance of patient-driven research and data collection. It is an honor to share our journey. And if you are listening in today, then you probably already know how selecting the right measurement is critical to the success of clinical trials.

And the foundation recognizes that it is one of the most important things that we can do to expedite the process and reach our vision of a cure for all *SCN2A*-related disorders. We have spent the last few years focused on collecting data, analyzing existing tools, and educating the FDA and industry on what is most important and meaningful to us, the patients and the caregivers.

So I have no disclosures. There you go. So, who we are: "Families" is in our name for a reason. It is rare and devastating, and *SCN2A*-related disorders affect the entire family, not just the patient. Our team of leaders strive every day and in every way to improve the lives of not only the patients but the entire family.

Our core values provide us with a set of guidelines to help us fulfil our mission and our vision. We coordinate and collaborate with the global scientific community to understand the function of the *SCN2A* gene in order to develop effective treatments and a cure. We increase medical community and public awareness of the complexity and potential severity of *SCN2A*-related disorders. We

provide educational and emotional support to those affected. And we raise money to fund our goals.

Our team consists of the most brave parents and incredibly generous professionals I have ever known. These individuals stood up when their lives were shattered by a diagnosis and chose to fight back. I added this slide not only to recognize our staff and Board of Directors but also to make the point that this battle takes a strong and diverse team who will show up every day and speak in one united voice to advocate for those we serve.

It is not something that can be done alone or with just one or two others. So, if you are just starting out on this journey, it is the most important thing I can stress today: Start by building your team, your army.

So what is *SCN2A*? I'm not going to go into the science too much here. I'm just going to let you know that *SCN2A* is a gene that encodes the instructions to make a protein in the brain called a sodium channel. Consistently, *SCN2A* is one of the most prominent single-gene causes of neurodevelopmental disorders, including autism spectrum disorder and infantile epilepsy.

All patients with *SCN2A*-related disorders have a pathogenic variant or mutation in this gene. The majority of the variants are de novo, which means they are not inherited. Pathogenic variants in *SCN2A* can cause a wide range of neurodevelopmental disorders, ranging from babies having seizures when they are first born to autism spectrum disorder to ataxia and other movement disorders.

No matter what type of variant or how affected the individual presents clinically, they all have a voice. And while the majority are nonverbal or minimally verbal, it is our job to ensure that their voice is represented as treatments are being developed for them.

In our community, we have a mix of phenotypes, many with seizures, many without. When we polled our group on what was most important to them to see a change in with a future treatment, many stated that an increase in communication would be most meaningful to them. It ranged right up there with seizure reduction. And that is not really surprising

to me, as I agree, because I would give anything to help my son communicate his basic wants and needs.

So, despite the fact that we've defined what is important to our community, pharmaceutical companies continue to run clinical trials using seizure reduction as the only endpoint measurement. Why? Well, because it's easy to count seizures. And most of the time, they're obvious. And no one was going to argue that reducing seizures is [not] really important. But that leaves out many of our really sick kids in our community who do not have enough seizures to qualify for the eligibility for the trials. And back to our point, stopping the seizures is not always what is our biggest priority.

But how do we prove that the other things are measurable and worth considering in clinical trials? Our community is quite profoundly affected with intellectual disability, autism, and very little purposeful movements, which can be super difficult to measure improvement in. And this gets risky for pharma and where the foundation has been focused and what I want to tell you about today.

So we started with a full analysis of existing *SCN2A* data pulled from the Simons Searchlight. Specifically here, I am going to show you some of the violin, too. If you have a disabled child, you already know that dreaded violin. When the scientists completed this deep dive into the results, it proved to have shortcomings for addressing growth or regression in individuals with *SCN2A*-related disorders. Some sub-domain raw scores reflected substantial floor effects. And raw scores increased so slowly over time that standardized scores declined. So this leaves us with being unable to distinguish why the standardized scores decrease with age. Is it because *SCN2A*-related disorders is — there is regression? Is it degenerative? Or is it because our kids are plateauing and not making any progress? Or do they just have a much slower acquisition of skills, and when compared to typically developing children, the gap widens with age?

Okay. So we are making progress. We now knew what measurement tools did not capture the tiny, granular inch stones of progress our kids are capable of making. And we also knew what was considered most meaningful within our

community. So we were left with the choice of starting from scratch to develop new measurement tools, which definitely has its disadvantages given our urgency to get to treatments, or adapting the already existing, validated measurements to fit our community.

So we used all of that as building blocks for the *SCN2A* clinical trial readiness study, a.k.a. CTRS. As novel treatments were coming down the pipeline, we knew that we needed to help industry groups to understand what to measure and how to measure it within our very impaired, unique disease group.

The CTRS is a project developed by multiple key opinion leaders, including patients, clinicians, researchers, and industry. The foundation is fully funding this work, and the primary investigator and heart of our entire project is epidemiologist Dr. Anne Berg.

This study is going to provide information on the reliability of specific measurements over a short period of time and the rate at which they change over time and in any individual affected person.

So we are starting to define *SCN2A*. I am not going to read everything on this slide, but I am going to share — this is also unpublished, early data from our trial. I am going to point out a few key learnings.

Only 5 percent of the patients can use a toilet or dress themselves independently. Almost three-fourths have a visual impairment. The majority live a life completely dependent on others for almost all of their cares. How can we not find a way to measure this level of impairment? To us, it was so clear that even the smallest improvements would be very meaningful.

Just a few more graphs here as a glimpse into the life of an *SCN2A*-related disorder. A third of the kids depend on a feeding tube. Seventy-five percent have moderate to severe gross motor delays. Many are in wheelchairs. Only 12 percent have a pincer grasp.

And here we are, proving the majority of our community can’t talk or express themselves. So it only makes sense to listen to the people who know them best: their parents or

other loved ones. In the case of *SCN2A*-related disorders, caregiver-reported outcomes become strong evidence and should be considered in clinical trials.

So our impact started to evolve. We believe what is most important is our community. And you can see this picture was taken 3 years ago and at our last conference before COVID. We are stewards to our community. We build programs to support them financially, emotionally, and empower them with education to advocate for their families. Industry groups are now coming to us before they build their preclinical programs, because they want to learn from the data to ensure that they are using the right tools to measure the right outcomes from the beginning.

So, in summary, non-seizure outcomes are critical to clinical trial readiness for rare neurodevelopmental disorders such as *SCN2A*. Rare diseases equal rare outcomes. We have to start thinking outside the box. Many times, you can't meaningfully assess with instruments standardized for the typical population. So alternative approaches are promising, and this is what we are finding in the CTRS. We can adapt the tools. We can use them outside of the specific age range that they're intended for. And a full understanding of the disease before you start measuring is critical.

And that is Ben. And we would like to thank you for listening to us today, and I am happy to take questions.

MS. JACKLER: Thank you, Leah. That was incredible. We are actually going to move to our next speaker, and we'll do discussions when we finish up our panel. So our next speakers are Amanda and Bailey, and I am going to pass it over to them to tell their story.

MS. AMANDA REGALADO: Hi. I am Amanda, and this is Bailey. We live in Midlothian, Texas. Say hi.

MS. BAILEY REGALADO: Hi.

MS. A. REGALADO: I am the Type 2/3 New Family Representative with the Gaucher Community Alliance, and I am so grateful to be there for newly diagnosed families as they navigate through this journey.

Bailey is 13 years old and loves riding horses and watching YouTube. We look forward to the day that there is a cure for Gaucher's disease. In the meantime, we would love for Bailey to be able to take a pill to treat the Gaucher's rather than having to have her port accessed weekly for infusions.

When Bailey was 10 months old, she had a cold. The doctor said her spleen was enlarged and that it was probably just because she was sick. A few weeks later, she still wasn't feeling better, so we went back to see the doctor. This time, her liver was also enlarged, and we were immediately sent for blood work. By the end of the day, we were contacted by oncology, and they said that they suspected that Bailey had leukemia. She was scheduled to have a bone marrow aspiration, and that is when she was diagnosed with Gaucher's disease. Before her first birthday, she had her first port placed and first enzyme replacement therapy. Bailey's [had] nine surgeries. The hardest of all was when she suffered a fracture to the left femoral neck and had to have plates and screws placed in both of her hips. She had been given a much lower dose of the ERT than what she needed for her weight, and her bones were in such bad shape that she suffered a fracture that is typically caused by a high-impact injury, and she didn't have an injury at all. It just fractured on its own. She had to use a wheelchair and a walker for a very long time and still has them in case she's in pain. We have since found almost an entirely new team of doctors, and we monitor her very closely to make sure that her medical care is never neglected again. She is now on the correct dose and receives her infusions every Tuesday, and her bones have shown major improvements.

A little over a year ago, Bailey began taking ambroxol, and her labs are already showing promising results. She takes this medication three times a day, every day. This medication is not available in the U.S., so we have to work really hard to get it here for her. She was diagnosed with epilepsy a year and a half ago but has never had a clinical seizure, which we are so thankful for. She takes a timed anti-seizure medication as a preventative, and she sleeps with a watch that can detect convulsions. Bailey also has a cognitive impairment and has had two strabismus repair surgeries. Bailey has worn hearing aids since 2018, with

mild to moderate loss in each ear. In February 2020, in just 1 day, she lost all of the hearing in her left ear. Last September, she had a surgery to get a cochlear implant for her left ear. She works every single day to be able to understand words and sounds with the new device. It has been challenging and a major adjustment for her, but we are so thankful for the ability to help her hear again.

Every Tuesday is Treatment Tuesday. In 2016, I learned how to access Bailey's port, and by 2018, I was mixing the medication as well. We now do every treatment on our time and plan it around our lives rather than planning our lives around treatment. Every four weeks, I call to refill Bailey's medications and supplies, and we get a 4-week supply delivered. The mixing process takes about 2 hours. Setting things up for treatment takes about an hour, and Bailey's infusion runs for an hour and a half. During the infusion, Bailey usually watches YouTube or a TV show, and she always gets to pick what we have for lunch or dinner that day, which is usually Chick-fil-A.

We are grateful for Bailey's overall health, but that does not negate the fact that this life has not always been easy. There have been many painful and heartbreaking days thrown our way, but there have been far more good days than bad. Bailey is a sweet and happy girl, and we work incredibly well as a family unit in taking care of Bailey together, and we could not be more proud of where she is today. We long for the day that there is a safe cure for NGD, as do so many other families. We are proud and thankful to be the first family to register with the first ever registry for NGD. We decided to register because we know that by participating in the registry, we are contributing to further research, which will hopefully lead to more treatment options. We also believe it's important to have as many families as possible to sign up, because the endpoint for each NGD patient varies greatly, and the more data that can be gathered, the better. Thankfully, the registry received start-up grant funding from industry for the first year. But in order to maintain independence, we would need the registry to have a sustainable source of funding, possibly including government grants. The registry is set up to be very simple. And while it's a small thing for each family to take the time to answer the questions,

it can make monumental changes within our community. Thank you for allowing us to speak and be a part of this panel.

MS. JACKLER: Thank you so much, Amanda and Bailey. Thank you so much for sharing that with us. It's great to have you here with us. And next, I'd like to pass it on to Brad, who will tell us more about his story.

MR. BRADLEY WILLIAMS: Thank you, Karen. I am Brad Williams. I have a type of muscular dystrophy called dysferlinopathy, which is also known as limb-girdle muscular dystrophy type 2B or R2. I work as Director of Research for an advocacy organization, the Jain Foundation, that's dedicated to finding treatments and cures for this disease. In the picture, you see me with my co-workers. You can tell which one is me, because I am the one that's seated. Then, on the screen, you see my disclosures.

About 10 years ago, the Jain Foundation started planning a natural history study in dysferlinopathy, because not much was known about the disease. One of the major questions the study tried to answer was which tests (or outcome measures, as they are formally called in clinical trials) would best be able to track the progress of the disease and the effectiveness of potential treatments. For this reason, we called the study the Clinical Outcome Study [for] Dysferlinopathy. I was a participant in the study.

Before I share my personal experiences, here are some overall facts about the study. As you can see listed on the slide, it was quite a large study for such a rare disease and involved a number of clinical centers in several countries. It also lasted for several years, roughly 2013 through 2018. And this was necessary because dysferlinopathy has a fairly slow progression as muscular dystrophies go, so the study had to last long enough to see a change in the participants.

So I had seven study visits between 2014 and 2018. During the first four visits, I lived in the Washington, DC, area, which, as you can see, was one of the study centers. So I just had to drive across town. But then I moved to Seattle, so the last three visits involved very long trips. This brings up an important point about travel and natural history studies. Not only can it be expensive and difficult

on the participants, but in a study like this one, where one of the things you're testing is a person's strength, them being tired from just having traveled a long distance can affect the data you're collecting. Depending on the disease and what disability it may cause in study participants, it may be necessary to make some allowances — for instance, letting people rest for a day between their travel and when they're being evaluated — or to bring a companion along to assist them during their trip and during the study.

Fortunately, one silver lining from the COVID era is that now the concept of remote assessments is gaining acceptance. So I would encourage anyone designing a clinical natural history study to think about how they can use remote assessments either in place of or to supplement in-person evaluations.

So, for my participation, I had seven visits from 2014 through 2018. Each of the visits lasted most of a day, and they did a lot of tests on me, many involving muscle strength, heart and lung function — they took a few MRIs, collected blood samples — did a skin biopsy for isolating cells, some surveys about how MD impacted my life, and more. Now, during the study, I wasn't ambulatory, and the people who were ambulatory had some additional tests that they were going through. It was quite a long period of testing — lasted most of each day. It wasn't unpleasant in any way, but, you know, I was pretty tired by the end of it. Mostly, I was happy to know that after having lived with the disease for so many years — I had onset when I was 18 — that someone was really making the effort to really learn about the disease so that clinical trials could happen.

Okay, so what did the study accomplish? Well, it gave some really good information to design clinical trials. It found what is really the best outcome measure for this disease. It was abbreviated NSAD, which was actually adapted from an outcome measure called NSAA, which is used in Duchenne muscular dystrophy clinical trials. And NSAD is actually being currently used as a read-out in clinical trials for other LGMD subtypes, even though it was developed for dysferlinopathy type 2B/R2. It told us how many patients you would need to get statistically significant read-outs

for a hypothetical treatment, which maybe didn't improve a person's strength but stopped further progression. And then there's a couple of other side benefits for this. It created a group of clinicians that were used to working with each other — became familiar with the disease — at doing the tests for these outcome measures. And really, if you think about it, a natural history is a dress rehearsal for a clinical trial. It only lacks the interventional component. So having a bunch of clinicians in different places who have worked together on a natural history study is a huge benefit for clinical trial readiness. Also, COS has taught us enough about the disease that we're now developing a standard of care. So, even before a treatment is approved, this knowledge will help patients get better disease management from their clinicians.

So this is a point that Dr. Bryan made in his presentation earlier, and I'll reiterate it: The most important thing is to start your natural history study before you think you have a medicine to test. When we first started planning COS about 10 years ago, we were nowhere near having a treatment to test for dysferlinopathy. But now that we do have treatments that are in or close to clinical trials, it's really good that we started the natural history study when we did. For a lot of diseases, and this includes some types of muscular dystrophy, there are treatments that are ready to test but a lack of knowledge of the natural history to be able to confidently design a pivotal trial. So that means that the drug developers have to do a natural history study before they can actually test their prospective treatment. And that delays things and is absolutely not what you want. Also, having natural history data and information about which outcome measures to use in clinical trials makes a disease much more attractive to drug developers. So just the act of doing a natural history study improves the chances that you will have treatments to test sooner than you think, because drug developers will start to be interested in your disease area.

I also want to mention, personally, that COS isn't the only natural history study that I've participated in. I did a couple of others, which, unfortunately, didn't result in any publications. And that's both a big loss for the medical and scientific community as well as making me and

the other participants feel like we wasted our time. So it's important for natural history studies to document what they found and put it in a place where other people can learn about it and also to give feedback to the participants. After all, they're part of the natural history study. They are not guinea pigs; they're active partners in clinical trial readiness and drug development, and it's important to share with them what has been learned in the study.

So that concludes my remarks. And thank you much to the FDA for inviting me.

MS. JACKLER: This is Karen. Thank you, Brad, for that presentation. And lastly, I am going to pass this on to Dr. Marshall. So when you're ready, Dr. Marshall, we're ready for you.

DR. BRUCE MARSHALL: Thank you, Karen. I appreciate the opportunity to participate in this session today.

I don't personally have any conflicts of interest or disclosures, if you could go back to that previous slide. But there are some disclosures related to the Cystic Fibrosis Foundation that are outlined on this slide. I will pause there briefly so you can scan through that.

So you might say the modern history of cystic fibrosis dates back to Dorothy Andersen. And she was a pathologist, a physician pathologist, who distinguished cystic fibrosis from celiac disease, and she published this in the late '30s and went on to make some other important discoveries, one, in fact, related to the diagnostic test that still remains as the diagnostic test for cystic fibrosis: the sweat chloride test. She was up at Columbia Medical Center in New York.

The Cystic Fibrosis Foundation was founded in the mid-'50s. And it was founded by parents of children with CF who would not accept the dismal prognosis they heard from their physicians. This is the mission: to ensure the development of the means to cure and control CF and improve the quality of life for those with the disease.

Now, there was some evidence developing in Cleveland and New York and other sites across the U.S. and across the

world that a multidisciplinary care and an aggressive approach to the disease might have some benefit. It appeared to have benefit. [INAUDIBLE] and that started in the late 1960s — that early evidence. And then in the late 1960s, the CF Foundation funded Dr. Warren Warwick at the University of Minnesota to start a registry. And those two initiatives — the patient registry, which started as a natural history study, and that early evidence about multidisciplinary care, which led to the development by the foundation of the CF care center network. And what this did was to aggregate the patients. Instead of just a handful of patients cared for by clinicians across the country, it aggregated the patients into care centers of excellence with the explicit criteria for multidisciplinary care and then, side by side with that, the registry to track progress over time. I think those were the two critical elements in this story. They date back to the ’60s. Aggregating the patients in centers of excellence, better care, exposure of trainees to the disease, the opportunity to do research, and then the natural history study, which started as a patient registry, and tracked people over time — very important initiatives and the foundation, really, for all of our work.

This slide shows that study that was led by Emily Knapp and Aliza Fink. It is essentially a methods paper published in 2016 looking at several key features of this registry, which was deployed as an observational research study. The generalizability — we estimated 81 to 84 percent of individuals with CF in the U.S. were included in the registry. The lost-to-follow-up rate is indicated here. The completeness of the data was examined, and the accuracy of the data. And to summarize, the data wasn’t perfect, but it was pretty good and good enough for the use cases that needed it.

So, as mentioned, the registry started as a natural history study, but it has proven to be valuable in so many different ways: as a framework for clinical trials — everything from helping to design the study to finding out where the patients were located to make this study feasible and on and on and on — very important for the setup of clinical trials. We have used the registry for post-marketing surveillance studies, as was mentioned earlier.

The FDA often mandates studies following approval, and we have done a number of these post-marketing studies and provided that data not just to the FDA but to the European counterpart, EMA, to support these products staying on the market. We have also used it to drive quality improvement. And I won't go into depth here, but this has been a critical resource to help us drive improvements in care and then also comparative effectiveness research.

We pivot now to a way that we've used the registry to track the impact of therapies. And I will start with a really major breakthrough in cystic fibrosis, which was the discovery of the gene in 1989, the *CFTR* gene. And this is a picture, one of my favorite pictures of Danny Bessette looking back at a picture of himself on the cover of *Science Magazine* in 1989. And the basic defect proved to be a membrane glycoprotein that was an anion channel. We heard about a sodium channel earlier. This is an anion channel that transports chloride and bicarbonate.

So, just to summarize what we have learned about CF — and again, this is a lead-in to the development of treatments — CF is a complex, multisystem disease — nearly 40,000 people with CF in the U.S. and well over 100,000 worldwide. It is a genetic disease, autosomal recessive. The major mutation was described when the gene was discovered with a three base-paired deletion, referred to as F508del, and now over 2,000 variants have been discovered, and over 200 or so are disease-causing. And then *CFTR* modulators, starting in the late '90s, developed to address the basic defect.

This shows just some reports that we developed from the registry data. And we develop these on an annual basis. There's a highlights report. It is actually the middle report. It's 2 to 4 pages, just as the title signifies, just the top-level highlights. Each CF-accredited center and program gets their own report. Again, this is back to quality improvement. They can see where they stand as compared to their peers — and then, all the way to the right, the annual report, which is sort of a dense report that looks at every aspect of the disease that we have information on.

I'm going to talk about the *CFTR* modulators. With drug development starting in the late '90s — and the first drug

that was deployed to just a small fraction, just a few percent of the population that had gaiting mutations, dates back to 2012, and we've tracked over time, through 2020 and now even through 2021, the uptake of this initial drug called ivacaftor. And then there've been three subsequent drugs developed, the last of which, depicted in green, is a combination of three drugs aimed at the basic defect in this protein. And you can see now the majority of individuals with CF now have eligibility to one or more of these *CFTR* modulators. I am just going to show you a few of the striking outcomes — the impact of these drugs.

When I started in CF care and research in the late '80s, the median predicted survival was about 30 years of age. And now we've just crossed the threshold of 50 years of age. In 2021, we're just getting our arms around that data, but it looks like median predicted survival is about 53 years of age. [INAUDIBLE] the outcomes and prognosis for cystic fibrosis. This slide shows a growing adult population: Now 57 percent of the population are 18 years of age and older. And as we project into the future, by 2040, we anticipate over two-thirds of the population will be adults.

This is another metric that we track: the annual number of transplant procedures that are done in the CF community. And you can see liver and kidney transplants have relatively small numbers and stable. But in the yellow line, you can see lung transplants averaging about 250 transplants a year until 2020, down to 91 transplants, and in 2021, about 50 lung transplants. We believe this is the impact of that last *CFTR* modulator that was approved in late 2019.

And then the next slide shows another metric that we track in the registry: the number of pregnancies in women 14 to 45 years of age. And you can see, in 2000, 180 pregnancies; 2015, 235 pregnancies; and then again in alignment with the approval of this CFTR modulator, over 600 pregnancies in 2020 and even more in 2021. And I will close with this.

Actually, I will stop here and mention one thing: Not all people with CF are eligible for these *CFTR* modulators, so what we're dealing with now is a rare disease within a rare disease — those who are not eligible for *CFTR* modulators.

And we are really going after the genetic therapies to treat this last 7 to 10 percent of the patient population.

And my last slide is next, and this is Queen Elizabeth in the late ’60s, and she’s wearing the crown jewels. And we really think of our patient registry as one of our crown jewels. It’s so, so important to everything that we do.

And I’ll close there and thank you for your attention.

MS. JACKLER: Thank you so much, Dr. Marshall. It was wonderful to hear from all of our panelists today and to learn about their unique stories.

So now we are going to open up our panel discussion. We appreciate all the questions that people have submitted so far both during registration and throughout the webinar today. And while there are far more questions than we have time for, we will try our best to answer as many as we can.

Oh, good. It looks like we have everybody up on the screen. Maybe, Amanda, if you want to turn on your video — thanks. Great. So this first question I have is for Dr. Marshall.

So, Dr. Marshall, the Cystic Fibrosis Foundation began its patient data registry in 1966. And the numbers of CF patients enrolled and retained in the registry are astounding. Can you tell us about some of the methods the CF Foundation uses to reach so many patients and keeping them engaged in the registry?

DR. MARSHALL: Thanks, Karen. First of all, we promote the registry to the community — the importance of it, and we try to get the data back in their hands. We post the highlights report. We post our annual report; it’s on our website. So we always emphasize how important it has been and continues to be. And then the other thing that we do is integrally linked to our care center network. We provide some degree of funding to all of our care centers, and that amount of money that they receive is in part related to the number of patients they enroll in the registry and the completeness of that data. So it’s sort of, you might say, a virtuous cycle. The patient obviously has to consent and understand the study and agree to participate. But we provide us some additional funding on a per-patient basis back to the care centers.

MS. JACKLER: Thank you. The next question I have is for Leah. So, Leah, from your experience in a rare disease with a smaller population, with a more recently identified genetic cause, can you tell us more about the methods FamilySCN2A Foundation uses to reach new patients to participate?

MS. MYERS: Yeah. Well, I'm happy to. Well, most of you today are speaking about rare diseases and have an understanding of rare diseases. But, I mean, it just adds so many layers of complexity onto what is already challenging, right, especially when it comes to long-term engagement. For us, like I said in my talk, it always starts and ends with our community and our integrity. So we've prioritized our families from day 1. So we support them where they are, we empower them, and we also really, truly believe that trust is not earned overnight. So we have a great relationship within our community. So when we bring something to them, we also take the time to have them understand it. Speaking as a leader but also as a parent to an affected child, we need to understand the purpose of why the data is being collected. I can't tell you how many violin surveys that I've done in my son's 11 years. But if I understand why it's important, I am much more apt to stay engaged. So understanding that it plays a critical role in developing new treatments — so we spend a lot of time educating. Other ways we've successfully kept engagement [are] through frequent and personal outreach and reducing the burden to the families whenever possible, like very simple aspects — scheduling interviews outside of the regular 9-to-5 hours or accommodating their schedules — things like that.

MS. JACKLER: Thank you. Brad, I have a similar question for you. So you participated in a natural history study. You also work for a foundation that funded a natural history study. So what are the best ways to recruit and engage patients throughout the studies?

MR. WILLIAMS: So, for us, a large part was using our patient registry. So we have a patient registry in our disease, which is now up to about 1,000 people worldwide. About a third of them are in the United States. And it turns out, for recruiting for a natural history study or, for that matter, a clinical trial, the U.S. isn't the easiest place to do it, because we're a big country. The medical system is very decentralized, so a lot of times, what we did was,

we weren't conducting the study, so we couldn't recruit ourselves, but we would look at patients who were close to one of the clinical centers who might be interested who were in our registry, called them up, and told them that there was a study going on, and if they were interested in participating, here's who they should contact. Now, in a lot of European countries, it's not so big; there often tends to be sort of one specialist center on neuromuscular diseases. They already knew most of the patients in their country, so they handled the recruiting. So it kind of depends. But I think having a registry — and our registry includes — everyone in the registry has been diagnosed genetically, since it is a genetic disease, and without a genetic test, you don't know whether they have this specific type of muscular dystrophy or a different one. And so, that's very important, as well as for all the data collection purposes that Dr. Marshall spoke of.

MS. JACKLER: Amanda, I have a question for you and Bailey. So I understand that you've been a champion for the Gaucher Registry. Can you give our audience an idea of what it takes to be both a champion of this type of research to get the study off the ground and a care partner for Bailey?

MS. A. REGALADO: It takes a lot of thought and planning — organizing. But I think that people work hard for what they care about. And doing everything in my power to help make a better future for Bailey and everyone with Gaucher's, for that matter, is something that I hold very close to my heart. I want to be as involved in the community as possible, to help spread more awareness, and to hopefully inspire Bailey to be more involved as she gets older. And I just think that the more that we can put into it, the more that we have better chances of having better treatment options.

MS. JACKLER: Great. So, Leah, I have another question for you. So you mentioned that when your son was diagnosed with *SCN2A*, there was no online support group that existed, so you decided to create one yourself. For others who may be in a similar situation, can you tell us a little bit about the steps you took to create that support group and any advice that you have that you can share with others?

MS. MYERS: Oh, sure. Yeah, so Ben was diagnosed in 2013, right

when the GeneDX panel came out. I think there were 53 genes on the early epilepsy panel, and he was the first one to be diagnosed at this big epilepsy center that we were attending, and they had no other cases of it. And they said that it was super rare and it was very similar to another disease and just to kind of join their group. And I did do that; I joined the other group, and I learned a lot from them. But most importantly, what I learned is that it wasn't the same thing. It was a different gene; it was a different disease, so I started a group to try to find other parents to connect with. It was pretty selfish. It was just for me. I really wanted to talk to another mom who totally got it and was walking our path.

My advice to anybody else that's in a similar situation is to first check all the umbrella organizations. I went to NORD. I went to Global Genes. I checked all the epilepsy groups — the infantile spasms groups, just to make sure that there wasn't already one that existed. And so, the last thing you want to do is start another group if one already exists, because that can have a devastating result on a very small community like ours. And then my advice is, build it and they'll come. But just be careful. Nowadays, you have to think about your platform and keep in mind the preference of the social media channel that is best associated with your patient's generation. Like, for example, a lot of young moms now are preferring Instagram over Facebook. And I don't want to age myself, but I think I was a MySpace user. So if you want to take it to the next level, even after a Facebook or social media support group, and start a nonprofit, my best advice is to build your army first. You know that old saying: "If you want to go fast, go alone. If you want to go far, go together." It's really true here. I've done nothing on my own. It's really important to have a great team.

MS. JACKLER: Thanks. Brad, I have a question for you: Is there anything you wish you knew before participating in a natural history study or any type of research? As a patient, what questions would you encourage others to ask before joining a natural history study?

MR. WILLIAMS: Let's see. I think in a natural history study, I'd say the bar is somewhat lower than in a clinical trial, because, of course, in a clinical trial, you are testing a

drug which — you know, whose properties and potential risks aren't completely known. In a natural history study, for me personally, I kind of had a ring-side seat as it was being planned, so I didn't really have any outstanding questions. But I think some of the key things are what are they going to be studying, what amount of commitment am I going to have to make, how may visits, how long, how much travel, what expenses are reimbursed, etc. Are they going to do any biopsies or other invasive things? And what is it aiming to achieve? It is one thing to let people look at you, but you would really like to know that, at the end of the day, something is going to be learned from this that is going to enable therapy development.

MS. JACKLER: Okay. Amanda and Bailey, a similar question for you: What questions would you encourage others to ask before participating in research?

MS. A. REGALADO: I would definitely tag off of what Brad said. I mean, you definitely want to know what the end result is — what they're looking at, and I think a lot of caregivers want to know that anything that they get involved in is worth our time, because it's valuable, because you're spending your life caring for your child. They want to know how long the questionnaires are, and for me, I just know that it's worth it. You want to know that it's worth it to fill something like that out — that if you do take the time to do it — that it's going to have an impact. I would just encourage people to make sure that their privacy is being respected and to ask anything that you can think of. And I know asking questions can be intimidating, but this is for yours or your child's future, and you should be able to ask anything that you think is going to be helpful to knowing and understanding the registry. And once you understand the logistics of it all, you'll understand that your voice really matters.

MS. JACKLER: Thank you. This question is for the whole panel. It's about COVID. (What isn't about COVID these days?) So, has COVID impacted your participation in a study or enrollment or retention of patients in a study that your organization supports? And if so, how have you managed doing that?

MR. WILLIAMS: Well, I can start, because I have kind of an

interesting story. Okay, so in the dysferlin COS study, we developed a good outcome measure that adapted one that was used in Duchenne muscular dystrophy. But since we used the data from the study to develop the outcome measure, you kind of need to close the loop and then independently verify it. So there's now a COS2 study going on whose major purpose is to verify that outcome measure we developed in an independent study with some overlap of patients but not the same cohort. So that started in 2019. It was a 16-center site. One or two of the centers were going when COVID hit. So the statisticians had to come up with some appropriate methods for changing the visits and sort of filling in the blanks, because the visits didn't happen when they were scheduled. Also, most of the sites were delayed by a couple of years. I think they are all going to be up and running by about the middle of this year, and all the patients should be seen. But that was, you know, close to 2 years later than what we were planning. So it definitely has an impact.

Now, one silver lining (I sort of referred to this briefly) is that the concept of remote assessments (and this can apply to both clinical trials as well as natural history studies) to evaluate patients is gaining more acceptance just out of necessity from clinicians, drug developers, and, I assume, the FDA as well. And there's a big advantage to that, because then you're observing the person in their natural environment, in their day-to-day life, rather than having traveled however long, in an artificial environment — something that they are not doing every day. And that can also improve the quality of the data.

MS. MYERS: For us, COVID didn't really impact us, because we were doing all of it virtually. And like Brad said, COVID kind of opened up doors for doing more things virtually and with ease, so it actually didn't affect our recruitment or our study. The only thing it did affect was fundraising, of course, which affected our ability to pay for the study. But we're working on that.

DR. MARSHALL: Karen, I will jump in. In the CF population, COVID did have a pretty significant impact, particularly on those with advanced lung disease and transplant recipients. It really impacted their health. But with respect to the registry, there was a big drop-off in the number of visits

and more lost to follow-up than we typically see year over year. And then, from an analytical standpoint, the pandemic is just a major confounder. You know, we are going to have to adjust for biases related to the pandemic.

MR. WILLIAMS: So, Dr. Marshall, if I can throw in a question, were you able to develop any CF-specific guidance, you know, in dealing with COVID?

DR. MARSHALL: Yeah, we did, Brad. We formed a medical advisory group, and we did put out regular communications to our care centers, making them aware. I mean, it was a deluge of information, as you all know. We really tried to cull through it with this medical advisory group to give them what we felt was the best information. We also really connected with our patient-family community and did a number of webinars to keep them up to speed and then facilitated our care centers if they wanted to do webinars or town halls with their patient population. You know, we facilitated that. We did our best to support the community. And then the other thing we did was — you know, pulmonary function is a major — is one of our key metrics, and it was difficult for people to come in, and the spirometers to measure — they were difficult to access. So we provided little portable, handheld spirometers so people could still track their lung health and report it to their care teams.

MS. A. REGALADO: I'll say our registry just went live. I don't know how much of an impact COVID had on that. I know, for us personally, a lot of meetings were pushed back, because they were supposed to be in person — just different meetings for different things within the community. And they were pushed back. And then for Bailey, a lot of type 2/3 kids with Gaucher's have pretty severe lung involvement, so there was not any chance in the beginning that we were going to do anything in person. So I think the timeline of it worked out really well, and we have really utilized Zoom. So that's been good.

MS. JACKLER: A few people brought up questions about privacy and things like that. So I want to pivot back. Actually, Dr. Marshall, this question is for you. Actually, it may be a couple of questions. So, given the type of information the Cystic Fibrosis Foundation Patient Registry gathers, what privacy measures can patients expect, and what data

protection measures does the CFF (Cystic Fibrosis Foundation) take?

DR. MARSHALL: Thanks, Karen. That's a really important question, and I think it was Leah that mentioned the importance of privacy. And we take it very seriously. You know, it's not like a drug study, where you're exposed to a drug that hasn't been tested in humans very much, where there are safety risks; that's not true in a registry, but the privacy is really, really important — to be all over that. So we take that very seriously. We have a limited number of employees that have access to that data, and we educate them every year; they go through the HIPAA regulations — how important privacy is. And our IT folks have sort of sequestered off the registry data, and then they audit who's coming in to view it on a regular basis. So that is really kind of kept separate from the other data that we have. You know, we have a vendor; we are on a vendor's platform, so we do periodic checks of that vendor and their security measures to make sure their platform cannot be penetrated in any way. And you know, even beyond that, we sometimes will hire a vendor to come in and look at everything from A to Z: our processes, the platform, the way — once the data is in house — how we are managing that — and make sure there are no gaps there. So we take it very seriously. People are willing to share their data, and we want to protect it.

MR. WILLIAMS: So, can I add something to that? So our registry is international. So there's something called GDPR — Global Data Privacy Regulation, I think it is, which is an EU standard, which is in some ways considerably more stringent than HIPAA. It came into being about 5 years ago. And so, if you have an international registry and have any people in the registry from EU countries, you need to follow that standard as well. So just be aware of that. If you have a purely U.S. registry, that probably doesn't matter. But for a lot of diseases, it makes sense to go globally just to get more patients.

DR. MARSHALL: Yeah. Important point, Brad. Thank you.

MS. JACKLER: If we could talk a little bit more about data management: We talked about privacy. Let's hear a little bit more about what that means. How is data managed in a

patient registry, in a natural history study?

MR. WILLIAMS: Let's see. In ours, there was actually a statistician, as part of the study, whose job it was to do all of the data analysis. Now, since we had the multicenter trial, that means that there was kind of one lead center, which was actually in the UK, and they were sort of collating all the data from the other clinical centers. And then they obviously needed a secure way to transfer the data. There is some software that clinical centers have that can do that. And the other thing, when you are managing multiple people in multiple places, is to make sure that the data is all being collected in a similar way so that if person A at one site does a measurement that — you know, if they get the same number as person B does at another site on a different patient — that those mean the same thing. And then, typically, there can just be data entry errors. So you need to sort of scrub the data a little bit; just make sure there isn't something that makes sense, and if they go back to the center later, "Are you really sure about this? This looks like you might have an incorrect data entry, because this person is showing dramatic change over 6 months that we weren't expecting." So yeah, it's a big deal.

MS. MYERS: We also have a statistician that reviews all of our data and analyzes it. It is really important for the test reliability to ensure that the data is, like you said, Brad, scrubbed and accurate. We use a system called Clearinx [PHONETIC] — I am happy to link to it in the chat — that manages it and also use GDPR compliance.

MS. JACKLER: Any final comments on data management, go ahead and jump in. [PAUSE] Okay. Great.

So I want to thank you all. Thank you, panelists, for answering these questions and for sharing your perspectives and experiences with us. Each of you is making a difference in helping to advance the understanding of diseases, and we are very appreciative that you have taken time to share your knowledge and stories. I think we all are. That was a wonderful panel.

So I am now going to pass it back to our moderator, Anne.

MS. ROWZEE: Excellent. Thanks, Karen. Again, just to echo what Karen said, I just want to give a big thank-you to our panelists, to Leah, Amanda, Bailey, Brad, and Bruce, for that, I hope, inspirational panel. It was inspirational to me; I hope it was for our audience members as well in trying to really provide some tangible examples of what a natural history study can achieve. I really appreciate you all taking the time today to share your stories and knowledge with us. I wish we were in person so I could ask for a round of applause, but I think I might be able to hear it from our audience near and far. Thank you all so much again for your time today. We're now going to move into a 30-minute break for lunch — lunch for some of us, maybe a mid-morning snack for others. Our next panel is going to begin at 1:30. To help kick off this break period, I just want to share this 5-minute video with you. And this is about natural history studies, and the Office of Patient Affairs put this video together and shared it with us. It's also available on our website, but I'll see everybody back here at 1:30, and thank you all so much again.

[BREAK]

DR. ROWZEE: Welcome back everyone. Thanks again for joining our workshop today. We've had some great discussion and questions so far. I just want to say that we've been receiving some really good questions, and I think a lot of the answers, you'll find in this session. I don't want to overpromise, but there's some really good content coming up. Like I said, I think you're going to get some really great resources from the presentations and the discussion that's coming up.

Our next and final session is a panel discussion featuring speakers from FDA and the National Institutes of Health. These panelists have great expertise and resources to share with you, including information about grant programs and tools to help you develop your own natural history studies for your particular disease and condition. I'm now actually going to pass it over to my colleague, Devaveena Dey, who will be moderating this session. Take it away, DD.

DR. DEVAVEENA DEY: Thank you, Anne. As Anne mentioned, my name is Devaveena Dey. I'm a Scientific Reviewer at OTAT. I'm very excited to be here today, and it's been an amazing two

sessions so far. This is our final session, where we get to feature our very own experts here at the FDA, as well as from the NIH, to learn about the various resources, programs, and tools to support natural history studies.

With that, I will introduce our panelists for the session. First up, we are joined by Julienne Vaillancourt. Julie is a captain in the U.S. Public Health Service Commissioned Corps. She also serves as our Rare Disease Liaison and Policy Advisor in CBER at the FDA. Our next panelist is Katherine Needleman, who is the Director of the Orphan Products Grants Program in the Office of Orphan Products Development here at the FDA. Finally, we'll hear from Dr. Eric Sid. Eric is a Program Officer for the Division of Rare Diseases Research Innovation at the National Center for Advancing Translational Sciences at the National Institutes of Health.

Thank you all for joining us today. Before I pass it over to Julie to kick off our panelist presentations, I do want to encourage everyone in the audience to submit questions for our panelists in the Q&A box on Zoom, and we will have a few minutes at the end of the presentation for a discussion on the questions you submit now and all the questions that have been submitted before.

Now I will pass it on over to Julie to share FDA CBER's perspective on the importance of natural history studies in advancing gene therapy treatments for rare diseases.

CAPT JULIENNE VAILLANCOURT: Thank you so much, Devaveena, for that really kind introduction. It is my pleasure to talk about CBER's support of natural history studies for rare diseases. It's also my pleasure to be here on this panel with Eric Sid and Kathy Needleman, both colleagues that I have worked with in different ways and reached out to. It's going to be a great panel, and I'm looking forward to questions from the participants.

I want to start by saying that CBER sends a consistent message about natural history studies. We advise and encourage natural history studies of rare diseases in many different venues and in many different ways. These include during dialogue with individual sponsors in regulatory meetings that would be under investigational new drug

applications, for example, or pre-IND meetings — also in related regulatory correspondence or letters to sponsors. This is proprietary information, of course, and it's on a case-by-case basis, but it's very common for the Office of Tissues and Advanced Therapies, when sending regulatory correspondence to sponsors of regenerative medicine products and development, to advise the conduct of natural history studies.

We also have CBER staff who speak in FDA health public meetings that send this common message, as well as when CBER staff are invited to speak at stakeholder health meetings. In their presentations, they typically, as appropriate — may be some encouragement — and advising on conducting natural history studies to help advance development of products for rare diseases. It may also come up in patient engagement meetings, such as in patient listening sessions or even patient-focused drug development meetings.

Finally, it's typical for us to have one-on-one interactions often with patient advocacy organization representatives, and I've had discussions in this regard. Sometimes Anne Rowzee and I and Karen Jackler, CBER's patient engagement coordinator, will talk with a representative from a patient advocacy organization, and often it's very early on. One topic of conversation is inevitably about natural history studies and the importance of them. We typically provide them with lots of resources and try to connect them with others, including Eric Sid at NCATS.

We have regulatory guidance that addresses natural history studies. This quote that you see is pulled from one of those guidance documents, and I really like it, because it sums up our perspective on natural history studies. I'm going to read it to you: "The need for prospectively designed, protocol-driven natural history studies initiated in the earliest drug development planning stages cannot be overemphasized." Again, I think this really nicely sums up FDA's perspective and CBER's perspective.

I just want to show the four guidance documents. At the top of the list here, you see "Rare Diseases: Natural History Studies for Drug Development." This is a very comprehensive

guidance that's a joint CBER/CDER guidance. It's a draft, and it was issued in March of 2019, but there's lots of advice on how to design natural history studies and the different types of natural history studies. I'm sure you heard earlier in this workshop about those types of issues and various considerations.

There's also a guidance called "Rare Diseases: Common Issues in Drug Development." That has a section devoted to natural history studies. Both of those are CBER and CDER joint guidances.

However, we have a couple of CBER-issued guidances that focus on "Human Gene Therapy Development for Rare Diseases." One is more general, as I just said the name. It's third on the list here. That has some language in there advising consideration of conducting natural history studies. Then finally, "Human Gene Therapy for Retinal Disorders" is another guidance with language and a small section devoted to natural history considerations.

Now I'd like to tell you about a very special project that CBER has supported and continues to partner with NORD on. NORD, of course, is the National Organization for Rare Diseases, and NORD is taking the lead and sponsoring a natural history study of metachromatic leukodystrophy, or MLD. This is quite a project, because it's multipurpose. It is a natural history study of MLD; however, it's also serving as a template or a pilot study so that it will hopefully provide a novel framework for building regulatory-grade natural history studies incorporating patient information. It has truly been a learning experience from the very beginning. You'll hear a little bit more about it. Our intent is that this could be a template. But again, it will serve as a natural history study for MLD, and that's incredibly important as well. A real nice feature of this study is that it provides an opportunity for dynamic data collection using two different virtual platforms: NORD's IAMRARE registry platform and a new platform. It's another CBER-supported project, the CBER SHAPE app, and I'll tell you a little bit more about the SHAPE app.

The MLD HOME Study is actually listed on ClinicalTrials.gov. I've provided the identifier number on

my slide. You'll find a summary of the study there and information about the status and points of contact, etc. Also, the primary study aims are listed in that summary on ClinicalTrials.gov.

In a nutshell, the aims are that this study or the purpose of this project is to design and implement a natural history study for MLD so that it might serve as the source of external control data. That, as many of you know, could be a real plus or interest in any rare disease clinical development program, particularly for gene therapy products, where there are reasons why it might be difficult to have a control arm or a placebo arm. With this study, the hope and the aim is that those data could be used to either augment or replace a control arm or control data. Another aim of the study is that it will be a source of guidance for how to design, conduct, and analyze data from a natural history study that might be used to support adaptive trial designs for regulatory use. Another aim is that this study will provide an approach for reducing burden on patients and caregivers in trials and also an approach for addressing recruitment challenges. Finally, this study is providing design approaches to support remote participation in studies by using that IAMRARE registry platform in the CBER SHAPE app.

The MLD HOME Study's current status is that it is ongoing and recruiting. As of the end of April of this year, there were 26 registered participants. We're hoping to get more participants. So if you are the loved one of a patient with MLD, I would really encourage you to visit this hyperlink here on the slide, or you could type in "NORD MLD HOME Study" into your browser and the website on the NORD site will come up.

I want to expand on the common expression that it takes a village by thanking and giving a great shout-out to everyone who's been part of getting this study off the ground and conducting it. There have been so many people who have contributed. In addition to those at NORD who are working on the study, including Josie, who is the nurse coordinator and the primary investigator at NORD, there have been representatives from patient advocacy groups — staunch patient advocates like Maria Caflis, who's an amazing woman. I'll just take this moment to say how much

Maria has done, and our hearts go out to her, because she recently lost her daughter, Pal, who is an MLD patient. Maria, thanks. If you ever hear this webinar recorded, or if you're listening, thank you for all your support of this study.

Also, to all of the patients and their caregivers who've enrolled in the study, thank you — and the other patient advocates who have served on the advisory group, including the Riley family. Please visit the website, because there's a great video. Also want to thank the industry representatives, the academic researchers, and my colleagues at CBER in our Office of Epidemiology — our Office of Biostatistics and Pharmacovigilance. They have been really wonderful in working on this project, which has many purposes — a natural history study of MLD but also a pilot study so we can have better natural history studies for regulatory purposes.

I mentioned the SHAPE app. "SHAPE" stands for "Survey for Health and Patient Experience." The SHAPE app is a CBER-supported virtual app that was developed by IBM, and it's a platform for collecting patient experience data via surveys. The users will develop the surveys, but it's really easy to use, so the surveys can be uploaded and used in the context of various types of studies to collect patient information and data. Anyway, this app is designed so that the recording can be done in real time, and it's also compatible with mobile devices, as well as a desktop device. The good news is that this app is currently open source, so it's not just being used in the context of the HOME Study, but anyone participating right now — if you are conducting a natural history study or clinical trial and interested, this app is available. So I encourage you to visit the website listed at the bottom, PatientExperience.app, or you can download the app from the Apple App Store or Google Play. There's a contact there on the website, and I encourage you to provide feedback if you are interested and have questions.

At this time, I want to mention that there are other FDA efforts that are ongoing and, in one way or another, support natural history studies. CBER has opportunity to have some participation in one way or another with these efforts and/or dialogue. The Center for Drug Evaluation

[and Research], or CDER, has been supporting a really exciting program or project called the Rare Disease Cures Accelerator-Data and Analytics Platform, or RDCA-DAP. This is in collaboration with NORD and with the Critical Path Institute, or C-Path.

The data analytics platform provides a centralized and standardized infrastructure. It's a platform where data from many different sources, especially patient-level data, comes in. It's curated, standardized, and compiled. Then it's available for use for analyzing all those interested. Certain rare diseases are being worked on in this regard, so I know that Friedreich's ataxia is one specific disease for which the platform is being used and data from all different sources are being compiled, curated, and standardized. You can learn more about the program on C-Path's website.

It supports natural history studies because the natural history data are one of the sources of data that are used in this platform, but also, the analyses of data once compiled and standardized can help inform new natural history studies, as well as help with designing clinical trials. This is another innovative way that FDA is trying to help advance development of products for rare diseases, including regenerative medicine products.

Finally, CBER does participate in different ways with the Office of Orphan Products [Development] Natural History Studies Grant Program. I'm not going to go into detail about that because I know you're going to hear from my colleague, Kathy Needleman, from the Office or Orphan Products [Development], and she'll tell you all about that program. But I will say that CBER's very supportive, and even some of our staff have served in regulatory reviewer roles in that regard.

I just want to conclude by saying that natural history studies can inform regenerative medicine therapy development for rare diseases. We send a consistent message in advising and encouraging the conduct of natural history studies for rare diseases. Several FDA-issued guidances addressing natural history studies are available. The MLD HOME Study and the SHAPE app are both innovative ways that CBER supports natural history studies. Again, as I

mentioned, CBER participates in other innovative FDA efforts that support natural history studies.

Thank you so much. It's been a pleasure, and I look forward to your questions.

DR. DEY: Thank you so much, Julie, for sharing your work and the excellent resources with us. Thanks to Eric and Anne for posting the links for the MLD HOME Study, the SHAPE app, and the RDCA study. It's all there in the chat box. Now I'll pass it over to Kathy to talk more about what the FDA is doing to support natural history studies. Kathy?

DR. KATHERINE NEEDLEMAN: Hi, everyone. Thanks so much. I really appreciate being here today to talk to you about our program and how we support natural history studies.

Before we get into our program in general, I think it's important for everybody to see our interactions within the agency. A lot of folks may have heard of [the] Office of Orphan Products [Development] — may not know exactly where we situate within the organization. I wanted to take a brief step back and look at some FDA rare disease interactions across the agency.

We're identified in this organizational chart by the zebra. OOPD is under the Office of Clinical Policy and Programs, which is under the Office of the Commissioner. But we have quite a bit of interactions around the agency with the Center for Drug [Evaluation and Research], [the] Center for Biologics [Evaluation and Research], [and the] Center for Devices [and Radiological Health], as well as [the Center for] Food [Safety and Applied Nutrition]. We also interact quite frequently with the Oncology Center for Excellence and Patient Affairs. But of course, this doesn't represent all of what the agency is doing in rare disease research and programs, but these are the folks that we're certainly interacting with quite frequently as we are moving forward.

A little bit about our core programs: Our mission in the Office of Orphan Products Development, or OOPD, as you may hear it quite frequently, is to promote the development of drugs, devices, and biologics and medical foods for patients with rare diseases and special populations. We have several ways to do this. We have several designation programs that we administer that provide incentives for

moving products along in regulatory development, and they're listed here. We have several grant programs that we also are able to fund different research.

The ones that I'm going to talk about today are our Natural History Grant Program, but you may also know a little bit about our Orphan Products Clinical Trials Grant[s] Program. We also have a Pediatric Device Consortia Grant[s] Program and then a new program that just recently was enacted at the end of 2021, the Rare Neurodegenerative Disease Grant Program. I'm not going to discuss all of the programs today but certainly want you to be aware, and they are available on our website, and we can talk about them in the future.

A little bit about the Orphan Products Grants Program: It's our main standing program, with an overall budget of $17.7 million. That is really split between clinical trial grants that we fund, as well as our Natural History Grant Program. Our goal is really to advance the development of orphan products (which, again, are drugs, biologics, devices, and medical foods) that demonstrate promise for diagnosis or treatment of rare diseases or conditions.

Our [Orphan Products] Clinical Trial Grant[s] Program funds around 75 ongoing studies at any one time, and this program has led to over 80 product approvals, numerous thousands of publications, different regulatory milestones — as well as had quite an impact on different fields of rare diseases. The focus on that program is really efficiency and innovative clinical trials, but I'm not going to spend a lot of time today talking about that.

I am going to talk about our Natural History Grant Program. It is currently funding eight grants. It has a budget of about $2 million out of that $17.7 million. The impact that we've seen so far is in clinical trial development, several collaborations with industry, as well as patient groups, as well as many publications.

When did it all begin? The Natural History Grant Program was launched back in 2016, and it was really launched after continually seeing the need in this space. We see obviously within our [Orphan Products] Clinical Trial Grant[s] Program quite a number of studies and proposals come through with almost an embedded natural history study

within its proposal — really not the greatest and best avenue to do that within our clinical trials, and it really needed a separate source of funding and its own mechanism.

We broke it out, and we really wanted to support drug development for rare diseases through an increased understanding of the impacts of the courses of these rare diseases. We saw quite an overwhelming response when we launched it in 2016. Again, this was a $2 million grant program when we first piloted it. We had close to 90 applications that first cycle, which, for maybe NIH, is not that many, but for our smaller grant program, especially with only $2 million, that was quite a bit of interest in a very short amount of time. You could see it within the applications and within the stakeholders, and it was a great need for this area.

We were able to fund six natural history studies that year, $2 million with our budget, and then we funded [an] additional two applications that year with [the] support of NCATS. We reissued that funding opportunity 2 years later, so it's on an every-2-year cycle. When we reissued that funding opportunity, we really narrowed the focus a little bit. We focused more on efficiency, innovation, as well as — we really wanted to hear about the patient input and infrastructure, and we did some slight changes to budget that year. Again, that goal was very similar to the previous goal of really supporting studies that advance medical product development through the characterization of the natural history of rare diseases and conditions with unmet needs. Through that second cycle, we were able to fund an additional two awards.

This slide will show you the eight currently funded studies that we have ongoing right now. Several of the ones from 2017 are coming to a close, and we've picked up those two additional ones in 2019.

You've heard about applications of natural history studies earlier this morning. We were certainly seeing the same sort of things within our proposals — really, how are these natural history studies being used to facilitate drug development to try to inform clinical trial designs — looking for the best, defining that target population. They have the potential, obviously, to serve as historical

controls. Many are developing clinical outcome measures, as well as biomarkers. We were seeing all of these things within our applications as a main need and a main goal within the applications.

We wanted to start planning for the future. As we always do, we look and see how things are going — look at the needs, the wants — things you need to consider when we're going to revise those cycles. Some of the things that we were considering — obviously, we wanted to see studies that provide optimal support for rare disease product development. We wanted to make sure there are some standardized approaches to ensure data quality. These can really be best configured to use later on in regulatory development. We wanted to have well-defined and -documented protocols before study initiation. There was emphasis on collaborative and efficient approaches, as well as the use of patient engagement.

Then, because we know we only had about $2 million, again, to spend, we wanted to ensure that we were exerting a broad impact. We wanted to see what kind of impact we can provide with the studies that we were looking at funding and ensuring some of those and thinking about data dissemination, as well as budget. That takes you into that idea of what kind of budget — what kind of focus.

We announced another funding opportunity. We actually just had a receipt date in February 2022. It's not on the slide; however, our next receipt date under the same RFA will be in 2024. The main purpose here of this funding opportunity is to provide support of efficient and innovative natural history studies that advance medical product development in rare diseases or conditions with unmet needs. Through the support of these natural history studies with high quality and interpretability of data elements, we really hope to address clinical knowledge gaps, remove major barriers in the field, progress the field, and exert a significant and broad impact on specific rare disease or multiple rare diseases with similar pathophysiology, and facilitate rare disease product development. You can see here the focus of the particular funding opportunity announcement where efficiency and innovation — that within this, there's a large emphasis on data quality, interpretability, and leveraging that patient input infrastructure, as well as

financial resources. How can this particular proposal that people come in with place themselves in a better optimal base for future use of this data?

Some of the eligibility and — number of awards and thoughts about this: Basically, anybody who's not a federal agency may apply. We will provide grants — and this goes for our clinical trials as well as [the] natural history program — to foreign as well as domestic, public or private, for-profit or nonprofit entities. You do not need an orphan designation to be applicable to the program; however, your disease must qualify as rare, as we define it: as less than 200,000 people in the United States.

The number of awards, of course, will be contingent upon FDA appropriations and a sufficient number of good and meritorious applications, but we are expecting about $2 million, again, within this Natural History Grant Program to fund at least two to four grant applications. Of course, that will depend on the types of applications and their budgets. Funding is going to be dependent on the quality of the application, as well as the availability of federal funds.

This slide gives you an idea of the caps for budget. So for prospective studies that you've heard about this morning, they're eligible for up to $400,000 in total costs per year for up to 4 years — would be a 4-year grant, and a retrospective study will be eligible for up to $150,000 in total costs per year for up to 2 years.

I wanted to give you an idea about a general review process that we use, and I think it's important to kind of see how this all fits in and what we do when we get our applications. Generally, our applications will be submitted to our office, and we will do an initial pass-through, really looking for initial review for responsiveness. Do you have a rare disease? Have you submitted in what you need to in order to meet the basic criteria of our application proposals?

If you're nonresponsive, we will send you a notification of such, but those responsive applications will go on to be individually reviewed and scored by independent, ad hoc experts for technical merit. And now, who are those

reviewers? We, in natural history especially, will obtain external folks from the agency, people who are experts in these diseases who are really seeing and doing research in these rare diseases; they will come to be a reviewer for us, as well as our internal folks, who — as Julie mentioned, we'll reach out to our centers and get their regulatory expertise to sit within our panels as well so that when we make sure that the data being driven and being used in the program is going to be actually useful for regulatory development, we'll take into account patient perspective. So we'll go and recruit patient representatives and patients who are interested in evaluating these applications and really bring that feasibility and that patient's perspective to the application.

Applications will be discussed at the review panel; they'll be scored, and then we'll fund based on scoring, and summary statements will be issued to the applicants with our review specifics, and pre-funding checklists will be issued, and we'll fund our top-scored applications.

Once a grant is funded through our office, we assign it to someone from our office to oversee the grant. We will make sure it's meeting its goals, its objectives, its regulatory requirements, etc.

Another thing that OOPD believes strongly in is early interaction with the FDA review divisions, and this is very beneficial to ensure natural history studies generate high-quality and relevant data to inform medical product development and regulatory decisions. To facilitate this interaction, we implemented a pilot program, which is called the Grantee FDA Connect Meeting. The objectives of those meetings are to connect and support communication between our FDA review staff and our funding agency and grantees and to discuss key challenges faced by investigators and strategies to address those challenges.

These meetings are nonbinding. They're a great way to have scientific dialogue with the agency, as well as with our review division experts, to try to optimize those natural history studies and best utilize the natural history data to inform a clinical trial, as well as support regulatory decisions.

Some ways to interact with our office, developing a treatment for a rare disease can present unique challenges. Teamwork and innovation are critical to make this happen, and health in the community is essential to ensuring that these studies are successful. One of the important community-wide efforts we had — you saw a Patient Matters video right before lunch. There is another Patient Matters video that focuses on our program in OOPD. The link is provided there. It will give you a little bit more of an insight into not only our program, who we funded, but really the impact that rare disease patients can make within those studies.

You can also become a reviewer. We look for patient reps to sit and give their feedback. You, as patients, know the feasibility more than anybody, so — having that perspective and having that input within our protocols. We do ask that our investigators take into account patient perspective when developing the protocols. It's essential for making these successful.

Helping recruitment: It is sometimes really hard to conduct a natural history study; getting the right enrollment for any rare disease study is really hard, but certainly for a natural history study. Being able to help through your communities in recruitment is really important so we can get the information we need, and then folks can utilize that to create a good clinical study that can move therapies along in development.

And then future proposals: Just this last cycle, we've seen several patient groups come in with applications themselves, really spearheading that in their community with physicians. This is an essential way to move these along and to make sure that they're successful, as well as being conducted. We always encourage folks to utilize their outlets and their resources to be able to put together some of these proposals for our grants. You are an eligible entity, and it's important to work with those clinicians to have a really well-developed natural history study.

This is just some contact information about myself. I'm in the office for general information, always here for questions, even after today, if your questions aren't answered, but looking forward to the panel, and thank you

for having me today to talk about the Natural History Grant Program.

DR. DEY: Thank you, Kathy, for that wonderful presentation. And I think an important takeaway message from Kathy's presentation is an early interaction with FDA, which is critical to ensure planned success for a natural history study. Finally, I'd like to pass it on to Eric to tell us more about what his team at the NIH is doing to support rare disease research and natural history studies. Eric?

DR. ERIC SID: Thank you, DD. I'll start by saying that I have no conflicts of interest to declare. I'm the Program Officer within the Division of Rare Diseases Research Innovation at the National Center for Advancing Translational Sciences. Our mission within our division is to advance rare diseases research to benefit patients.

What exactly is a rare diseases division doing within the translational science center? Let's start with what translation is. Translation is the process of turning observations in the laboratory, clinic, and community into interventions that improve the health of individuals and the public. Now, when we talk about rare diseases, we oftentimes talk about several universal obstacles and challenges that all rare diseases in common face.

Research on rare diseases has collective obstacles — for example, challenges of small patient population sizes, limited history of research studies — and then oftentimes, patients with a rare disease may face common challenges. There may be very narrow clinical understanding of that disease, so limitations in terms of diagnostics and even a lack of treatments.

When we talk about translations, we often talk about translation as a team sport. There are many hurdles that have to be addressed to go from research candidates in terms of drugs or biologics to a possible treatment. Central to this entire process is really two themes: one, that patients are essential to this entire process that you see here, and before you even can get into the approach of thinking about IND-enabling studies, engagement with patient communities is vital. In addition to that, when you think about the drug development process as a whole, this

complex side really just provides you an idea of all the possible activities and steps that are involved in the entire drug development process. The red circles that you see in the middle are where natural history studies are. Natural history studies are onramps to clinical research and development.

Let's go through an example. Jansen's metaphyseal chondrodysplasia, or JMC, is an extremely rare disease. Less than 25 cases are known to exist. It's a disease of bone development, and it's caused by mutations to the PGH receptor type 1 gene. There are currently no effective treatments for it. How do you do drug development for such a small patient population?

Julie mentioned earlier that it takes a village. All of the different stakeholders that you see here are critical to drug development, and it all starts with patients, in this case the Jansen's Disease Foundation. Their role was really to connect all these different partners together in this disease space and engage the patient community in clinical research. In addition to that, the two lead investigators from Massachusetts General Hospital provided scientific and disease expertise, as well as care for patients. It took a clinical site, in this case the NIH Clinical Center, to be able to provide the apparatus for doing the natural history studies, as well as to execute these clinical trials. And lastly, it can sometimes involve government partners.

In this case, within NCATS is a therapeutics development branch that focused on preclinical support or providing drug development expertise and coordination to help transition from preclinical research to clinical research.

This just shows you this entire process, from beginning to end, starting with outreach, academic research, preclinical drug development, clinical planning, and treatment. All of it starts and ends with patients. In particular, I want to focus on the role of natural history studies, both in supporting initial outreach but also continuing through the different stages of clinical planning.

When we think about clinical planning, oftentimes we're thinking about clinical trial readiness or how do you get to the stage where you're able to support not just a

natural history study but also eventually clinical trials for drug development. That involves many different questions, and many of these questions are touched upon by the results from a natural history study. How should the trial be conducted? Who do you treat? Who will conduct the trial? What is the desired treatment outcome? Where are the patients, and where are the experts? When is the best time to treat the condition? And why is this the best proposed treatment?

These all provided much foundation from that natural history study data to really answer as well as set up the plans that you must have in order to have a successful clinical trial for treatment development. At this point, I'm hoping that we've all sold you on the need for robust and strong natural history studies. Now, what does that mean for you?

I'm going to highlight a couple of resources that NCATS provides that can help support you in determining next steps, as well as — I wanted to demonstrate how we're making use of the findings from these natural history studies. Two of these resources are educational websites that have been informed by some of my colleagues here at the FDA, like Julie; community leaders; researchers; and others involved in rare disease research efforts. The last is a public health program that targets providing rare disease information for patients and caregivers.

The NCATS toolkit for patient-focused therapy development is an example of one of two websites that we've developed that are user-friendly, focused on providing educational information and background, and are designed to really cater to patients and patient advocates. They're in plain language, and they're really generated to try to capture and highlight the reliable resources in the community.

Rather than creating another resource, our goal with these two websites is to provide an idea of the landscape, as well as links to those resources that have already been developed. Many of those were examples of programs that were illustrated earlier today, such as the C-Path.

In particular, the toolkit focuses on the overall process of drug development and really targets some of the areas

that patient advocacy leaders have identified as pain points in that process.

For many folks that are thinking about how to get started with a natural history study, registries are where we oftentimes are describing. Why do we talk about registries and natural history studies? Patients oftentimes know the power of stories. This is something that many of you have experience with, both in terms of thinking about how to get others to engage in concerns that you have for your patient community and the struggles that you're facing, but also to build partnerships and alliances with that.

The same thing applies when you look at research. With research data, our currency is data. Data is what we use to measure success. What registries do is help turn individual patient stories into a community of patients' data. That translation process from story to data is what we do in natural history studies to make use of that information at scale, but also to report it in a way that it's able to eventually be used for regulatory use.

As an example of this, one of the things that we're trying to do within NCATS is to think about how can we make use of this research data produced from natural history studies and other types of publications. One of the efforts that we're trying to do has been around reimaging a public health program that has been around for almost 20 years now, since the Rare Disease Act of 2002.

This is the GARD, or Genetic and Rare Disease, Information Center. GARD is a program that offers both a free contact center, which anyone in the world can access by either email, phone, or going to our website and basically sending an inquiry to our information specialist for support around trying to find information about a rare or genetic disease.

In addition to that, we've had a website that we've developed since 2008, which was really needing a new facelift in terms of updates. Part of what we've been exploring is, how do we take and think about the way that information is translated from research data into actionable information that can be used by patients and caregivers? For example, how do we identify all of the different rare diseases that may be associated with a

symptom such as autism that we can then provide a standard set of content or information about resources and support that caregivers may want to access in order to find common support for those diseases?

One of the things that we're trying to do is to leverage complex disease ontologies already established by some of the other groups that exist within the rare disease research space and use them as ways to funnel and transform some of the information that we know is out there. Similar to what we're doing on the patient advocacy side when thinking about resources for patients at large in any type of rare disease, we're trying to think about the same approach that we need to apply translational science practices like this to standardize and hopefully accelerate the ability to deliver information for all rare diseases.

One of the things that we're considering with this is, how do we tailor and fine-tune these website resources for a patient and caregiver audience? We recently relaunched our website with a new design; that's still heavy in development right now. A lot of what we're going to be doing is try to understand how patients and caregivers are looking for information on the Internet and what is it that we can then do to streamline that process for them so that we can deliver information, hopefully, that's as useful as possible for their needs.

Another example I wanted to call attention to of where both the FDA and NIH are trying to think about opportunities to advance collective research solutions that can impact as many rare diseases as possible is the Bespoke Gene Therapy Consortium. This is through the Foundation for the National Institutes of Health, NIH. One of the issues that they're trying to address is that, based on the current paradigm we have for commercial drug development models, companies in industry cannot cover the cost required to develop gene therapies to treat rare and ultra-rare genetic disease, particularly because these diseases affect relatively few patients. The solutions that they're trying to target within this consortium are really to create tools to streamline the gene therapy development process — for example, looking at common viral vectors used to transport gene therapies to the target cells or looking at manufacturing or ethical issues that must be addressed in

common round gene therapies. What they're trying to do is to reduce the associated costs as well as encourage companies to ultimately pursue more gene therapies for more rare genetic diseases. There's quite a bit of information about this out there, so I just wanted to provide some links for this in case you wanted to look up more.

In addition to that, we've tried to understand within our division how do we start to change the discussion around rare disease — rather than thinking about it one disease at a time, that we think of the entire field as a whole, as a collective. One of the challenge projects we'd had in the past was to help find social media or multimedia tools that we can use to advertise this. This was called the "Rare Diseases Are Not Rare!" Challenge. That's one of the winning challenge awardees talking about — rare diseases are not rare — and that more people might know about unicorns than rare diseases. We're exploring many different approaches that we might need to help us understand and communicate better the needs of the rare disease community.

I just want to thank you for this opportunity, as well as a chance to participate on this esteemed panel. Here are some of those resources I was pointing to earlier and my contact information. Thank you.

DR. DEY: Thanks so much, Eric, for sharing this very valuable information with us. That was a very powerful message of the importance of translating patient stories to data, which highlights the need for patient registries and natural history studies.

Now we open up our panel discussion with Eric, Kathy, and Julie. We really appreciate all the questions that people have submitted so far, both during registration and throughout the webinar today. There are some very good questions and lots of them. We might not have time for all the questions, but we'll try our best to answer as many as we can during the panel discussion.

I'll start off with a question for Eric. If a patient or caregiver is looking for a natural history study for their specific disease or condition, where would you suggest they start?

DR. SID: Great question, DD. For anybody that's in that situation, where you're unsure of how do you start going about looking for this, it can be really hard to go through and search for information in publications, for example, or clinical trials around rare diseases; that's a resource that we can offer as the GARD contact center. Again, our Genetic and Rare Diseases, or GARD, Information Center provides free information service and support for anyone in the world that's looking for questions like this about how to find either information about a natural history study that has already occurred or to find out if there's a natural history study on the clinical trial currently available. If there isn't one, I think part of the first step for you might be, as a patient advocate or a patient leader in your space — is to help with starting to organize your community. We have resources around that radar website to help develop a contact registry, but there are many different platforms that are available out there to help with this process.

Sanford Health's CoRDS was mentioned earlier — NORD's IAMRARE. There are other platforms, like RARE-X, that are also being developed. So there are quite a lot of resources that are out there to support you in helping to build a natural history study if you don't see one in your space.

DR. DEY: That's very helpful. This next question is for Kathy and Eric: How can patients tell if a natural history study is legitimate and well organized and is designed with a patient's best interests in mind? Second, is it correct to use a natural history study to help understand unclear data from a trial, especially in the case if the data of patients in the placebo arm are dubious?

DR. NEEDLEMAN: Certainly, our program events are always available online; they've gone through rigor. And certainly, be comfortable; know that those are legitimate trials.

I think one of the things to think about for our studies — that we're looking to make sure that they do have quality data — that they will be utilized for future development, either in place of a placebo, which is always a hopeful goal — at the minimum, to ensure that the study is better designed, getting the right types of patient subjects,

making it more efficient, making it better so that we can spend less time worrying about some of those development thoughts, really understanding how this disease is progressing and where and who should be the best candidates for the end of the product that you may chose for that disease.

DR. SID: I would say there's two thoughts on this, so thinking about how to make sure if a natural history study is legitimate and well organized, I think part of this starts from an organization perhaps having either — a scientific and medical advisory board. You would probably want to capitalize on experts within your field that you can turn to to help weigh in and say whether or not a trial actually is legitimate and well organized enough to be successful. The other part of this, I think, in terms of thinking about how to make sure that you design a natural history study with patients' best interests in mind — patient advocates are particularly well situated to be the stewards for the patient community, so I think oftentimes — issues like data ownership and making sure that that data from that natural history study may be leveraged for multiple uses and ensuring that it also has the best interests of the community in mind.

What you don't want to do is trap yourself. For example, all the natural history study data may be owned by a single company. Therefore, if that company no longer has an interest in the field for your disease, they no longer pursue any kind of uses of that information. You really want to make sure that you're able to act as champions and stewards for your community.

DR. DEY: Thanks, Eric and Kathy; that was very helpful — and great stances on that issue. There was a very relevant question for both of you: Does FDA and/or NIH fund and support natural history studies? — which I think was addressed extensively by Kathy. Now, in terms of NIH funding or supporting natural history studies, Eric, do you have any comments there?

DR. SID: There's a lot of different funding around rare disease efforts. Unfortunately, there is not one single mechanism we have for natural history studies in rare diseases. But I do think that the FDA grant, which we do help support, is

probably the best model out there right now. Each of the different institutes and centers of NIH may sponsor natural history trials within their own space. There's quite a bit out there.

DR. DEY: Kathy, do you have anything else to add to that?

DR. NEEDLEMAN: No, I think Eric covered it perfectly.

DR. DEY: Thanks. I'll go on to a question which is actually for all the panelists: What are the biggest challenges to consider when aiming to use natural history study data as a control group for a clinical trial?

DR. NEEDLEMAN: I think you heard a little bit about it this morning, but certainly data quality. We really need to see, if you're thinking about utilizing some of this data later on, ensuring that the quality of the data is there so that later, when you are actually testing a product — things to consider, like timing, intervals — when are you going to be collecting samples? Having it as close to what you anticipate your clinical trial to be is essential. How that data collected is so rigorous that you can make sure that that our regulators, when looking at the data, can compare the data — the data has to be something that they can show will be in substitute if they do that — a placebo, and I think it is certainly a challenge, especially when you are so early on.

Sometimes you don't know all of those answers yet. That is just one of those hard things. But to be able to sort of rigorously think about that even as you're going on with your natural history study — maybe you find a good amount of information, and then you can kind of tailor an adaptive design and tailor that natural history study a little bit more as you understand more. That's essential. One of the things we're certainly focusing on is that data quality, because we hear that need to be utilizing this data for development. They have to be rigorous, and so thinking about that quality of data is essential.

DR. SID: Kathy did a great job in describing both clinical trial design, as well as data quality. I'll add to that by saying equity is a huge part of this as well; that's very important. We want to make sure that whatever is generated (for example, if a natural history study is applicable to

as generalizable a group of the population as a whole) is possible. What you don't want to do is collect only information or data from a small subset of that population that doesn't reflect everybody. You may then have challenges, for example, of access to treatments in the future or even just actual outcomes that are going to be different if you're not paying attention to making sure that you're approaching this from a very equitable perspective.

DR. DEY: Thank you so much for that. There's a question for Julie: Does participating in a natural history study impact a patient's eligibility to participate in a clinical trial?

CAPT VAILLANCOURT: A natural history study is an observational study. There's no intervention, so there should be no reason why a patient could not participate in a clinical trial if the patient has participated in a natural history study. However, say you're in a clinical trial for an investigational product, and you also are interested in participating in a natural history study. You may or may not be eligible to participate in the natural history study. It really depends on many things, like the purpose of the natural history study, what are the eligibility criteria — and that would be something to look into and to ask questions about.

The reason is because, if that natural history study is intended to provide a source of data to serve as external control data for another clinical trial of another investigational product, there could be some confounding or difficulty there in assessing the first investigational product. It does get a little complicated, but if you have a rare disease and you're on standard of care, most natural history studies are not going to exclude you, because that would be very important to have patients, especially for rare diseases, when there are so few patients in general. There should typically be no reason why patients on standard of care wouldn't be able to participate in a natural history study, but it might get a little complicated when it comes to being on an investigational product. That would be something to ask about or look into.

DR. DEY: Thank you; that addresses that question. There's a question for Kathy: How are the reviewers for the natural

history study grant applications chosen? And the second part of the question is, can people from outside the FDA volunteer?

DR. NEEDLEMAN: We have external and internal reviewers that review our natural history panels. For our external folks, we'll look into our applications and see what we have in terms of the disease specialties, and then we kind of scour the research as well as things that are going on in that rare disease. We find experts in those fields who are non-conflicted and able to provide their expertise on these applications.

If you're interested in being one of those reviewers, feel free to reach out to me or the general contact info I showed on my slides, and we have a whole database listing of well over 1,000 reviewers that we used. We're happy to add you to that and get some of your information. What was a second part to the question?

DR. DEY: The second part was, can people from outside the FDA volunteer?

DR. NEEDLEMAN: Yes, they can. If you're a patient representative, the same thing. If you're interested in being a patient representative on the applications, please reach out to me or our office so that we have that for future application cycles. That would be helpful.

DR. DEY: There's a question for all of our panelists: What research advancements have you seen that have been made because of natural history studies? I know Dr. Wilson Bryan had touched upon a case earlier today, but if you have any comments on this, that would be great.

DR. NEEDLEMAN: What we've seen in terms of some research advances — in our studies and even ones that we don't fund that lead into some of our clinical trials, like I've mentioned — finding a better kind of trial design but also really developing biomarkers, finding a biomarker that really hits the head of what's needed or a clinical outcome assessment that's really needed for a clinical trial in the future. I think those are huge steps forward, when sometimes you start off with a disease that no one knows really much about, and you can really find someplace that you can start homing in on a molecular target so you can

kind of identify what can be done to help treat these folks.

We've seen that through our applications — that the other thing is collaboration. We see quite a bit of this. Some of our studies, once they're funded — and they tend to move forward — they catch the eye of nonacademics of industry who are now willing to come forward and also support some of this research. I think, in a different way, that really does help move the needle forward as well, when you can catch that eye. I think that's an important thought when folks are moving forward, and they're really finding some of these important questions and answers to these questions during these studies.

CAPT VAILLANCOURT: I would second everything you said. I think biomarker identification and development is really important. Sometimes identifying subtypes of diseases — and then that can help with developing eligibility for studies. I did want to mention, in CBER, we had a recent approval for a product, which is a regenerative medicine product. It's basically allogeneic sinus tissue that has been processed, and it's for congenital athymia, which is such a devastating rare disease where children are born with no thymus. It's typically fatal by age 3, because they succumb to infections. This was such a success story; however, it really took decades to develop and approve this product, because there are lots of manufacturing obstacles to overcome. But it was a success as well in using compiled natural history study data from multiple sources over several years to serve as external control data in assessing the safety and efficacy of this product. I think it's a really great example, and I will also add that the investigator was a recipient of Office of Orphan Product[s Development] clinical trial grant funding. I just love this successful story and approval, because it took a village; it took so many people collaborating at all different levels, but now there is a cure for these children. I think it's just so important.

DR. DEY: Eric, if you have any comments on that, I think we are reaching the end of the session. I know we have several questions but limited time to answer all of them, so we will post these somewhere so that everybody is able to access this. With that, I would like to thank all of our

panelists for answering those questions and giving great insights and for sharing your perspectives and experiences with us. It was a great discussion, and we are hopeful it was informative to all of our attendees. I will now pass it back on to Anne.

DR. ROWZEE: Thank you, DD, and thank you to all of our panelists, Eric, Kathy, and Julie, for your presentations, for answering the questions and sharing your experiences and perspectives with us. Like DD said, we had a lot more questions that came in to us than we could answer, but we are taking these all back, and we're going to be able to use them to inform some future events from OTAT.

Before we conclude today's workshop, I'm going to turn it back over to Dr. Bryan, who is OTAT's Director, to share a few final remarks.

DR. BRYAN: Thank you, Anne, and hello again to all of our attendees. Thank you so much for joining us today for the second Annual Patient Engagement & Regenerative Medicine meeting. I really enjoyed that last panel discussion, and thank you to Devaveena, Julie, Kathy, and Eric. I particularly enjoyed the first panel discussion, hearing from the patient advocates. I hope that you found the presentations and discussions informative and inspirational. Our goal was to raise awareness of natural history studies and how these studies can lead to advancing regenerative medicine and the development of cell and gene therapies, among other types of products as well.

After listening to and engaging with our panelists and speakers today, I hope you feel empowered to explore clinical research opportunities. Maybe you can start a natural history study or have the opportunity to participate in a natural history study.

As you heard today, patient participation is so important to improving the understanding of diseases and informing future treatments and therapies. Patients, patient advocates, and caregivers, it's you that have such an important role in advancing science. Patients and families, you are experts in your diseases, and you can provide valuable information. Please consider taking on a natural

history study or joining forces with other groups that may be working on related research.

OTAT is committed to engaging patients, caregivers, patient advocates, and stakeholders and finding opportunities to work together. As discussed today, regenerative medicine therapy's hold promise to transform medicine and create treatment options for patients who are living with difficult, even incurable diseases. The FDA is committed to working with you to speed development of regenerative medicine therapies. Thank you so much for being part of this event. We will be having more OTAT events like this in the fall. Please join us and continue the conversation. And Dr. Rowzee, I'm going to turn it back to you for some final thoughts.

DR. ROWZEE: Thank you, Wilson, and thank you one last time to our amazing speakers and panelists for joining us today and sharing your perspectives and experiences with us. For those who are following along with the chat and providing links and other resources for our audience, it's so helpful and very much appreciated. I want to thank everyone for attending today, for all of your great feedback and questions throughout our sessions. Like I said, we're going to take those back and see what other programming that we can put together, sort of help answer those broadly, and to put that information out on our website.

If you'd like to continue learning about natural history studies, I want to make a plug for an upcoming conference that FDA is putting on. And if you want to dive a little bit deeper into the use of natural history studies in the clinical development of cell and gene therapy products, I encourage you to register for the upcoming Regulatory Education for Industry Annual Conference and look for my colleague Rosa Sherafat-Kazemzadeh's presentation, which is "Design Considerations for Clinical Trials in Rare Diseases." The conference is free and will be held virtually June 6 through 10, and I'm going to put a link into the chat box to the conference.

Please stay up to date with us. Visit the CBER website. Sign up for our newsletter, "What's New at CBER." Follow us on Twitter at @FDACBER, and I encourage you to use the hashtag #RegenMedEd on social media to share your thoughts

on today's events. Let us know what information and resources you're interested in seeing from OTAT at future events. We look forward to continuing to work together to advance regenerative medicine therapies. Thank you again, everyone. Have a great day.

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