FDA CBER OTAT

Natural History Studies to Support Regenerative Medicine: A How-To Webinar

October 27, 2022

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Ubiqus/Nation-Wide Reporting & Convention Coverage
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Welcome

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ANNE ROWZEE, PH.D.: Hello everyone. Thank you for joining our event, "Natural History Studies to Support Regenerative Medicine: A How-To Webinar." Today's webinar is hosted by the Office of Tissues and Advanced Therapies, or as we usually say, OTAT; within the Center for Biologics Evaluation and Research; and the U.S. Food and Drug Administration.

My name is Anne Rowzee. I am an associate director for policy at OTAT. I'll be your host for today's event. Some of you may have joined us for our annual Patient Engagement on Regenerative Medicine Workshop back in May of this year, so welcome back. We're glad to have you here with us again. In that workshop, we discussed natural history studies and why they are so important for advancing development of regenerative medicine therapy, especially those targeting rare diseases. If you missed that workshop, though, don't worry. You can find a recording of it on FDA.gov.

Today's webinar is meant to serve as a follow-up to May's workshop through an in-depth discussion with natural history studies researchers, participants, caregivers and advocates for participants. We hope to provide you with practical information on how to organize and execute a natural history study. Wait a second and we'll hit the next slide.Very good.

We have a great agenda planned for today. We'll kick off the webinar with a deep dive into natural history studies, including what they are, why they're important, and how they contribute to the drug development process. We'll then move into presentations featuring researchers, patients, and advocates. We'll get to hear about their experiences conducting and participating in natural history studies, as well as some recommendations they have for those who are interested in starting a natural history study. Lastly, we'll finish up with a Q&A discussion, which will feature audience questions both submitted in advance and some life questions as well.

Before we get started, I'd like to share just a few notes about today's webinar. The webinar is being recorded. A recording and the slides will be posted on FDA's website in the next few weeks. Closed captioning for this event is available directly in Zoom, and we'll have some time during the panel discussion for questions. If you have a question for our panelists, please type it directly into the Q&A box in Zoom.

Note, though, that we are unable to answer questions about specific medical conditions and diagnoses. We encourage you to discuss those questions directly with your health care team. We also can't answer questions about the status of specific investigational products or drug applications. We appreciate your questions and comments, and we're going to do our best to address as many as we can today. Finally, if you have a general comment that you'd like to share, or if you're experiencing technical difficulties, please use the chat box in Zoom.

While I've got the floor, I'm going to take a few minutes to mention that today's webinar is part of a series of virtual events that we call RegenMedEd. The RegenMedEd event series includes educational webinars and workshops where we invite patients, caregivers, advocates, and other

stakeholders to learn about topics related to regenerative medicine therapies. As I mentioned earlier, recordings of our previous RegenMedEd events can be found on FDA's website. I'd also like to invite you to use the hashtag RegenMedEd on your social media channels if you'd like to share your thoughts on today's webinar.

Let's go ahead and get started. Our first presentation today is a deep dive into natural history studies. Our first speaker is Dr. Wilson Bryan. He's OTAT's director. He's going to provide an overview of natural history studies and explain why they're important for drug development. Thanks for joining us today.

Natural History Studies: Introduction

WILSON W. BRYAN, M.D.: Good evening everyone. I'm Wilson Bryan. I'm the director of the Office of Tissues and Advanced Therapies, or OTAT. Welcome to our natural history studies how-to webinar. As Anne mentioned, we're just so glad that you could join us today. We're going to give you an overview of natural history studies, including what they are, why they are important, and why we need patients and caregivers to participate in these studies and the critical role the natural history studies play in developing new treatments for all types of diseases and conditions, particularly rare diseases. Because my office, OTAT, is in charge of regulating cell and gene therapies, we'll also spend some time talking about this exciting field of medicine. Most importantly, we will talk about ways that you can get involved to help advance the development of cell and gene therapies.

OTAT is one of the offices responsible for regulatory oversight of biological products within the Center for Biologics Evaluation and Research, or CBER. OTAT's mission, like all of FDA's mission, is to promote public health. We do that by ensuring that medical products are safe and effective. In doing this, OTAT's regulatory decisions must be data-driven, impartial, and compassionate.

At OTAT, one of our primary responsibilities is to make sure that regenerative medicine therapies, including cell and certain gene therapies, are safe, effective, and of high quality for patients. Regenerative medicine can involve using stem cells, engineered biomaterials, gene editing, and other scientific technologies to repair or replace damaged cells, tissues, or organs.

Regenerative medicine is complex, and it's important to note that while regenerative medicine has been around for decades, it continues to evolve and progress through scientific advancements. That's one reason we're here today, to talk about some of the advancements that we've seen in regenerative medicine.

There are several different types of regenerative medicine therapies. These include certain gene therapies — that is, those gene therapies that lead to a sustained effect on cells or tissues. This includes products that incorporate gene editing, cell therapies, therapeutic tissue engineering products, and xenogeneic cell products. Those of you not familiar with the term, "xenogeneic" refers to products that come from other species. For example, there is substantial interest in

potential for pig organs, such as hearts and kidneys taken from pigs to replace the failing organs of patients with heart failure and kidney failure. Xenogeneic studies is a very exciting field right now.

At this time, OTAT has over 2,000 investigational new drug applications, or INDs, for cell and gene therapies. Approximately 50% of these INDs are for the treatment of rare diseases. We estimate that 80% of rare diseases are caused by defects in single genes. There are currently only four. We have only four FDA-approved gene therapies for single-gene disorders, including two products that were approved in the past few months, one for adrenoleukodystrophy and one for beta-thalassemia. This makes the field of regenerative medicine, particularly gene therapy, so promising for the treatment of thousands of rare diseases.

Gene therapy to treat rare diseases that are caused by single-gene defects could mean improvements in health outcomes, quality of life, and disease management for millions of patients and their families. Unfortunately, most rare diseases are not well understood, and that makes drug development difficult. Bringing these products to market will require the participation of patients and caregivers, particularly participation in natural history studies.

To fully appreciate the importance of natural history studies, it is critical to understand the drug development process. This figure provides an overview of the major steps in bringing a new medical product to market. If you look at the left of the figure, it starts with preclinical development, and these are studies that are done sometimes in animals, sometimes in test tubes or cultures, to try to get an idea of whether a product might have an effect on a pathway that's important in a particular disease or might have an effect on an animal model that appears to mimic a particular disease.

After those initial preclinical studies are done, then we go into the initial clinical trials, phase I studies that are typically focused on safety or tolerability but also can get important pharmacokinetic information and, in some cases, preliminary evidence of efficacy. These are followed by phase II studies, which sort of try to iron out the population that's most likely to respond to the product, the endpoints that are most useful, and the eligibility criteria. Then phase III are the studies that provide the important evidence of effectiveness and safety to support a marketing application, such as a biologics license application or a new drug application, what we call a BLA or an NDA. Then there are also some studies that are done postmarketing after a product is approved.

OTAT is involved in all stages of development. That starts early on through the clinical trial phases and after products are approved and on the market. Because of various considerations, these steps are often modified for therapies to treat rare diseases, including many cellular and gene therapy products. For example, two of the gene therapies that we have are approved for single-gene defects. One is Luxturna, for a rare form of blindness, and Zolgensma, for treatment of spinal muscular atrophy. The entire clinical development programs for each of those products had only two studies. They didn't have a phase I/phase II/phase III — kind of bunched those together. The total development program was only 36 subjects. That's important that we can

abbreviate this process for rare diseases, particularly when we have products that have large effects.

As you can see, there are many ways that patients can get involved through advanced research and development. These include participation in clinical trials, patient registries, listening sessions and meetings such as today's webinar, and of course natural history studies, which are the focus of today's webinar.

Let's begin with what we mean by a natural history study. A natural history study follows a group of people over time. The people in the study can be patients who have a particular disease or groups of diseases, or it could be people who are at risk of developing a disease. The natural history study involves collecting data like age, risk factors, diagnosis, symptoms, impact of these disease on patient's quality of life, test results, and more.

Natural history studies are valuable tools for helping us to understand a disease. This helps us to develop new therapies for that disease. It is fairly difficult to develop treatments for a disease that we don't understand. We have to understand the disease to develop good treatments. Natural history studies can identify demographic characteristics, such as age and sex, as well as genetic environmental and other variables that correlate with disease development and outcomes.

Natural history studies help us to better characterize the disease and the patient population, especially for rare diseases, for which we often just don't have enough data. We don't understand the rare diseases well enough yet. Natural history studies can clarify the impact of a disease from the lives of patients and their families. They allow us to collect patient-reported outcomes and other disease-specific clinical outcomes. Natural history studies inform the clinical drug development process by providing crucial diagnostic information in establishing guidelines for disease management. This is so critical for the pharmaceutical industry. When drug companies look at a field and whether or not it's ready for drug development, drug development is a high-risk endeavor. What can we do to make it less risky? We make it less risky by understanding the disease. Natural history studies de-risk or decrease the risk of drug development.

There are four types of natural history studies. The first two types of studies rely on data collected from patient records. These are retrospective studies that use data collected from existing medical records. These types of studies are often a first step in describing the progression of the disease. I'm going to talk later about the steps that you take in putting together natural history studies. Retrospective studies are often a very early step.

In addition to retrospective studies, we have prospective studies, which use data collected from ongoing patient visits. These studies establish definitions in data to be collected ahead of time. If you think about this, if a clinic is following 100 patients with a particular disease, if the investigator says, "I'm going to go and look at all of my experience over 11 years with those 100 patients," then that's a retrospective look. That's looking back. That's a retrospective study. On the other hand, if a physician says, "I'm going to follow these 100 patients for the next 10 years," that's a prospective study, and I'm going to gather data going forward. Retrospective: looking back. Prospective: looking forward.

The second two ways to think of natural history studies is that we collect data from cohorts. A cohort is a group of patients. Cross-sectional studies collect data over a specified limited time period, whereas longitudinal studies collect data at various time points over a long period. For example, a clinic's got 100 patients with a disease. If the investigator says, "I'm going to look at the status and the clinical status and everything I can about those 100 patients that I see in my clinic this year," that's a cross-sectional study, as opposed to saying that "I'm going to follow those patients for the next 5 years and look at them over time," each patient might be seen 10 or 20 times over those 5 years. Longitudinal: looking at patients over time. Cross-sectional: looking at all of my patients, but just in one time period.

Cross-sectional and longitudinal studies can be either retrospective or prospective, so you can have a cross-sectional retrospective study, a cross-sectional prospective study, or a longitudinal retrospective or longitudinal prospective study.

Protocols are so important. A protocol is a document, and it governs every aspect of the natural history study, including who should be included in the study, also known as eligibility criteria or inclusion and exclusion criteria. The protocol specifies the type of information that will be collected and how the data will be collected and analyzed. Very important to have a detailed protocol when you start the natural history study, whether that's a retrospective study or a prospective study. Start with the protocol. Detail rigorous protocols protect the natural history study participants and help to ensure the scientific credibility of the study.

It's important to note that although natural history studies can be extremely beneficial, we at the FDA do not require them for drug development. We can't mandate that someone do a natural history study. If you are thinking of including a natural history study in a drug development program, it is important to start early, because these studies can take quite a bit of time, and the data can be particularly useful prior to initiating clinical trials.

Unfortunately, it's not unusual here at the FDA to have an investigator come to us to file an investigational new drug application saying they want to start doing clinical trials, and they haven't started the natural history study yet. Without that natural history data, they don't know how to design the clinical trials and we don't have the information necessary to give them advice. Natural history studies take years, so — very important to start natural history studies early when you're having those preclinical animal studies at the beginning. That's when the natural history studies should start, if not earlier.

The natural history study should cover a sufficient period of time to capture clinically meaningful outcomes and enroll enough subjects to determine the variability in the course of the disease. Many of these diseases are highly variable. No two patients are alike, and you really want to, in the natural history study, capture the full spectrum of the disease as much as possible.

Natural history studies should provide a wide variety of benefits to rare disease research, ultimately serving as the foundation for the individual treatment of a disease. These studies inform important aspects of drug development by refining the target patient population. You'll look at the natural history study, and that will help you to decide which patients are going to be most informative in a clinical trial: identifying and developing clinical outcome assessments or

endpoints, finding endpoints that are likely to be sensitive and likely to be meaningful for patients, identifying and developing biomarkers that may help to identify which patients are most likely to show change in a clinical trial, informing design of future clinical trials — for example, natural history data can help determine the size and duration of a clinical trial. Without good natural history data, it can be almost impossible to know how long that clinical trial is going to need to be in order to see changes in the patients.

In limited circumstances, natural history data can serve as an external control in clinical trials. Some folks think that when I gather natural history data, the goal is to have an external control in clinical trials. In most cases, the natural history data is not good enough. In some cases, it is, but in most cases, it's not good enough to serve as a control in a clinical trial. But what it does is, it tells us how to do those clinical trials.

Natural history studies play a critical role in rare disease research. This is especially true in the progression of a particular disease that is poorly documented or described, as is the case in many single-gene disorders. When knowledge about a disease is insufficient to guide clinical development, a natural history study can provide crucial data on patient diagnosis, treatment, symptoms, and outcomes, and that can save years in drug development time.

We hope that you will come away from today's discussion with some ideas and suggestions on how to start your own natural history study, for both researchers and advocacy groups looking to advance drug development through a natural history study. There are several steps we encourage you to do. These are sort of in the number that they should occur. Number one: Do a literature review. This will help you to understand what information already exists on the disease and where there are gaps. Don't just try to understand the disease from doing the literature review. I'm going to recommend looking at the FDA guidance on Rare Diseases: Natural History Studies for Drug Development. Reading that guidance will help a lot, I think, as you're thinking about how to design your natural history studies. But do a literature review to get a preliminary idea of understanding the disease.

Now, what's in the literature is always biased. It's never completely accurate, so read it, but read it with skepticism. Talk to experts in the disease area. Reading literature will help you to understand who the experts are, and these individuals can counsel you on research that has already been done and may also be able to connect you to patients or patient advocacy groups. This process of doing literature review and talking to the experts — those two things can happen in parallel at the same time. It doesn't matter which one you do first, but you have to do both. You have to talk to people, and you have to read the literature.

Next step is a retrospective natural history study. That can be a retrospective cross-sectional study — a retrospective longitudinal study. It requires a protocol. After you do your literature review and talk to your experts, put together a protocol for a retrospective natural history study. When you do that retrospective natural history study, you will realize all the things that you don't know about this disease.

The next step that I would recommend is to try to design a clinical trial and maybe even a full development program for a product based on what you know from the literature in the

retrospective natural history study. When you try to design that clinical trial, you will see all the gaps in your knowledge. Seeing those gaps in your knowledge will help you to understand what information needs to be gathered in a prospective longitudinal natural history study.

Several steps here. Start with a literature review. Start with talking to experts. Then write a protocol for a retrospective natural history study. Try designing a clinical development program based on what you know, and then you will really understand what you don't know and design a prospective longitudinal natural history study to gather the information that you don't know. It's very much a sequential process. It takes years. It's very important to start early.

There are many ways that stakeholders can work together to advance regenerative medicine, particularly taking on these natural history studies, finding opportunities to work together, and collaborating with one another early on in the drug development process. We can't hope to cure and treat rare diseases without patients, families, and advocates. OTAT is committed to finding opportunities to work together. During the next session, you'll have a chance to hear directly from researchers, patients, and advocates about their own experiences and expertise as it relates to natural history studies. You're going to find their stories inspiring and helpful.

I've listed my contact information. It's pretty straightforward, wilson.bryan@fda.hhs.gov, if you have any questions or feedback you would like to share that we don't get to later today.

This slide also includes some additional points of contact and resources for the FDA, particularly OTAT and CBER, the Center for Biologics. With that, I want to say thank you to everyone for your attention today.

DR. ROWZEE: Thanks so much, Wilson. You set the stage well for the next portion of our event, and we'll look forward to hearing from you again during our Q&A panel, so don't go too far away. Now that our viewers have some information about what natural history studies are and why they're important, we're going to move into our panel presentation, which will highlight perspectives from researchers, patients, caregivers, and advocates.

I'm now going to pass it over to my colleague, Dr. Katherine Needleman. She's Director of the Orphan Products Grants Program at FDA's Office of Orphan Products Development. She's going to moderating the session. Thanks so much, Kathy.

Panel Presentations: Natural History Studies — Perspectives from Researchers, Participants, and Caregivers

KATHERINE NEEDLEMAN, PH.D.: Thank you, Anne, and welcome, everyone. As Anne mentioned, my name is Kathy Needleman. I am the Director of the Orphan Products Grants Program at the Office of Orphan Products Development, also known as OOPD, here at the FDA. I'm excited to be your moderator today for today's panel discussion, where you'll hear directly from our experts about their firsthand experiences designing, conducting, and participating in natural history studies.

With that, I will introduce our panelists today. Our first panelist is Dr. Richard Finkel. Dr. Finkel is the Director of the Center for Experimental Neurotherapeutics at St. Jude Children's Hospital. Dr. Finkel is a published medical researcher with interest in pediatric neurologic and metabolic diseases, as well as pediatric neuromuscular diseases.

Our next panelist will be 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/R9. Having a scientific background in physics, Brad decided to change his career path and work on identifying treatments for muscular dystrophy.

Lastly, I'd like to introduce Erin Ward. Erin is the president and co-founder of MTM-CNM Family Connection. Erin is involved in the MTM-CNM community as both a parent and advocate to help bring families together and connect them to top researchers and potential MTM-CNM treatments. Thank you all for joining us today.

Before I pass it over to Dr. Finkel to kick off our panel presentations, I do want to encourage everyone in the audience to submit questions for our panelists in the Q&A box on Zoom. We will have some time at the end of the presentations for a discussion, where we'll address some of those questions. For general comments, please add those to the chat box in Zoom. And now I'll pass it over to Dr. Finkel to talk about his research experience.

RICHARD S. FINKEL, M.D.: Thank you very much. It's certainly a pleasure to be invited to participate in this webinar. I am a pediatric neurologist, as was recently described. What I'm going to share with you today is some of my experience in working with natural history studies for rare diseases. Much of this will amplify what you already heard from Dr. Wilson Bryan.

Let me go to the next slide, which is going to just go through some of my disclosures. I do want to point out that I've had a variety of research support from both pharmaceutical companies and nonprofit patient advocacy groups, the NIH — and that's listed here. I've also served in an advisory capacity on some foundations.

What I want to summarize in these next few minutes is from my perspective why natural history's not just important but really essential if we're going to build a successful clinical trial and interrogate whether a drug is both safe and effective — then talk about the types of natural history studies and some of the challenges and lessons learned. Thirdly, I was challenged by Dr. Bryan to talk about how do we actually use this information. It can be used well if the data is collected in a good way and analyzed properly, but also, there can be some obstacles along the way, which I'll highlight.

Why are natural history studies important? Again, this is I think in some ways to amplify what you heard from Dr. Bryan. To understand this particular disease and its progression, you need to start with a patient. Before a doctor starts collecting information on a patient in a natural history study, you need to have a focus group or some sort of sense of what's really important to the patient, — or, in the case of a little baby or child, the parent will serve as a surrogate for that patient with the disease.

Always keep in mind, what is the endgame? The endgame here is to get a successful drug approved by the FDA or, in Europe, by the EMA. To do so, you need to demonstrate effectively that a drug is both safe and effective. On the effective side, does it improve survival for particularly severe diseases? Does it improve how the patient functions or, importantly, how they feel? The natural history study — you want to design it to be able to capture those three basic elements, because that's what's going to help drive the design of the clinical trial.

The second point is, we need to understand what are called trajectories of change. What do we mean by that? Most of the diseases that we deal with do not follow a linear course of either up or down. There might be periods where they're relatively stable and unchanging. There might be periods where the disease process is accelerating more rapidly and periods where it's accelerating more slowly. You need to identify that in the natural history study, because ultimately, you're going to pick a certain subgroup, as you hear from Dr. Bryan, a subgroup of patients that you hopefully will reflect the entire population of patients with that particular condition. But that's the sweet spot. That's the population that you're going to study in a clinical trial, which may be a very small number in the case of a rare disease.

Before you make the assumption that the clinical trial is going to capture something that you can extrapolate to the entire group, you really need to understand what that entire group looks like. I'll give some examples of that in a moment. You need to understand by the age of the patient what their developmental status is at that point, particularly if you're talking about in an infant or young child. Are there differences by sex? We know boys and girls are different, but are they different in this particular context of this disease? If so, that's really important to know when you design the clinical trial.

Also, by the stage of disease. If they're shortly after diagnosis, you may find that the feature's changed very differently from a mid-stage or a late stage and perhaps even presymptomatically if you can identify a child with a genetic disease before they even have the onset of symptoms. Well, how would you begin to evaluate that child?

The third point I want to really hammer home is the impact of standard of care. When we talk about a natural history study, in one sense, it's not really a natural history if you are providing some intervention. That intervention is not necessarily a drug. It could be the impact of the standard of care — for example, good nutrition, pulmonary support — things of that nature, which fundamentally change how that child or adult survives, functions, or feels. That's really important, because ethically, we need to provide the optimal standard of care or at least basic care. Then we're going to add on top of that this investigational drug.

For several reasons, it's important to try to identify what the standard of care is and how we apply that in this natural history study. At the same time that we are trying to collect information in a natural history study, it's important to identify what in fact is the standard of care. For a lot of diseases, that's not really known, so there's a parallel effort here to get a group of experts together, and that has to include patients living with that disease, their parents, patient advocacy groups — all working together to try to say, "Here's what we think the basic standard of care

should be and how we apply that in a natural history study." Ultimately, that's going to be used also in a clinical trial.

The next point is to consider how this information that you're going to gather in the natural history study is ultimately going to be used. It would be what we call fit for purpose. How will it be used by the pharmaceutical company or the academic researcher to do what's called a power calculation? How many patients are needed? How many participants in a clinical trial? For what duration to be able to identify whether or not this drug has a clinically meaningful response as it's measured with these outcome measures — all of which is based upon the natural history information that we've gained through these studies.

It's also important to identify what we call a clinically meaningful change. What's the minimal change that would be considered clinically meaningful? Because we know that if we do a test 2 days in a row, we may get two different numbers on a particular test or a measurement. So we have to say, "Well, what is the test/retest variability from one day to the next?" Because we're not machines. We don't function at the same level every day. We may not function as well at the end of the day if we're a little tired as to the morning. All of these have to be taken into consideration when we try to identify what would be the clinically minimally significant change so that we're convinced when we design a clinical trial to say, "Well, if a child changes or goes up 3 points on a scale, that's something that we don't see even with the best supportive care." We feel confident that that change reflects a favorable response to the drug.

Similarly, we need to be able to identify if there are safety issues, if there's an adverse response to the drug. If a child goes down, let's say, 3 points on a scale, we say, "Well, wait a minute. That shouldn't be happening during this course of observation." Maybe the drug is in fact having an adverse response, so it can give you an important signal both in a favorable way and in an unfavorable way. We need to be able to capture both of those.

I'm going to just share some examples of four different types of diseases that I've worked on and highlight how they are different in their aims, their funding support, and some of the challenges. Let's start with Duchenne muscular dystrophy, which occurs in about 1 in 3,500 boys. I've been involved in three different natural history studies, each of which had a different objective. That's the point I want to highlight here — is, what's the objective? A natural history study doesn't try to do everything.

The first of these was an NIH-sponsored — called the United Dystrophinopathy Project, and that was where Dr. Kevin Flanigan, who led this effort, tried to identify how different mutations or genetic variants in the DMD gene relate to certain clinical features. Do some of these predict a more rapid progression or a slower progression? We call that a genotype–phenotype association study.

The second one was sponsored by the Department of Defense, which sponsored the CINRG Network. These were all multisite studies, and they all had protocols, but here in the CINGRG, we were looking at outcome measures, trying to identify — develop outcome measures, validate them, and try to see which of these were responsive in picking up the change in these boys with

Duchenne over time. How long would a clinical trial need to be? Well, we needed to do this kind of study to determine that.

A third one is one that I'm involved in now, which is industry-sponsored, and it's called the DMD Natural History Study. This is designed to just select a small portion of patients, little boys with DMD who have a particular mutation, and it's called a run-in to a gene therapy study. The idea was to look at these patients let's say over 1 year before they get the gene therapy to try to get an idea of how much they are changing in that 1 year. Then after they get the gene therapy, we can look for a change relative to that run-in. So three different studies with three different objectives.

The next example is spinal muscular atrophy. For this, the Spinal Muscular Atrophy Foundation sponsored a network, and this has been going on for 20 years. I'm going to highlight that in a minute, but I want to compare that to an industry-sponsored study called RESTORE. This is where you have to understand: Are we having what's called a disease registry, meaning all patients with a particular condition or disease? Or is it a drug registry where we're really trying to just get patients on a particular drug after it's already been FDA-approved?

In this case, the company was required by the EMA to do a study that captured patients that were treated mainly with a gene therapy, because that was their charge, and to show how they did over the next 15 years. On one hand, this was a disease registry. Any patients with SMA could get in it, but it was really focused to capture patients treated with the drug called Zolgensma.

Third example is inherited neuropathies. This was NIH-sponsored, and it's been going on now for about 13 years. The point here is that this condition, Charcot-Marie-Tooth, is actually 100 or more different genetic conditions that all cause the nerves not to work. It is not a single situation but multiple ones.

The final one is Pompe disease, which is a metabolic disorder, and we needed to do that to understand how the drug worked.

This is a study group, and this has been going on now for almost 20 years. This was protocol-driven, and we tried to structure this in a way that was very similar to a clinical trial. We tried to make sure that standard of care was used. Patients came in at certain identified points. They were trained clinical evaluators, and we tried to figure out what worked and what didn't. We also developed a lot of biomarkers, which is a separate topic but really important to include in this discussion of a natural history study.

Let me give you an example of how this looked. So starting here on the upper left is the protocol. In the middle is this observational study for SMA. We published this. On the right are some examples of two of the types of data that we collected. These were very instrumental in the design of clinical trials for SMA, with the baby as the most severe form. In the bottom is another publication that highlighted patients who are older and with a milder form of SMA. The bottom left is a figure that said these patients don't change much over 1 year. We need to do a 3- or even 4-year study if we're going to capture that change. The duration of the study was defined by this study.

The next slide just highlights some of the challenges. Very briefly, we need to make sure that parents and patients understand the importance of this. Why bother participating in a clinical trial? They want a treatment, but they need to understand that this is a necessary preliminary phase to better understand how to design a clinical trial while these drugs are in development. It's really important to get doctors to be motivated to participate. We need to understand that not all of the testing that we're proposing to do will necessarily be covered by insurance, so we may need some external funding support for this to be effective.

We need to understand that this needs to be successful over years. I'm talking about a longitudinal study, not a cross-sectional one, as Dr. Bryan mentioned. There may need to be travel support for families that live at a distance from the study site. There may need to be flexibility both by the family and the doctor to make sure that they can come in periodically. We need to make sure that this is a sustainable effort. We may be collecting blood samples — things like that, so there may need to be funding to support that. That turned out to be really important for, let's say, SMA, to have some of those samples that we could share with pharmaceutical companies. Who owns the data? How do we share it? What's the governance of all this? These all have to be worked out.

On the next slide, I just want to finally say that we need to make sure that we share the data. It needs to be presented at medical conferences. It needs to be shared in publications that I showed. There need to be data agreements, and in some cases we need to even have international collaborations, which we learned along the way, and we need to make sure that we're sharing this with the drug companies that are developing these drugs so that they construct informative clinical trials — that their protocols reflect what we've learned from these natural history studies.

I'm going to just stop there, but I hope that this will generate additional questions in our Q&A. Thank you for your attention.

DR. NEEDLEMAN: Thank you so much, Dr. Finkel. I want to now pass it over to Brad to tell us a little bit more about his experience.

BRADLEY WILLIAMS, PH.D.: Thank you, Katherine. My name is Brad Williams. I work for the Jain Foundation, which is an advocacy foundation working on findings treatments for dysferlinopathy, also known as limb-girdle muscular dystrophy type 2B or R2. So my title is Director of Research at the Jain Foundation. I'm also a patient living with dysferlinopathy. So I'm going to be talking primarily about a natural history study that I participated in a few years ago called the dysferlinopathy Clinical Outcomes Study. You can see on the map the different study sites, so it was an international study that lasted about 4 years — involved about 200 patients.

As you heard from the previous presentations, there are a number of components of a natural history study. I'll go over these in some more detail in succeeding slides. Kind of the central thing is to come up with goals for a natural history study for your disease area.

What I would encourage any advocacy organization or disease area thinking of doing a natural history study: First, I would encourage them to do a natural history study but to think about what the barriers are to clinical trial readiness in their disease area. If, say, someone from a pharma company came to you tomorrow and said, "I think we have a really promising prospective

treatment for this disease; we want you to work with us to tell us how we can set up a clinical trial and get this tested and hopefully approved and to patients," think about what would have to happen in your disease area before a clinical trial could happen. There are a number of aspects that might come into play: how well documented the symptoms and progression are or the aspects of the patient population or outcome measures. Do you know what you would actually be measuring in the clinical trial? What would be a meaningful benefit to a treatment? Those are just a number of things to think about. This is going to be particular to any particular disease area.

Using that, you want to set goals for your study. Often, just given the nature of finite resources, it's not possible to address every need for a particular disease area in a single natural history study, as Dr. Finkel alluded to in the last presentation. But you want your study to address at least some of the needs for being clinical trial–ready, and this may hinge on different aspects. Study the perspectives of the patients. What are they looking for? What are better documenting the symptoms and progression — and develop or validate outcome measures for using clinical trials?.

Finally, one thing that you're doing in running a natural history is developing a network of clinicians who are familiar with the disease — familiar with the outcome measures who can be study sites for future clinical trials.

Then there are a number of study parameters. I won't go into these in a lot of detail. Who are you testing? What are you testing? In general, I'll just say that in the study I was in, we tested everything we could think of. Not everything worked well as an outcome measure, but we just wanted to make sure we weren't missing anything important. Then how long is it going to be? How many participants are going to enroll? Is it going to be at one site or multiple sites? Often, for rare diseases, given the limited number of patients, it's more efficient to do this at a number of different centers.

One quote I want to share with you — and I consulted with a number of the organizers of both the dysferlinopathy Clinical Outcomes Study, as well as other natural history studies in the limb-girdle muscular dystrophy space, and one of the quotes I wanted to share from one of the people I talked to is, "We always start too late." It takes a long time to do a natural history study. Just the setup can take a couple of years, particularly if it's a multisite study. There often is one head site and then several satellite sites. They all have institutional review boards. They all need to approve the study protocol. It may take some time to recruit the patients.

Then after all of the data are collected, remember, that is not the end of the study. It needs to be analyzed. It needs to be communicated. Really, the bottom line here is, start before you think you need to.

Recruiting for a rare disease natural history study can be a challenge. I'll just mention that the U.S. is actually not one of the easier areas in the world to recruit. The reason is that our medical system is very decentralized, so there's no one place where they're going to know most of the patients in the whole country in a particular disease area, which is very different from the case in many European countries, where there's a centralized health system and there's some center of excellence in the disease area which will know many if not most of the patients.

This is where having a disease registry is very critical. You can't directly recruit into the study from a disease registry, but you can contact the people in a disease registry — tell them that the study is going on and is looking for patients and where to reach out if they're interested in participating.

The first thing that a patient does when they start a natural history study is the consenting process, which, for the patient, is just a formality. You read over and sign a few pieces of paper, and then you're in the study. But it requires some advanced thought, because the data that are being collected and also maybe blood samples, biopsy samples — other biological samples might be used by a number of different categories of people for a number of different purposes at some time in the future. It's very hard to think of all of those in advance. Very often, there will be some sample, and there will be some scientific study that wants to look at a certain thing, and "Yes, we got samples from this study." "Yeah, but the consent doesn't really cover this usage, so we can't use those." It's hard to think of everything, but doing as much thinking and consulting with others who've organized natural history studies is very important for making sure that everything that's been collected in the study can be used as widely as possible.

Another thing that I want to emphasize, from my perspective participating in it, is to be aware of the patient experience. There are a number of reasons why people like to participate in natural history studies. There's the altruistic motive of helping knowledge of the disease, potentially helping other patients, as well as to be evaluated by someone who's very knowledgeable about this disease, which often will never have happened in a person's previous experience living with this disease.

But there are some downsides also. Travel can be kind of exhausting if you're doing a lot of tests in one day. That can be tiring, as well as having to confront emotionally the experience of living with the disease and giving an unvarnished assessment of what your experiences have been like.

One thing that I want to emphasize that's very important from the patient perspective is to give feedback of what is being learned in this study, as well as to see that there the knowledge is being collated, analyzed, and shared. I've had a couple of experiences with other natural history studies I've been in where I went in, I was evaluated, but no publications ever came out of the natural history study. That's a waste of both the researcher's and the patient's time, as well as a loss for the state of knowledge on the disease area.

Quality control. You're collecting a lot of data. Particularly if it's a multicenter site, you want to make sure that it's being collected consistently across different centers. Also, if it's a study that lasts for a few years, there's likely to be some turnover in personnel. You want to make sure that the new people are doing things in the same way that the old people did and also just checking data to make sure that there just wasn't a typo in entering the data.

It's very important to have a biostatistician on the team from the very beginning, not only because sometimes things like pandemics happen but also just to realize what data need to be collected. You generally want to collect data in a way so that it's structured, because if it's unstructured, getting free comments from participants is helpful, but it may be a little bit hard to analyze.

Secondly, you need to plan and budget for the data analysis, which will happen after the end of the study visits. I'm happy to report that in the dysferlinopathy COS study, we're up to, I think, 11 or 12 publications on different aspects of the study and counting. That formally ended almost 4 years ago, so really there's a bunch of stuff that's happening with the data analysis with publication of the data after the study visits end.

A lot of times you're not only going to be collecting data, but also biomaterials, blood samples, biopsies, etc. You need to think in advance about some questions. What should you collect? Who will have access? Under what circumstances, long-term custodianship? Then, of course, because some of the data, if it's not depersonalized — you need to be compliant with rules in various parts of the world.

This presentation has been informed by several of the people who have been involved in planning both the dysferlinopathy COS study as well as other natural history studies in the limb-girdle muscular dystrophy space. I want to acknowledge several people from the University of Newcastle, UK, which was the lead site for the COS study, as well as Nic Johnson at VCU and also my co-worker Laura Rufibach from the Jain Foundation, who was the lead person within our organization in the COS study. Thank you much.

DR. NEEDLEMAN: Thank you so much, Brad. Thanks for sharing your experiences and your expertise and providing such good things to think about. Lastly, I want to pass it over to Erin to tell her story and share her perspectives. Erin?

ERIN WARD: Thank you so much, Katherine, and thank you to all my fellow panelists— just a wonderful job setting the stage for this full discussion on natural history studies and especially for integrating patient and family perspectives into this talk.

I'm Erin Ward, and I'm the president and co-founder of MTM-CNM Family Connection, which is a nonprofit that looks to connect patients and families with MTM or CNM with research, resources, and relationships. What brought me to this world is, my son Will lived for 20 years with X-linked myotubular myopathy, and he's pictured here with my husband, Mark. We continue on this advocacy in his memory. You'll learn a little bit more about him in a few slides forward.

My goal is really to integrate some ideas around the caregiver experience, and also, as a patient advocacy leader, how can we really have a better understanding of the landscape of natural history in our rare diseases? I also really appreciate the panelists for also talking about co-designing natural history studies. That's a really strong passion of mine: How can we better integrate the voices of patients and families in all drug development, and specifically natural history studies, and the importance of also collaborating with multi-stakeholders?

I'll start with the story of my son, Will. Very briefly, he was born at Boston Children's Hospital. We were born at a major medical center, and although the disease was still really not well understood 20 years ago, we just happened to be at a place where we had a researcher, Dr. Alan Beggs, that was actually researching X-linked myotubular myopathy at the time. Our family was really provided an opportunity to participate in groundbreaking research. Early on, we consented for those opportunities on his behalf to learn as much as we could about the disease.

As he grew, he had a passion for being involved in these activities as well. Around the conferences that we've held, he oftentimes would be the individual that would test out first equipment that would later be used in the natural history studies and observational studies that built on clinical trials. He also had a passion for sharing his story as an advocate and partnered with the FDA on telling his story during Rare Disease Week 2 years ago, as well as patient listening sessions.

I want to be encouraging to all of you who are working in rare disease spaces. The patients, the family members, the individuals who care about us are all really raising funds and working really hard to better understand these diseases. To give you some sense of hope that even if a cure or a treatment is not developed in your individual or loved ones or you yourselves' timelines — that participating in these learnings and understandings and studies can have such incredible impact on the field at large, better understanding the disease, but also in your own personal life.

We definitely benefited from, like Brad had mentioned, connecting to researchers who probably saw more individuals with our son's condition than anyone else in the world. When we were learning new things about what he was experiencing, having those resources to reach out and really work together to better understand how to manage the disease were priceless.

Through our efforts of nonprofit, one of our big goals is to always host a conference. I put this picture here just so again those of you that are starting out with building your own foundation, building your own organizations or trying to gather your very ultra-rare communities together, that families and patients in the research community, there is this drive and this passion to come together and learn together and it is possible. A lot of our individuals live life with the use of tracheostomies, ventilators, wheelchairs, and very similar to the SMA community, they're very inspired to get together and to learn from one another.

Actually, the conference really served as a vehicle. Maybe it wasn't well articulated at the time, but when we think about it, the past 10, 15 years has really been the time for our community to get ready for the clinical trials readiness. The conference really served as a vehicle for many of these activities.

Here I list a few of those. We really have a patient-professional collaborative model where the whole entire weekend, we're learning together, and it's a model we've shared with other communities that have benefited from this. Again, it's the platform for having these early discussions, bidirectional conversations, and learnings where we actually facilitated natural history studies on site. We also had an opportunity to be thinking about early engagement with pharma and getting them to learn who our individuals were, what the challenges were, setting priorities, and this really led to our very active patient engagement and drug development.

The last 2 years, even through COVID, when we weren't able to meet in person, we continued that evolution of engagement with the FDA by hosting both a patient listening session and an externally led patient-focused drug development meeting. We did that in collaboration with Will-Cure, one of our other nonprofits in the community. I just encourage you to really be thinking about how all of this ties together in addition to natural history study of the clinical trial readiness.

Just as professionals in this space, academic researchers and industry have to be thinking about why to focus on natural history studies. It is also something that patients and family members and caregivers have to be thinking about as well. The importance of those same goals of better understanding the condition across the disease to help develop the standards of care, to understand areas that maybe were not previously understood — anytime you can de-risk your disease, it makes it more attractive for others to study. Of course, one of the things I think that's so important is although everyone is looking for that treatment for improvement, it is equally so important to make sure that we're talking and attending to the cares and needs of today.

Some of the challenges, especially in ultra-rare/rare diseases, is that the population can be small, and it can be difficult to access. There sometimes can be lack of academic researchers, or even the medical professionals seeing our patients may only see one patient at different, dispersed places in either the country or across the world. There can be sometimes lack of industry interests at first. You can also have participation and fatigue when there are competing efforts, when there are low numbers of patients.

We can also, as a community, I think, sometimes feel limited or pressured to make decisions about what our landscape will look like, because we're so concerned that if we don't respond immediately or consent to everything, people will lose interest. I think that's one of the messages that I'd like to share: that there is such power and there is such hope in the voice of the patients and families. Your perspective really matters, and it can really help to shape what it looks like collectively and collaboratively with those you're working with.

Of course, sometimes you think that there's no tangible effort, but as we heard Brad speak about and I just spoke about in our situation, there are absolutely benefits to participating even without a direct treatment. Sometimes the challenges are, of course, the financial piece that we heard about from Dr. Finkel. It is very real, especially at this time.

Tips for getting started. As previously said, better understand what actually exists. Come into the space and learn what's already been done. Definitely collect information from all stakeholders. We've also found great value in looking at our peers and other spaces like the Duchenne community, as well as the SMA community. Then you just have to be in this process of continually learning and having conversations together about how to better partner and accelerate development.

This is kind of a concept I've been working on. I was recently invited to participate in writing an article with a new issue of *Clinical Therapeutics* by Dr. Jill Maron. I was so thankful she wanted to integrate the caregiver and parent perspective of clinical trial development. This idea is around the idea that we're really a culmination of participation and growth and the idea of building on each other in a rare disease space. Our ability to come in and to collaborate with others really increases our likelihood of success. If everyone can really do what they can when they can, we really optimize the idea that more and more treatments are going to be able to cross the finish line together.

Again, take inventory of what exists. Are there registries? Are there multiple registries? How can we be collaborating more on those things earlier so it makes things more streamlined? Natural

history studies: Are they disease-specific, as we heard Dr. Finkel say, or are they driven by academic or institutions? The preclinical observational studies is where a lot of our efforts lie. Then also, quality of life is an important piece, and I think that I just want to echo what Brad had shared — is the idea of — when families and patients are going through these experiences, the ability to really draw feedback on the actual experience will only, hopefully, better the next experience for the next patient that agrees to consent to these. Of course, what's a really important topic in a lot of conferences these days around the space is real-world evidence.

These are very similar to the questions that the academic world and the industry people are talking about, but also, you have to be thinking about this from a patient, a family, and also an organizational perspective: Who owns the data, how it can be accessed, if it is portable. The other term that we're using a lot: Is it precompetitive data, where it may be part of a natural history study that an industry member has done, but is there important value and information that's known through that study that needs to maybe be extracted so that the whole disease community can learn together? Will it really stand the test of time, and how adaptable will it be in the future?

One of the examples I just highlighted, I'll go a little bit more in detail about is how we really took an opportunity with our community conferences to partner with academic industry sponsors to actually hold the collection of natural history studies on site. This took a lot of organization and communication and also aligning of expectations of what that would look like in the context of our conferences, so that we could add value to the experience and not maybe detract from other things that the family has come to benefit from at the conferences.

In the rare disease space where there are not trials going on, it was incredibly empowering for patients and families to come to our events and have an opportunity to participate and to know that they were a part of the process of collecting this really important information. It also provided a window of opportunity for us to be co-designing what that will look like leading up to the conference.

I can almost hear some of the researchers that we partnered with in my head as I share this, the excitement at the end of the weekend when they were able to, over the course of 3 or 4 days, collect data from about 25 patients that would have taken them months if not years to collect, as well as the resources. It just really is a concrete example of how accelerated collection of data can happen when you partner together with the family organizations. Of course, we identified some barriers of individuals that maybe couldn't attend the conferences and also some of the team's constructive ways to then do home visits to supplement.

Again, there are a lot of challenges when you're thinking about what the benefits and strengths are of each of these types of models of natural history studies. But just to very briefly illustrate that, it's an important conversation to have with those that are sponsoring this, whether it's academic space in just institutions or with sponsors in industry. I think the whole landscape is really shifting to a place—we want to make sure that the data that are collected can be usable across the disease spectrum and really help accelerate all pathways forward.

These are some of the things that you may want to be thinking about if you are a rare disease leader or a patient yourself that's being involved in natural history studies. What's the plan in

place for that data, like Brad said, where maybe a paper wasn't run up? What's the plan in place if the sponsor unfortunately has to end a program?

There are positive examples of that as well. We had a participation of a natural history study where, early on, a sponsor decided that their product was not going to work for our condition and did put in place that a new sponsor took on a new ownership of that data.

For those of you that are listening that are industry and academic partners, engage us early and often. Really try to complement what's already happening in the community. The key thing is open communication and aligning expectations. Are the needs being met of what you need for your product, as well as looking at the community as a whole, and are the patients' and families' needs being met? Co-designing together I think only strengthens this entire process. Also, there are new avenues for ways that families and patients can be involved in the analysis of the data to make sure that it's accurate.

In the publication of data, we add an example of retrospective chart review natural history studies. The first publication was shared with advocacy leaders. It was a great publication. We are excited for it to go to print. But we also recognize there were some key questions that we thought would be important. Then the team went back and actually extracted additional data and wrote a second paper to supplement. Again, ultimately patients do own their own data. Think about all the ways to run patients that they can also be empowered with their own data in these experiences.

Really I think it's a commitment to a process. As we heard, these things can take years and evolve over time. It's really about coming together and recalibrating if things aren't going well or if things need to be readjusted or added to. The ability to try to make it as adaptable as possible is going to withstand the test of time.

To summarize two things, I think as a patient advocate and as a caregiver, in my experience, the lessons I've learned is thinking about when you're considering natural history studies, to think about what the best way is for your community to learn as much as possible, as soon as possible, or as many as possible and for as long as possible, and in direct collaboration with patient communities. There's a lot to consider, but those are things you want to be thinking about. Also, never underestimate the power of patients and caregiver voice, and really insist on the inclusions of patients and families in also the development, the monitoring, the use, and the publication of natural history studies.

I just want to be your cheerleader for that. If conversations don't go well the first time, never hesitate to try to readdress, or if there are problems that come up, I have a lot of optimism for the role of the patient and family in making this process stronger and better. You can do it.

These are just ways that you can connect with us at our organization. Again, I just want to thank the FDA and OTAT for being a part of the conversation and for providing these educational series for our communities. Thank you.

DR. NEEDLEMAN: Thank you so much, Erin, for sharing your family's story, as well as challenges and things to consider when folks are moving along in this space. It was wonderful to hear about all of our panelists' perspectives today and learn about their unique stories.

I'm going to open up now for panel discussion. We'll bring back Dr. Bryan to answer some questions, so if all our panelists could put on their video…. We really appreciate all the questions that people have been submitting so far, both during registration and throughout the webinar today. We're going to try as hard as we can to get through several of these questions, as we have a little bit of time left. While there are probably more questions than we'll probably have time for, we'll do our best to answer as many as we can.

Natural History Studies Q&A

DR. NEEDLEMAN: I'm going to direct our first question to Dr. Bryan. Dr. Bryan, thanks so much for sharing your perspective today on natural history studies. For folks looking to start their own natural history studies, do you have any advice on when and where to go for feedback to ensure that these studies are well designed, so that our data can be eventually used to inform clinical trials? And are there specific groups within FDA that organizations could reach out to for advice?

DR. BRYAN: It's not easy to do natural history studies. It takes a lot of effort, and you do need help. I really encourage people to reach out, and reach out to as many different places as you can think of. I'll name a few. If you're working with a scientist who has a drug that they're planning on bringing to development, then you can approach the review division at the FDA for what's called an INTERACT meeting or a very early meeting. There are also meetings that the FDA has with advocacy groups where they present their proposed natural history studies. They get comments on those. So there are mechanisms at the FDA to do that.

I'll also mention, Dr. Needleman, your own organization, Orphan Products, which sponsors grants for some natural history studies, and that's a wonderful program that you've had in place for a number of years now. The NIH, the National Center of the Advancement of Translational Studies, I think, has an interest in natural history studies. There are organizations such as the National Organization of Rare Diseases, which has an interest in natural history studies. Then there are so many groups that have done natural history studies already, such as the Jain Foundation that we heard from, Dr. Williams, from Erin Ward's group. I know the folks in cystic fibrosis and Friedreich's ataxia also have well-established natural history studies.

In my experience, these people that have experience are very willing to help other groups and to learn from their experience. I encourage you to reach out. And you ask about when to do it? Early, soon, as soon as you're thinking about it. Again, as I mentioned earlier, in addition to reaching out to different organizations and individuals to get help and advice on your natural history study, I do want to again mention the FDA guidance document on natural history studies, which I think is an excellent resource as you're thinking about how to put that together.

DR. NEEDLEMAN: Thank you so much, Dr. Brian. Dr. Finkel, I'll ask you a subpart to that question. Did you happen to work with FDA to ensure that your natural history study met its intended goals? What did those interactions with the FDA look like?

DR. FINKEL: Thanks. That actually happened in different ways. In one case, there was a very impactful workshop that was cosponsored by FDA and NIH in what's called the precompetitive space. Because there were these drugs in development for spinal muscular atrophy, but we were struggling with trying to identify which of those we thought were clinically meaningful. It all fit into the topic of clinical trial readiness. That workshop I think was particularly useful to get us focused on what would be acceptable or what would be of interest to the FDA ultimately.

In addition, there were numerous discussions, as Dr. Wilson just mentioned, where we came to the FDA early, before the studies even began. I and other clinicians would come with sometimes a pharmaceutical company, a sponsor with a proposed drug study, and get some feedback on that, on the outcome measures and does the natural history support it? It helped us fine-tune things as well, because as the drug study is going on, you're still able to collect natural history data as well, so they can go in parallel. But you do need to start early. I would agree entirely. Start as soon as you can so that you have as much information, because you're not really sure in the beginning what's going to turn out to be useful and informative and what isn't. To that point, go early and go long.

DR. NEEDLEMAN: Thank you so much. Brad, you have a unique perspective, because you have participated in a natural history study, and you've also helped design one. Can you tell us a little bit more about maybe one or two learnings from both of those perspectives? Was there anything unexpected that you found or any unexpected findings or outcomes or lessons that you have?

DR. BRYAN: Let's say I think one thing particularly — I'll answer the part from the patient perspective first — is that so many patients with rare diseases are experiencing different symptoms or functional impacts but have never met another patient or really compared notes. That tends to be somewhat less common now in the era of social media, but just to see, once some of the data first got published — What is the age of onset? What is the progression? What symptoms are people — kind of how I wasn't such an oddball after all. Really, my experiences were very typical of this cohort of patients. I mean, it wasn't really a surprise. I mean logically I kind of knew that, but just seeing that data come out in a publication was kind of really impactful for me.

I think, as far as some of the lessons learned, well, I gave a lot of them in the presentation. I think one of the things that we became aware of is that there really needs to be more development of good patient-reported outcome measures. We found some functional tests that seemed to work really well, but PROs — we tested some of them, and they weren't always great. I think that needs to be kind of in keeping with FDA's focus on including the patient perspective and the patient view of what's meaningful to the patients or caregivers. Having better outcome measures in that category is something that's very important to improve.

DR. NEEDLEMAN: Thank you. Erin — and Brad — you also have a very unique perspective as both a caregiver and advocate in rare diseases. In your presentation today, you spoke about the use of community conferences to support data collection for natural history studies. How impactful was this strategy, and how did it change preparations and planning for the conferences?

MS. WARD: Yeah, it was incredibly impactful. I think the researchers would attest to the way it accelerated their ability to collect data. Also, for the researchers to see that many patients in such

a short period of time was invaluable. Also, I would say that being a part of the collaborative conference over the whole weekend experience — getting to see patients in really relaxed experiences and interact with caregivers in ways that you would maybe never get to do, like at a talent show. You also learn so much more beyond just the context of what data are being collected for a natural history study.

In terms of preparation for the conference, there was extra work added to the team, but it was definitely worth it. I would say that the best thing to do is to really start your preparations early and have clear communications and expectations. Really, I think we had very respectful researchers that didn't want to infringe on the conference in any way or make it detract from the conference, so we aligned different times that would optimize not conflicting with other things happening that families would want to participate in. I think those are some of the key things. Also, just the advanced communication with families to make it really clear what was going to be occurring, what opportunities there would be, but also making sure families felt completely comfortable not participating as well. So a lot of it had to do with communication.

DR. NEEDLEMAN: Thank you so much. That's great.

DR. WILLIAMS: I want to just mention that in our disease area, we had a conference across all genetic subtypes of limb-girdle muscular dystrophy in 2019. We also had a couple of different groups of researchers that approached us and asked if they could do some natural history testing on some of the participants at the conference now. Unfortunately, due to COVID, our 2021 conference was all virtual, so we'll need to get back to that. Yeah, our experiences are very much like Erin described.

DR. NEEDLEMAN: Right. This next question I'm going to direct to Dr. Bryan and Dr. Finkel. I hear this question quite often. Throughout your careers, I'm sure you've both observed and played a part in many studies. Based on your experience, how long do successful natural history studies typically last? Is there a minimum time period that folks should really consider in designing a study?

DR. BRYAN: I'll start here and then turn it over to Dr. Finkel. The duration of the study — and I think we're talking about prospective natural history studies here — how long do I need to follow these patients? That varies from one indication to the next. If the disease is changing rapidly, then a natural history study that follows each individual for 2 or 3 years might be sufficient, and I'd be interested to hear from Dr. Finkel about the duration for his study in type 1 spinal muscular atrophy. But if the disease is changing very slowly, then that natural history study may need to be 5 or 10 years, and certainly the ideal natural history study just follows these patients indefinitely. There are natural history studies that enroll patients and just keep following indefinitely. That's the ideal, because there's no such thing as too much data. We're always looking for more data, and it can always help us. There's this feeling as we're starting to get treatments, as Dr. Finkel talked about, you get a study that's done in a small group of patients, and you really want to know how that treatment and the efficacy might extrapolate to other patients who weren't included in the study. To have a good understanding of that depends on having more data about those other patients that aren't included in the study who may be the slower progressors. I encourage having the study as long as you have the capacity for. Dr. Finkel?

DR. FINKEL: Thank you, Dr. Bryan. I echo exactly what you said and would maybe emphasize that in a rare disease, where you have a smaller population of patients that you're going to be studying in the natural history, and in particular those conditions where there's a lot of variability, even though they may all have the same gene and the same disease, but there's a lot of variability, then that combination really requires a longer observation period to really understand what's going on.

Because when you design a clinical trial and you only have a small number of patients to draw from, necessarily, that's going to require you to be kind of creative and try to identify how to design that study effectively. The more patients you have and the more homogenous you are and the more rapid the rate of progression, then that could be the shorter observation period.

But in almost all the diseases I deal with, particularly in children, where children are growing and developing, which is very different from adults, where you're dealing with everyone's finished their development, we think — I know 35 is the new 25, but beyond that, children — you're dealing with all these other factors of growth and development, in addition to the underlying disease process.

I agree entirely. I think, in my experience, 3 years of a natural history study is kind of the minimum. In some cases, we've learned that you really need 5 years, maybe even 10 years, to really capture the full population. Going back to what Dr. Bryan said, I think now some of the pharmaceutical companies are getting kind of creative to say, "We're going to include in our study a pretty broad range of patients, because we want to get safety data on a broad population. But then we're going to narrow our focus on what the primary efficacy proof to maybe just children, let's say, between 2 and 10 years of age or this or that," because you think you're most likely to be able to show a response to the drug, an efficacy response.

So there are two objectives here. One is, I think, trying to identify, does your drug work, and is it safe? The natural history studies help you identify both of those.

DR. NEEDLEMAN: Great. Thank you so much for that. This next question is really coming at it from a patient perspective, so I'm going to start with Erin, but I would also like to hear from Brad. Erin, did you and your son Will ever run into the situation where you had to choose between a natural history study or where you had to decline to participate in a particular study? Could you share how you and Will came to those decisions?

MS. WARD: At the time we were involved in natural history studies, it was really before product-driven natural history studies. So we were in a place where we did have multiple different natural history observational studies that we participated in, but at that time it didn't have to be a choice. I think that a different kind of choice was, how many did we want to participate in and how much time and effort and so forth we were — because of our location, because of our accessibility through the conferences, we were in a place that we did everything we possibly could.

I would say that things I would be encouraging individuals to be thinking about — the depth and how broad the studies are. Are the individuals sponsoring the studies thinking about ways that data can be preserved long-term for the community, how accessible that data will be in the long run? I think there are definitely questions over experience and working with other families that I

think are important for people to be thinking about if they're in a situation where choices have to be made.

DR. NEEDLEMAN: Thank you. Brad, similar question for you: Did you have that experience as well?

DR. WILLIAMS: Well, I didn't, and I'm going to say that unfortunately I didn't, because if you have so many studies you have to pick and choose, that means that there's a whole lot happening in your disease area. That wasn't really the case, although I have been in I guess four different natural history studies. Most of them just involved a single visit, so it wasn't really a longitudinal thing.

Where things get tricky is when you're starting to have clinical trials in your disease area, and if the treatment actually affects the course of the disease, that's going to mess up the natural history data, and some sort of higher-level scheduling for that is necessary. That hasn't necessarily happened in my disease yet, but I know in SMA and DMD, that is starting to be a major issue.

DR. NEEDLEMAN: Thank you. We know that the pandemic has affected many aspects of health care. Obviously, telehealth has been utilized more and more these days. Dr. Bryan, I wanted to ask you a question about technology. Obviously, technology has made it much easier to conduct natural history studies over time. We received a very interesting question from one of the registrants on this topic. They ask, "Can electronic health records be used as natural history study data and then serve as a virtual control arm for a clinical trial?"

DR. BRYAN: There's not much good about this pandemic, but the move towards telemedicine and the move towards remote methods to capture data about patients really does facilitate clinical trials — very helpful in clinical trials for rare diseases, where you need to try to enroll the few patients sometimes worldwide. So applying that in natural history studies I think will be very important. That's just getting started, really, I think. I hope the natural history studies that are starting now and starting within the last year are really incorporating into their protocol design telemedicine and remote capture of data.

The electronic medical record has the disadvantage that it tends to have all the problems with it with medical practice, which is that doctors in medical practice often don't do things at regular intervals. They don't always test everything on every visit. They tend to be not quite as rigorous in their data collection as is done in a natural history protocol or is done in a clinical trial. The advantage of a rigorous natural history study is that it gathers data in the sort of systematic way that is going to be done in a clinical trial so that you can see what the data is going to behave like in a clinical trial. In clinical practice, that isn't what usually happens. In most cases, the electronic medical record from clinical practice doesn't serve us very well for natural history.

DR. NEEDLEMAN: Thank you.

DR. WILLIAMS: Katherine, if I could just add one more wrinkle to what Dr. Bryan said, one thing that's important if you're assessing medical records is to have a diagnostic code specific to the condition of interest. It was only recently that muscular dystrophies were even subdivided into codes. DMD got one a few years ago, and just at the beginning of this month there were ICD-10 codes implemented for several specific subtypes of limb-girdle muscular dystrophy. But for a lot

of rare diseases, there aren't ICD-10 codes yet, so it's going to be hard to figure out who actually has the disease just from perusing medical records.

DR. NEEDLEMAN: Thank you. Dr. Finkel, you had a question?

DR. FINKEL: I just wanted to add another comment. Something we haven't really focused on so much are registries run by patient advocacy groups. There's a lot of value to that, but I think we have to realize also the limitations, because these are typically self-reported by parents of patients. The data are often not curated. It raises a lot of questions as to the validity of the data.

On the other hand, I think if done properly, sometimes if the patient or parent can submit some supporting data that can be reviewed, that can be quite useful. It's not quite taking it from the EMR, the electronic medical record, but it is more what I would call self-reporting, a little bit different from coming into the clinic, having a very structured protocol, being evaluated by the physician, by the clinical evaluator on a well-designed protocol.

A blended model, I think, has also been useful in some cases where you collect maybe data on a very broad population of patients through these patient advocacy-generated registries. That may be just top-level data, not very granular, but you blend that with the more detailed and more precise data that are gathered through clinicians at clinic visits.

DR. NEEDLEMAN: Thanks. One of our questions we got today is, "Does participation in a natural history study have an impact on the participants seeking other medical treatments? For example, if they're in a natural history study, could they then participate in a clinical trial for a drug?" Dr. Finkel or Brad, would you like to field this one?

DR. FINKEL: I'll start. So the answer is yes. I mean, we have patients that come in and out of natural history studies. Because if you're in a clinical trial, you may be assigned to a placebo or a control arm. You're not necessarily getting an active intervention. So we have patients that are in a natural history, they go into a clinical trial, and we welcome them back when they're done with their clinical trial. I think there are those opportunities.

I think that maybe another aspect to your question is patients often come into a natural history studies with the expectation that it will lead to an opportunity to get into a clinical trial, to get access to a drug that is in development. I think we have to carefully manage those expectations, because there's no guarantee, of course, that by participating in a natural history study — that it will gain entry.

On the other hand, you are more likely to be selected or to be offered an opportunity to be in an intervention trial if you're in one of these natural history studies. You're known to the investigators who are then going to be participating in the clinical trial.

DR. NEEDLEMAN: Thanks. I know we're pretty much out of time, but this theme came up a lot today during the Q&As. Wilson, could you please expand more on what circumstances a natural history study can serve as an external control for a clinical trial?

DR. BRYAN: Well, so the natural history studies are most useful as an external control when the disease is predictable. It's homogenous. When we used Dr. Finkel's SMA natural history study as a control, we used the fact that these infants untreated reliably are not going to be able to sit up independently for 30 seconds. It just doesn't happen. So in that sense, they're homogenous, and you can use that as an outcome.

When the disease is very heterogeneous, and particularly if it's a rare disease, then it's very difficult to know if the patients in the study are similar to the patients in the natural history database. This was a problem that we really ran into with the adrenoleukodystrophy/BLA. When we looked at the natural history of the disease and we looked at the patients who were in the studies, we had a great deal of difficulty due to the heterogeneity of the disease in having confidence that the natural history patients were truly similar to the patients in the clinical trial. So it's going to vary from one disease to the next, and you don't know that until you do the natural history study and gather that information.

DR. FINKEL: If I could amplify, I know we're running out of time, but sitting on the other side of the table at the FDA, I think one of the comments that comes up is, "The standard of care in a natural history study may vary from the standard of care in a clinical trial, so can you convince us that those patients in the natural history study really got the same basic care?" I think that's a really important point to keep in mind. I want to emphasize, in a natural history study you want to make sure that these patients are getting the best possible care that's available at that time. It has to be contemporaneous to the clinical trial.

I think the second point is, if you're going to use an external control compared to group, you're almost raising the bar to a point where that drug has to really have a clear, almost transformative effect, as you heard from Dr. Bryan, and not just a couple of points on the scale. It has to have some major impact.

DR. NEEDLEMAN: Thank you so much, and thank you to all of our panelists for answering these questions today and sharing your perspectives and experiences with us. I'm going to pass it back over to Anne for some closing remarks. Thanks, Anne.

Closing

DR. ROWZEE: Thanks again to Kathy for volunteering to be our moderator today and to all of our panelists. The perspectives we heard today were just invaluable. I think it's just wonderful to hear from such a broad array of folks and the folks that have been on both sides of the table. Thank you all again.

Just going to run through some quick final slides and resources for you all. Thanks, everyone, for attending today, for your feedback and questions both during registration and during the webinar this afternoon. Please stay up to date with our latest news and events. You can visit our website. You can follow us on Twitter. You can also sign up for the "What's New at CBER" listserv.

I just wanted to make folks aware of some upcoming events. Please register for our Patient-Focused Drug Development virtual listening meeting. OTAT is hosting this on Tuesday, November 15. In this meeting, we're asking our stakeholders to share their perspectives on many aspects of gene therapy treatment. Please visit our registration page to reserve your spot to speak at this meeting.

The OTAT town hall. Our next town hall meeting for our manufacturing stakeholders is going to be on Wednesday, December 7, and the focus at that town hall is going to be cell therapy chemistry, manufacturing, and controls. Details are on our website there.

Also, we're hosting a webinar for practitioners on FDA's oversight of regenerative medicine products. That's coming up on November 17. Lots of events for everyone to tune in on.

Just one final plug for you to use the hashtag #RegenMedEd on social media to share your thoughts on these events. Let us know what information and resources you're interested in setting from OTAT at future events. We look forward to our continued work together to advance regenerative medicine therapy. Thank you again to our panelists, to our moderator, and have a great day everyone. Bye-bye now.

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