FDA CBER OTP Patient Engagement Workshop
Clinical Trials: The Patient Experience

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Contents

Welcome

DR. ANNE ROWZEE: Hello, everyone. Thank you all for joining us for our third annual patient engagement workshop, Clinical Trials: The Patient Experience. Today's workshop is hosted by the Office of Therapeutic Products [OTP], formerly known as the Office of Tissues and Advanced Therapies within the Center for Biologics Evaluation and Research (CBER) at the U.S. Food and Drug Administration (FDA).

My name is Anne Rowzee, and I'm an associate director for policy at OTP. I'll also be your host for today's event.

Some of you may have joined us in 2021 or 2022 for our previous workshops. And if that's you, welcome back. Thank you for being here today. And if today is your first time attending one of our workshops, we welcome you and are very happy that you've taken the time to join us today.

Our goal is to bring together our stakeholders to hear patient and caregiver perspectives on gene therapy clinical trials and how the FDA works to ensure that these trials are as safe as possible. We've designed this workshop to be both educational and interactive, with the hope that we'll all leave with a bit more knowledge and understanding of gene therapy clinical trials, what they're like, what the risks and benefits are, and the role they play in the development of gene therapy products.

Before we get started, I'd like to offer a sincere thank-you to everyone who helped make today's events possible, including my colleagues at the FDA's Office of Patient Affairs, who helped connect us with patient advocates who have volunteered to share their stories with you today. And today's speakers and panelists, thank you so much for spending time preparing for today's workshop and for being here to share your stories. Next slide, please. Great.

We have an exciting agenda planned today. We'll kick off the workshop with a brief introduction to gene therapy development process and what differentiates this process from what we think of as traditional drug development. Then we'll move into a panel discussion featuring rare disease patients and caregivers who are working towards or have direct experience within these trials. We'll finish up our workshop today with a Q&A session featuring some questions that were submitted during registration, and we'll also have some time for live questions from the audience. Next slide, please. Great.

I would 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 in Zoom. As I mentioned earlier, we'll have some time at end of the workshop for questions.

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

We also understand that people may have questions about the status of specific investigational products or drug applications. However, there are laws that limit the information we at the FDA can provide about investigational products. We very much appreciate questions and comments, and we'll do our best to address as many as we can.

Finally, just one last note: Please use the chat box within your Zoom window if you want to share a general comment or if you are experiencing technical difficulties. Someone will assist you. Next slide, please.

I'd also like to mention that today's workshop is part of a series of virtual events we call RegenMedEd. The RegenMedEd event series includes educational webinars and workshops like today's, where we invite patients, caregivers, and advocates to come and learn about topics related to regenerative medicine and therapies, and, like today's workshop, to come and share their stories with our stakeholders.

Our previous RegenMedEd events can be found on the FDA's website, and I also invite you to use the hashtag #RegenMedEd on your social media channels. Please use it if you want to share your thoughts on today's workshop, if you want to connect with other attendees, or even if there is a RegenMedEd topic that you'd like to learn more about. We welcome those recommendations. Next slide, please.

Let's go ahead and get started.

Gene Therapy Clinical Trials

Our first session today is an overview of gene therapy clinical trials. Gene therapy is an exciting and promising field, but these products also come with their own set of unique circumstances and challenges that we at OTP seek to address and monitor through our role in the product development process. I'm going to turn it over to my colleague, Dr. Rosa Sherafat, to tell us more. Rosa, if you want to turn on your video and unmute, we really thank you for joining us today and can't wait to hear your presentation. Thanks.

DR. ROSA SHERAFAT: Thank you, Anne, and good morning, everyone. I am Dr. Rosa Sherafat. I'm the lead physician at the Office of Therapeutic Products, or OTP. Welcome to our annual patient engagement and regenerative medicine workshop. We are very glad that you have joined us today, and as Anne mentioned, our goal today is to talk about gene therapy clinical trials and hear your unique stories, as patients, caregivers, and advocates, about your experience in these trials.

To get us started, I would like to give you an overview of what gene therapy is, how clinical trials for gene therapies are different from other clinical trials, and why your participation as patients and advocates is so important for the development of new and life-changing therapies. Next slide, please.

Gene therapy is a rapidly evolving field that is unlocking new ways to treat difficult medical problems, such as vision loss, cancers, and other serious and rare diseases. Many of you are attending today's workshop because you or a loved one have some knowledge about gene therapy. But for those who are new to the field, let me provide a brief explanation of how gene therapy works.

In short, gene therapy is the use of DNA to treat or prevent a medical problem. Every cell [in your body] has a copy of your DNA. Genes are the specific sections of that DNA, and different cells can express or use different combinations of genes, depending on the role of that particular cell in the body. Gene therapy products use genes to modify some of those cells to help treat a medical problem.

What makes gene therapy so exciting is the possibility to address serious medical conditions that have few or no other treatments available. For example, we know that about 80 percent of rare diseases are caused by a single gene defect. So how can gene therapies help?

If a particular gene is causing a medical problem, then scientists can use gene therapy to either turn off the faulty gene, repair that gene so that it no longer causes a problem, or replace the faulty gene with a new gene that does not cause the problem. Scientists can also add a new gene to help the body fight or treat a disease.

There are multiple ways [to introduce] genetic materials into the body. For example, physicians or researchers can take cells from a patient and send them to a lab. Then the cells are modified in specialized facilities, and once the genetic material has been modified, the cells can be reintroduced back into the patient, usually via an IV line. Other gene therapies use a modified virus to deliver pieces of DNA to the body. And in some cases, surgery may be necessary so that the product can reach the right cells inside the body. Next slide, please.

As new therapies are developed and tested, regulatory oversight is key to ensure that these new gene therapy products are safe and effective for patients. This is where OTP and the FDA come in. The FDA oversees these products in the preclinical development stage and throughout the clinical trial process to ensure that participants are protected. The FDA also works with researchers and scientists to provide guidance on clinical trial design and new manufacturing practices, as well as to verify the integrity of trial data. The FDA then performs a rigorous review of the available data to ensure that regulatory decisions are based on scientific evidence. The FDA monitors products before they are approved and continues to monitor them after the approval to ensure safety and quality through their entire life cycle.

Another key role the FDA plays in the field of gene therapy is to advance the state of the science by providing guidance and education to product developers and other stakeholders.

And finally, stakeholders and patient engagement are a critical aspect of our work. We consistently and proactively communicate with patients, caregivers, and advocates to improve our understanding of patient needs, and we work with researchers and other regenerative medicine product developers to make sure that products are designed to meet those patient needs. Next slide, please.

As you can see, there are many ways that patients can get involved in gene therapy research and development, including patient registries; listening sessions; natural history studies, which were the focus of last year's workshop, as well as our October webinar; and events such as today's

workshop, and, of course, clinical trials, which are the focus of our discussions for today. Next slide, please.

So, let's see how clinical trials fit within the drug development life cycle. The FDA is involved in each stage of the process, from early on in development throughout the various clinical trial phases and after products are approved and being used by patients. Before a product is allowed to be tested in people, it is developed and tested in lab-based studies and in animal studies, which are collectively referred to as preclinical studies.

The data from these studies are assessed by the FDA to determine if the product is safe to be tested in humans. If the FDA decides that the product is safe for human testing, then the product goes through a series of well-controlled clinical studies to establish whether it is safe for use in people and that the benefits outweigh the risks for the patients.

Clinical trials traditionally follow a structure that begins with early, small-scale exploratory studies to late-stage large studies used to confirm treatment benefits and evaluate side effects. Each phase of clinical testing helps researchers answer different questions, and the findings from one phase help guide the design of the clinical trials in the next phase.

So, phase 1 of clinical trials tests the new product in a small group of healthy adults for the first time. The goal of phase 1 is to assess safety. Phase 2 clinical trials test the treatment in a larger group of people who have the medical condition. The purpose of phase 2 is to determine how effective the treatment is, as well as to continue to assess its safety. Phase 3 trials assess safety and effectiveness on much larger groups of people who have the condition and over a longer period of time, to verify the treatment benefits of the product and also to monitor for side effects.

And after the product's been approved by the FDA, phase 4 trials can provide additional information on the treatment's risks and benefits in a broader population of patients.

However, there are some key differences between gene therapies and other products. And because of that, certain aspects of the clinical development process also need to be different for gene therapy products. Next slide, please.

Let's take a look at some important characteristics of gene therapies that set them apart from other medical products. First, gene therapy products require the use of new technologies that are still evolving, which can present certain

challenges. For example, if a product is manufactured using a new technique, it may be difficult to manufacture large amounts quickly, because the technology is not widely available yet.

Second, gene therapies often require surgery or other invasive procedures to deliver the DNA to the right cells in the body — for example, using a catheter to reach a particular region inside the brain — and these procedures usually involve considerable risks and may require general anesthesia, which also has added risks of its own.

Third, the effect of gene therapy, good or bad, can last very long or could evolve over time. Although we are still learning about the long-term effect of these products, scientists believe that gene therapy can offer long-term or even permanent treatment benefits. However, any problem caused by the treatment may also be long-lasting and could persist even after the product itself is no longer present in the body.

And finally, there are some possible risks connected to gene therapy specifically. For example, activity of the gene can be difficult to control after it is inside the cells, or it could cause a mutation in another gene, which may or may not then be transmitted to the patient's children. It's also common for the body's defenses to reject some of the components of the treatment, such as the modified virus that some gene therapies use to deliver the genetic material into the body.

So, let's see what these differences mean for the clinical development of gene therapy products. Next slide, please.

For gene therapy products, the early-phase trials are still exploratory, but they are designed to obtain data not only on safety but also on preliminary efficacy of the treatment. Unlike the standard phase 1 studies, early-phase trials for gene therapies do not typically involve healthy volunteers. Because of the possibility of permanent effects from gene therapy products and other risks linked to invasive procedures and uncontrolled DNA activity, trial participants instead are people who have the medical condition that the treatment is designed for, which can also include children.

For some medical conditions, a gene therapy treatment may have no possibility of benefit in later stages of the disease. So early-phase participants may be patients with less severe rather than more severe forms of the disease. And in the case of rare diseases, clinical trials include much smaller groups of people due to a smaller patient population, which may make it more difficult to confirm whether the product is effective.

To help manage unforeseen risks, the first patients receive a small dose and are monitored closely before the next group of patients receive a slightly larger dose, and so on, which helps limit the harm of any potential side effects.

And because of the complexity of the technologies involved, there are added challenges for a gene therapy clinical trial. For example, the trial often can only be conducted at a small number of specified clinical sites.

Estimating an effective dose can also be difficult and depend on many changing factors, such as how well the DNA is packaged during manufacturing, how easy it is to reach the region of the body where the treatment is needed, and how well the correct cells are able to take in the DNA being delivered.

And finally, the body's defenses typically react to certain components, such as the modified virus used to deliver the DNA to the cells, which means that the patient can only receive one dose. This is because after the first contact, the body's defense learns to recognize and fight against the modified virus. So, any new doses after the first one would get destroyed before reaching the right cells to deliver the DNA.

These unique properties of gene therapy products also affect how scientists at the FDA monitor them after they are approved. For example, many gene therapies require long-term monitoring for up to 15 years to identify any delayed side effects. Next slide, please.

Despite some of these challenges to develop these products, we are seeing incredible progress in the field of gene therapy. OTP is currently overseeing over a thousand investigational gene therapy products in clinical trials. Gene therapies to treat diseases that are caused by single gene defects could mean important improvements in survival and quality of life for patients. And while there's still much to be learned about rare diseases, we do know that about 80 percent of rare diseases are caused by a single gene defect.

There are currently 12 FDA-approved gene therapies, 4 of which are for single-gene disorders, and 2 of these 4 products were approved just last year. And we anticipate many more approvals in the coming years.

But we cannot hope to cure and treat difficult diseases without your help. Patients, patient advocates, and caregivers play such an important role in advancing gene therapies. Patients and their families are often the experts in their disease. They possess invaluable knowledge about the lived experience of

these conditions, and OTP is committed to finding ways to work together to understand patient needs and make them a priority. Next slide, please.

And this is exactly why we are here today. We want to provide an opportunity for patients, caregivers, and advocates to share their experiences, so that we can foster the design of clinical trials that incorporate patient priorities and support the development of new gene therapies that meet patient needs. Today's panelists will speak about their experiences and share perspectives on the following topics: What is it like to find and participate in a gene therapy clinical trial as a patient or as a patient's caregiver? What are the risks and benefits of participating in a gene therapy clinical trial? What are your hopes and expectations for the future of gene therapy? And gene therapy has much to offer, and OTP believes that patients will be the driving force for these scientific advancements. Next slide, please.

So lastly, to stay in touch with CBER, I encourage you to use the resources listed on this slide. For the latest information on past and upcoming events, you can visit our website, or you can follow us on Twitter. And thank you all for being here today. I'd like to turn it back over to Anne. Thank you.

DR. ROWZEE: Thanks. Thank you so much, Rosa, for that overview of gene therapy clinical development. We've received a lot of great questions from our registrants, and we're going to try to get to a few of those with Rosa right now.

So, first question: Patients are excited about potential gene therapy treatments but often feel that the slow pace of regulatory review and approval can delay these breakthrough therapies. Are there any ways for patients to get involved to help safely speed up the development process or any other parts of the process to get a gene-therapy product to market?

DR. SHERAFAT: Thank you, Anne. That's an excellent question. So here at the FDA, we are all committed to facilitating the development of safe and effective therapies for the patient. So, from the regulatory perspective, there are four FDA programs that are intended to facilitate and expedite development and review of new products to address unmet medical need in the treatment of serious and life-threatening conditions.

Patients can contribute by participating and remaining in the clinical trials. In the clinical development of gene therapy products, especially in the rare disease space, data collected from each and every individual patient counts. And both the investigators and sponsors and us, on the review team, are aware of how valuable these patients' resources are.

So, when a gene therapy clinical trial is designed, we all hope that the product would demonstrate a robust treatment effect. However, in this rare disease space, in which there exists a huge unmet medical need, a moderate or even a modest treatment effect also counts. So, the gold standard of clinical trial design is to be able to detect such modest treatment effects in a randomized concurrent, controlled, and double-blind clinical trial, to the extent that it is possible.

And therefore, even in the early stages of clinical development, such as first-in-human clinical trials, sponsors are encouraged to design randomized concurrent, controlled trials to be able to detect these small or modest effects, even in a, like, small phase 1 clinical trial.

So, keeping in mind that in these early stages of clinical development, the risks and benefits of the treatment are unknown. And, if an early efficacy signal is detected, patients in the trial can be crossed over but kept in the clinical trial and continue for the duration of the trial, so we can collect the safety and efficacy data adequately. Back to you.

DR. ROWZEE: Thank you so much. Are there other ways for patients to make their voice heard during the development process? So, thinking not just for, you know, the FDA's ears, but maybe also for people who are developing products as well, how can patients, like you said, make their voice heard throughout the process?

DR. SHERAFAT: Sure. So basically, the regulatory standard is to develop products that are safe and effective and have a clinically meaningful benefit or impact on how patients feel and function. Therefore, we really welcome partnership with our patients and caregivers who participate in the clinical trials. And we would like to incorporate these patients' voice in the design and conduct of the clinical trials.

So, patients can participate in patient-focused drug development programs that may be organized and led either by the FDA or by the patient caregivers and advocates. And there are other FDA patient engagement programs, such as patient listening sessions or FDA patient-representative programs, through which the patients have the opportunity to become special government employees, or SGEs, and engage with the scientific members or other experts on the FDA advisory committee or other panels of experts, or even consult with the review divisions.

DR. ROWZEE: So, we've heard from your presentation that gene therapies often have long-lasting, sometimes irreversible effects on patients. I think you

touched on this a bit in the presentation, but if we could circle back to how the FDA evaluates safety of the trials, as well as patient outcomes, given these long-lasting effects.

DR. SHERAFAT: Sure. So, obviously, during the clinical trial, safety of the product is very closely monitored. And again, the regulations require that sponsors and investigators promptly report any safety signals to the regulators throughout the duration of the study.

Also, the sponsors are supposed to submit annual reports of the ongoing clinical trials, including all the adverse events and serious adverse events, and these reports are being submitted both to the FDA and to the institutional review boards, or IRBs, of the investigational sites [where] the studies are being conducted.

After the study is completed, the sponsors submit the final study report to the FDA and include all the safety and efficacy data and findings of the trial. And depending on the type of the gene therapy product, additional long-term follow-up, observational studies, are sometimes required and sometimes are just recommended, depending on the type of the product.

So, throughout these long-term follow-up studies, the investigators continue to monitor the clinical trial participants to detect any delayed safety signals and also to assess the durability of the treatment effects of the product.

DR. ROWZEE: Okay, great. We're going to switch gears a little bit and get back to another one of our registrant questions. And this one's about natural history studies. As you mentioned, it was the subject of our previous workshop last year and another one of our webinars, so I encourage folks to go back and check those out, if they get a chance. But the question here is about the connection between natural history studies and clinical trials. So, can you tell us a little bit about how data from natural history studies can be used in the development of clinical trials to test products? How can patients know that their contributions to a natural history study will be valuable in advancing treatments and therapies, and generally advancing the state of the science for their particular disease or condition?

DR. SHERAFAT: Another great question. Thank you. So, the knowledge of the natural history of rare diseases is so critical in developing appropriate clinical trials and really guides the sponsors on the design and also on the duration of the studies, as well as in selection of the outcomes and the timelines of assessment of those study outcomes, so both in the design and conduct of the gene therapy clinical trials.

Also, in some certain circumstances, not always, but sometimes, if the product has a large treatment effect and the disease is a homogeneous disease, meaning that we know that there is not a significant amount of variability in the course of the disease amongst different patients, and the course of the disease is, like, well established and well understood, then the data from natural history studies can sometimes be used as an external control comparator arm for the future clinical trials of that rare disease.

DR. ROWZEE: I think we have time for just one more question. Maybe we'll sweep this one in really quick. So, you know, we've heard throughout the course of your presentation and some of the questions in our conversation here that the FDA oversees trials to ensure they're safe for patients involved in the studies. Are there some ways that the FDA is working to ensure a diverse patient population is represented in trials?

DR. SHERAFAT: Yeah. So, the FDA has issued several sets of recommendations to try to improve the clinical trial's diversity. These address a range of topics, including the collection and analysis of racial, ethnic data, and measures to enhance the diversity in clinical trials enrollment and broadening the eligibility criteria when scientifically appropriate. And sponsors are encouraged to develop a plan that outlines the operational measures that will be implemented to ensure diverse clinical trial participation and improve generating the evidence regarding safety and effectiveness across all the entire population.

So, these measures could include — but of course are not limited to — offering financial reimbursements for expenses that are incurred during participation, such as travel and lodging, or providing language access, or participating or partnering with a community-based organization to provide support for the participants of the clinical trials.

DR. ROWZEE: Great. Well, I just want to take another opportunity to thank you, once again, Dr. Sherafat, Rosa, for sharing your presentation and insight today. And you've really set the stage nicely for our panel presentations and the upcoming discussion.

So, we're going to move now into our first panel. During today's discussion, we'll hear from patients and caregivers about their experiences and perspective on gene therapy clinical trials. Our panelists today have participated in the rare disease drug development space and in the drug development process in one way or another, and sometimes have played

multiple roles. We're very appreciative that they're here today to share more with us.

It's also my great pleasure to introduce and welcome my colleague Karen Jackler, who will moderate today's panel discussions. Karen is the patient engagement program manager for CBER at the FDA, and Karen and I work very closely together, and we've done so over the past several years in CBER, and I very much appreciate her willingness to join us for such an important discussion. Karen, thanks so much, and I'm going to pass it over to you to get us started.

Panel Discussion – Perspectives from Patients and Caregivers (Part 1)

MS. KAREN JACKLER: Thanks, Anne, and thank you, Rosa, and welcome, everyone. As Anne mentioned, my name is Karen Jackler. I'm the patient engagement program manager at the Center for Biologics Evaluation and Research, also known as CBER, here at the Food and Drug Administration.

I'm excited to be the moderator for our panel discussion today. We know today's panelists will be able to share some important insights about their experiences with rare diseases in clinical trials and will shed light on many of the important factors and decisions in order to seek out and participate in these types of clinical research. I must say, we have an exciting two-part panel discussion planned for you all.

I'd like to take a moment to introduce the panelists who will be participating in the first part of today's panel discussions.

Our first panelist is Bobby Wiseman. Bobby has had hemophilia his entire life. In 2018, Bobby participated in a gene therapy clinical trial. In fact, he was actually the first patient in that trial to receive the experimental gene therapy treatment. He is here today to tell us about his journey and his story. Bobby, thanks so much for being here today.

Our next panelist for this discussion will be Suzette James. Suzette has four children, two of whom are living with CLN2 [atypical neuronal ceroid lipofuscinosis type 2] late-onset or atypical Batten disease. Suzette is on the board of the directors for the Batten Disease Support and Research Association and is a strong advocate for the CLN2/Batten disease community. And Suzette, thank you for being here today.

After we hear from Bobby and Suzette, we'll take a short break and then introduce our remaining panelists. I want to encourage everyone in the audience to submit their questions for our panelists in the Q&A box on Zoom. We'll have some time at the end of the presentations for our discussion. For general comments, please add those to the chat box on Zoom. And for now, I'll pass it over to Bobby to tell his story. Bobby?

MR. BOBBY WISEMAN: Well, good morning, good morning, afternoon, one and all. I would be remiss if I just jumped into my presentation without honoring [people] I need to honor first. So, you all have to forgive me. That is, first, I have to honor my grandparents, who birthed my mother, who birthed me. That's how I'm still here today. And I have to honor the Big Man/Big Lady upstairs for me being able to do what I still do.

Secondarily — it's grammatically incorrect — it's interesting to me that I get to go first, you know, as a patient, after a doctor. And with my medical experience, the clinicians that have made the most impact in my life have been female clinicians. Let me just go right on there. And so, I have never called my doctors by their full given name. So, like my pediatrician — she has a full name — I just call her Dr. K. So, Dr. Rosa, you're now elevated into that category.

No, I did not prepare a slide deck, because I just didn't, because, for some of the things to talk about my experiences, getting to where I'm at in gene therapy, could not be captured in a slide deck, for me. That's number one. Number two, but this is what captures part of it, and then I will go more in depth.

I looked up the meaning of the word *community* in the midst of Dr. Rosa's presentation, because something hit me. *Community* is defined as a familiar thread used to bring people together to advocate and support each other in the fight to overcome threats. As human beings, we need a sense of belonging, and that sense of belonging is what connects us to the many relationships we developed.

It's interesting to me that my three, four other panelists, we all are community. We're community in the sense of how we've been able to come together through adversity, trials, good and bad days. We've been able to come together because we've navigated the systems, either for our own self or ones we love, in order to get gene therapies. So that's part one of my framework.

Part two: my history. Now, this is the fun part. I'm a person effectively living with hemophilia B. Technically, on paperwork, I'm listed as hemophilia B severe. I'm a person effectively living with HIV undetectable since 2015. I'm a person effectively living with cleared hepatitis C through a prior clinical trial. I'm a person effectively living through and with sciatic and bursitis issues that — and all the other issues and -itis and things that tend to happen after a certain age. I'm a person effectively living with mental health disorder. I'm a person who has been kind of like the driver on a choo-choo train going down a tunnel trying to figure something out. Yes, as it was stated in the bio, beginning part, I'm the first person with hemophilia B to have gone on a current product that is now commercialized. Yes, me, little old fluffy 51 1/2-year-old me.

That was not an easy decision to make. For those who do not understand hemophilia and/or other related bleeding disorders, there are moments of sheer pain and sheer joy with it, that medications were developed in order to enhance, improve, and uplift my life.

However, there were challenges along the way. There were challenges in terms of quality of life, challenges in terms of education, challenges in terms of work. However, despite those challenges, I made it to the age of 40 with no quote-unquote "major challenges." Okay. I could still walk effectively, could work, all those things.

Well, in about — what year was it? — early 2000s, there was scuttlebutt going on that we hear gene therapy is coming to the hemophilia community. Now mind you, I've been hearing about gene therapy in the hemophilia community since the dawn of time. I'm 51 1/2. So, I was kind of like, yeah, whatever. It'll happen when it does.

Well, there was a trial that came available, so I did the regular thing: submitted the lab work for it, etc., etc. Got denied. Now, yes, there was a very small statement, but it was actually a lot of work that went into it and then to get the denial, so a lot of research that took place. There was a lot of phone calls that took place, a lot of back-and-forth to the lab, and hopes getting elevated on my end, and then to literally have the rug pulled out from underneath me.

Go-round number two, found out about another company or two or three, and my doctor and I said, "You know what? We're not going to look into this anymore." We said we'd just wait and go on with life, because there were

hemophilia products that were coming out at the time that would give better efficacy at that time.

So, we did that. We did the okey-doke, you know, trotting along, doing what I do. And on one of the days, I was at a national meeting for the hemophilia/bleeding disorders community. There was a display hall with vendors. Those of you who have chronic disorders and different medical conditions, you know how our conferences go — well, I know bleeding disorders. There's the hall where all the vendors got their stuff, so you can go talk to them and find out the information.

I did that. There was this one homey-looking table that had nothing on it, just the company sign, and the nice person sitting behind the desk. Me, being who I am, I just start talking to them. The family calls me the Geico dad and mom. Yes, they do, because I will talk to just about anybody, even if I'm going through the parking lot: "Hey, how are you doing?" Spark conversation. That builds community. We got to talking. Gave them a little 4-1-1: that's how this particular conference goes. We started a relationship, a friendship.

Lo and behold, what I come to find out, that particular person was the rep for a company that was making a gene therapy product. Go figure. Coincidence? Maybe, maybe not. Okay. That's one nugget of information about how people are coming together, just by talking, just by sharing experiences.

Point number two, I'm getting there. I'm going to stay within the 30 minutes, too. Suzette and I got the pleasure of meeting on one of our prep calls. Yes, there are prep calls before doing these things. And there was a term used, *infusion*. I'm like, wait a minute. What other — infusion, that's a normative term in the bleeding disorders community. So, there was education, even in that brief moment. There was connection in that even brief moment and a greater understanding for me, as an individual, of the true points of connection that we have in community around communities coming together from the stance of advocacy, education, support.

Now, we're trotting along, getting ready, gene therapy time. The decision was not easy, at all. Okay? There was reading volumes of paperwork. Did I read it all? No, I sure did not, because after a while, it's just a whole lot. Yet where the hardest decisions were was in the conversations with family of what will this mean, because my family knew, okay, if I had a bleeding episode because of the hemophilia, we knew what to do.

Yet with this gene therapy piece, there were many questions we had. Well, woulda, coulda, shoulda. What's going to happen with this? It got to the point

we had several running jokes around it. Would I grow a fifth finger, a sixth toe, another foot? We — that's the way we had to process it, because it was so unknown.

What many of you may not know, the bleeding disorders community, because of blood products back in the day, many in our community were co-infected with both HIV and hepatitis C. So, in our community, we have some trepidation about some things. We've gotten much better.

So, when the gene therapy option became available, it was one of those, okay, you're about to build a whole new coal mine. We don't know what's going to happen. Okay. Let me be very clear on that, that it was one of those times of stepping out in true faith. Granddaddy — that's my mama's father, my granddaddy, instilled in all of us to do that which is just, right, and honest. And he did not just say that as fluff. That was the reality of day-to-day. If Mama had like a piece of bread, give it to whomever needed it. And I still do that very same thing.

The hemophilia community poured a lot into me in my younger life — growing up, our summer camp programs, youth activities, all those things. And the mentors that I had and still have always talked about continue doing your best. If you can help somebody else, go ahead and do it. Because our numbers are so small in the hemophilia B population versus hemophilia A, it was a little challenging getting folks into a trial. And I'm like, well, I'm ready for it. The family's got all their stuff together. I work from home. Yada, yada, yada. So, I said, "Let's start this."

Well, as Dr. Rosa talked about the different ways therapies are administered, mine was administered — AAV [adeno-associated virus] vector in a very clinical, sterile part of a hospital, similar to a hospital back in 1905: no AC, just cold. I'm like, okay, this is supposed to be fun. I had to build myself up for it.

Now, I'm talking to the doc while the nurses are doing something. I wasn't paying attention to them. Literally, I was not. A couple minutes later, then, the doc asks, "So, how do you feel?" I'm like, "Feel about what? I'm waiting for you all to do this or do whatever the therapy is." The exact statement was, "We administered it to you 10 minutes ago." So, in the blink of an eye, my entire life changed. In a blink of a conversation, my entire life changed. In the blink of being supported by my clinical hemophilia team, my life changed. My mama was on the phone as well, which I come to find out later, listening in the background. My entire life changed.

I did not know how it was changing at that point in time. I'm now 5 years later in the trial.

Now, if you know anything about bleeding disorders, specifically hemophilia and when it's severe, that you have to treat prophylactically, either every other day or, depending on the medication, once every 7 to 10 days. Typically, for me, my bleeding episodes were all intramuscular — one joint bleed, that's it. Hemophilia, you bleed internally. You don't bleed out, just longer clotting time.

So, in 2018, in June of 2018, I had the vector given. I've only had to treat with clotting product three times since then, and that was because of having surgery, and that is it. I've been able to live fully — not saying I did not live before the gene therapy. But what I mean by that — those honey-do weekend projects I give my own self, I pull the ladder out and start with just trying to do one thing. Four or 5 hours later, I'm like, "Oh, all that's done, and my body is sore."

Before, my normal would be, "Okay, now I need to infuse my factor." Now I'm like, "Wait a minute, I don't bleed anymore, because I'm quote-unquote 'normal.'" If there's something traumatic, then I have to. Then, having to figure out, okay, is this just a sore muscle, because myself did not stretch before doing it, which I never did anyway. Do I need to ice it, shower, or what?

So, then I think, "Oh, let me just rest a little bit and see how it is the next day." Wake up the next day, and my body is fine. The blink of an eye, where life is changed, to where my go-to of just infusing is changed, to where my paradigm in understanding a different component of me changed dramatically.

Now, growing up, as a person of faith, of relationship, of then trying to figure out what does this all really mean, that in the blink of an eye, things change, what does that mean for me and the community that is coming up behind me within the bleeding disorders community, of how to advocate for change, how to access change, and how to navigate unknown waters, if you really want the truth of it, because there are so few of us in the overall bleeding disorders community who are on gene therapy and seeing the positive effects, of what does that mean in terms of care, what does that mean in terms of the mental health side of it, what does that mean in terms of the educational side of it.

But you see, in our community, if someone had a liver transplant, liver replacement, then they were completely cured of their hemophilia. Well, I still have it. So, if there's something traumatic, then I have to infuse. But on the day-to-day, I don't. So, for roughly — I'm, what, 51 now, 51 years — my norm has been I know what to do and having to shift that around.

This question has come to me many times: Would I give up the experience of gene therapy? And my answer has been a flat-foot no. Am I good, godly happy that it came out the way that it did? Yes. In the back of my brain, have there been thoughts of what if it did not go so productively well? Would I be okay if my clotting levels were in the mid-30s? I don't know, because I haven't experienced that long-term. What I did experience is it touched to that midrange and kept going higher.

So, then the question that I ask myself, even in preparation for this wonderful FDA OTP CBER regenerative medicine therapy campaign: What is the real purpose of all this? I thought, and I thought, and I thunk and thought, and thought and thunk, and all that, and came to a conclusion about the following thing: It's about voices coming together expressing their truth. It's about voices coming together in a stance of solidarity to say, "This is what is necessary." It is about voices coming together saying that the change is taking place. It's about voices coming together that may not be okay with the slow or the fast change, but of saying, "We see the change."

The purpose of all of this is not just to have another meeting to talk about stuff. I truly and earnestly — the purpose of all of this is to hear the individual perspective, collective perspective, and for folks to bring their unique perspectives together to form the pathway for those who can make, implement change happen. It's for those in community that have struggled with getting appropriate whatever, a voice to have it heard and say, "This is what we're working towards."

And it's — I'm going to go on my parents' side, because I'm also a parent, have kids, grandparents, all that. It's about, as a parent, doing the best that we can do for our kids, both biological and nonbiological. It's as a parent, as being able to support a sibling who may be going through a medical situation to where the current treatments are not effective and finding a way of what is available. It's as a parent, it's as an advocate, it's as a whatever, of saying this is what communities all need, that the nonrare diseases, if I can go there, have access to a whole lot of stuff, no negative shades and whatever, because of their numbers. Yet our communities where we are rare and our numbers that — our collective energies and forces to get us to that next point

of commonalities. Several things, for me, throughout all of this, is what's kept it going: my faith, my mama (because she's my rock, my mama really is), and, knowing that what I actively chose to do is helping the younger generation of the hemophiliac community.

Now, my challenge — and I'm going to say it, because the gene therapy protocols that currently exist for the bleeding disorders community are only directed towards biological males — our females, biological, are not able to access them. I'm hugely challenged by this. They are clinically defined as a person with a bleeding disorder. I'll get into that later, some other day, some other year.

So, for me, my experience it's just that — and it's continuing to grow, and I don't think it's stopping, because, yes, I'm in long-term follow-up. Why am I in long-term follow-up? There's no data. So, the data that's derived from myself and the other — two or three other folks that are in phase 2 will help the community long-term. Is it my hope that somebody will get the good-golly gumption to say we need the full inclusion of our women, so we can see the data to show what's happening with them there. Yes. Do I hope we will get to a point in time where there is not a veil between who can get something and who cannot, based on particular things? Yes, I do. Do I hope that communities are able to further band together for success and progress? Do I hope the midnight-hour cry, because of not knowing what else to do, will be able to dissipate? Do I hope that the midday laughter will continue to take place because life has a different quality of life and longevity for many? Yes. I do.

So, it's only fair to give my good, godly, Suzette some more time, because — and I said it in a practice session — she's a mother like no other. I'm going to go there. Her impact on so many levels is a faith. Y'all got to excuse me. I'm trying to be good. Okay? I'm a Baptist [Koji] child, and I'm feeling some things right about now. She's got a power and an impact. So, I'm going to turn it over — I'm going to relinquish whatever time I've got left — I don't know — on over to Suzette. There you go.

MS. JACKLER: Bobby, thank you so much. That's incredible, and I am — like you, I'm really looking forward to hearing from Suzette, as well. So, Suzette, I am just going to — like Bobby said, just pass it over to you. So please turn on your camera and unmute, and let's go.

MS. SUZETTE JAMES: Wow, Bobby. Thank you. Thank you for that introduction. I hope I live up to your expectation, for sure. Hello, everyone. Thank you for

the opportunity to speak today. My name is Suzette James, and I have four children, two of whom are living with CLN2 late-onset atypical Batten disease. Next slide, please.

Maya, age 19, was diagnosed at 10, and Xavier, age 15, diagnosed at 9. Maya has now been living with Batten for half of her life. For those that are not familiar, CLN2 is a progressive neurodegenerative disease that affects children. Most children develop typically from birth, meeting their milestones, then begin seizures, loss of motor skills, speech delays, cognitive decline, resulting in death by the age of between 6 and 12.

For the later-onset version, like Maya and Xavier, symptoms become apparent usually by around the age of 5 to 7. They include gait issues, fine-motor learning differences, speech issues, and, for some, seizures. Our CLN2 community lives in a continual and never-ending pandemic. One hundred percent of our population dies a torturous death. There is no chance for survival for our children, only a death sentence. We live in a continuous state of fight or flight.

Maya and Xavier met all of their milestones, some early, in fact. Maya could run like the wind and was one of the fastest kids on the playground, and Xavier was an incredible soccer player. He still plays with his brothers, but not on a club team any longer. He also has an insane amount of curiosity about how things work.

I would like to continue to tell you how Maya's disease started, but I'm going to read to you a piece that Maya wrote that best describes how she felt when her disease started to take over. It's called, "I Once Raced a Whippet" by Maya James.

"I once raced a whippet, as in the dog. I was around 8 years old, and I almost won. I used to love to run. I was the fastest kid on the playground, well, maybe except for my friend Alon. Running was my thing, but I also loved swinging, jump roping, biking, and swimming. I played soccer, too, but I didn't love it, not like my brothers. I could catch anyone, though, and beat them to the other side of the field, and life was good.

"And then my world started to change. I had a hard time balancing when I walked. I would fall out of the blue, and it frightened me. I started having a harder time reading. The words would just bounce around on the page in front of me. I sometimes would even hold the book upside down. It was so hard. I didn't know what was happening to my body or my world. And then

when I thought things couldn't get any worse, it was as if I fell off a cliff. I got sick, just a regular cold, but it hit me hard right before Christmas.

"All of Christmas break, I laid on the couch for nearly 2 weeks, and when my cold was over, I couldn't walk on my own any longer. I needed someone or something to hold me up. I was only 10 years old. I was so sad. I didn't want people to see me or look at me. It felt like my world was closing in.

"I tried all different therapies: PT [physical therapy], OT [occupational therapy], speech, acupuncture, shamanism, and, oh, turmeric, so much turmeric. You name it, my mom and dad either tried it or dragged me to it. I would get so tired, but I know I had to fight, even though I didn't want to talk about it very much. I knew I was in the fight of my life, fighting for my life."

Maya and Xavier's disease progression looks very different. I believe this is due to Xavier being diagnosed earlier than Maya and then able to access treatment before the disease progressed too far. This is why accelerated approvals for gene therapy and other treatment is so critical, and I am encouraged by the recent trade press article where Peter Marks, head of CBER, discusses the importance of accelerated approvals and the use of biomarkers in innovative trial designs.

These considerations would have made a huge impact on our community. Lives could have been saved, and more children like Maya could have preserved more of their abilities. Today, Maya, at age 19, can no longer walk independently, and she has a significant amount of ataxia and movement challenges. She can no longer dress herself. She now has trouble feeding herself. And although she can still eat by mouth, her food needs to be cut into very small pieces and sometimes mashed. She is very difficult to understand, and it is frustrating to her. She feels extremely isolated and lonely, and she is 100 percent dependent upon her caregivers.

Xavier, at age 15, is still independent. He makes his own lunch for school. He feeds himself and takes care of all of his personal hygiene. He requires special instruction at school and has an IEP [individual education plan], but learns well when lessons are tailored and scaffolded for him. The psychological trauma that living with this fatal disease — that, like Batten's, is horrifying, and it is very isolating for Xavier as well.

However, despite all this, the difference between their challenges speaks volumes to what it looks like to receive treatment 4 years earlier. Next slide, please.

I still remember the day we sat in our neurologist's office in San Diego. Maya's exome sequence results had come back, and we were about to learn about Batten for the first time. I was holding back the tears and bracing myself for the worst but praying for mercy. Our neurologist told us the result and instructed us to get a very big binder and place all of Maya's clinical results and tests in it. She told us that we, as parents, would become the experts on this disease, and she wasn't wrong. Next slide, please.

Shortly after this meeting, we flew to Boston to see another lysosomal storage specialist, and she told us about an upcoming trial with a company called BioMarin. They made and infused, through a port in the skull, an exogenous form of the TPP1 enzyme that Maya and Xavier lack. We were terrified and also hopeful. Maya's gait was getting worse, and her energy levels were plummeting. We needed something fast. We were terrified by the thought of brain surgery and the port placement, but we were assured by our medical team of its safety, except there was one catch. Maya didn't qualify.

Despite all of our unanswered pleas to the pharmaceutical company, she was too old, and the later-onset version of CLN2, previously known as SCAR7 [spinocerebellar ataxia autosomal recessive 7], wasn't really acknowledged much among the scientists in industry. In fact, it was sometimes referred to as Batten lite, or would be referred to as Batten wannabes. This protracted version is even rarer than early-onset version, and I compare it many times to early-onset Parkinson's or Alzheimer's versus late-onset.

Our only hope was the compassionate use trial, but that was 2 to 3 years away, so we waited, and we threw everything at the wall to help Maya maintain as much as she possibly could. And as you heard Maya's words earlier, we tried everything, and yes, a lot of turmeric. But the disease went into overdrive, and we were losing the battle fast. And in that time, we tested our three other children, and Xavier also came back as having Batten.

"Devastated" is an understatement. I just couldn't imagine Xavier facing the same fate. My husband had started a campaign called Fighting for Maya and was raising money for research by selling T-shirts. Maya's school surrounded her and lifted her up with all this overwhelming support. Children sold beads. Maya's friends had lemonade stands. And every Friday was Fighting for Maya Friday. All the kids and teachers wore their T-shirts, and all you could see was a sea of black T-shirts with white letters spelling hashtag #FightingForMaya.

We had actors, such as Chris Pine, Ralph Macchio, and Billy Zabka, sending messages out via social media. All the donations went directly to a well-known research facility. We were exploring all possibilities, desperately searching for anything that could address falling off that cliff.

There wasn't a playbook to follow. In the end, we raised $250,000 and had a mouse model with Maya's exact phenotype that we called them Maya's Mice. Except, the fellow whom we paid for and who was running our project left the lab for another job, and Maya's Mice fell by the wayside. That was almost 9 years ago, and we have yet to see anything produced from it. But we had to try.

Shockingly, this is a common story within the rare disease world, where parents fund research, because there is no other option, and there is no time to wait.

But finally, the moment we were waiting for arrived. Three years had passed, and we heard through our Batten community that the compassionate use part of the BRINEURA® trial was about to begin. A fellow Batten parent encourage me to reach out to the physician administering the trial. We had almost given up, but we made the phone call and booked our tickets to the Midwest for Maya and Xavier's assessments.

After several visits and a very long couple of weeks of waiting, we learned Maya was accepted into the compassionate use trial. We, along with four other individuals, would travel to Columbus, Ohio; have an intrathecal port placed in Maya's skull, where the enzyme would be infused every 2 weeks for about 4 hours, or for a total of about 8, when you include check-in, etc., etc.

We didn't yet know how much Maya would benefit. We had looked into the data and learned that the participants during the initial trial were seeing benefits and that the enzyme was slowing down the progression of the disease. We still didn't know how much, but we knew we had to do something, because this disease was killing our little girl, stealing her away from us bit by bit.

We knew BRINEURA® wasn't a cure or a long-term treatment. It was a steppingstone to a more effective treatment or a cure. And it was going to be part of the equation. We knew that eventually BRINEURA® would not be enough, but we were willing to take that chance, to wait for the science to catch up.

Gene therapy was 2 years from trial, or so we thought. The BRINEURA® preliminary trial data looked good. We knew there was a low chance of an adverse reaction. We had discussed all this with our medical team. We did as much independent research as we could, and we had to go with our gut, because the one certain thing we knew is if we didn't do anything, Maya would die.

So, when the physician called us on a Wednesday and told us to be in Ohio the following Tuesday, we went all in. We had been waiting for this moment for 3 years, and it was finally here.

We immediately began prepping for the trip. We contacted our kids' school and all of our therapists. Our uber-supportive school community was overjoyed and pitched in to help with everything they could. Beau arranged for his parents to come and stay with our three other children. Xavier was not included in this round of compassionate use. Beau constructed an elaborate calendar system filled with all the pickups and drop-offs for three separate schools, soccer practices and games, OT sessions, tutoring sessions, music lessons, and lunch instructions, and yes, the recipe for our turmeric concoction. All of it was on the master calendar.

We would be in Ohio for a month, initially, for the port placement and the initial infusion, and then we would travel back and forth every other week for the next 6 months. I stayed a better part of the initial month with Maya, and then Beau and I alternated for each infusion. Maya's friends and family texted religiously, and some actually even came to visit us.

Grandma and Grandpa held down the fort well, and it was a very special moment for our other children to be able to spend this time with them. I only have heard of one incident where Grandpa nearly burned down the kitchen, having turned on the oven, not realizing there was a pizza box with leftover pizza already in it. The kids tell me that didn't stop Grandpa from hosing down the pizza box in the sink and serving the pizza, parts of it now soggy, to the kids anyway.

Our first three infusions went well. Including flight time and a day of infusing, with a day of rest in between, we were gone nearly the entire week every other week. But after the third infusion, they noticed bacteria in Maya's port, Propionibacterium, or acne bacteria. She was a teenager, and acne was a part of her life, regardless how well or how often we washed her hair — and these ports weren't made for such frequent access, but it's what we had, and

for most, it was working really well. The port had to be pulled, no way around it. More devastation.

We flew back to Ohio, and Maya's port was removed, in more surgery. She was in the hospital for nearly a week, and it was a very difficult time for her healthwise, and it was psychologically draining for both of us. Maya had a round of intensive antibiotics and then was discharged to our Ohio home for a month with 2 weeks of antibiotics administered by me through a PICC [peripherally inserted central catheter] line. And believe me, I'm a former management consultant. I am no nurse. I was hesitant, for sure, but the 2 weeks passed, and now a spinal tap to make 100 percent certain that the bacteria were gone.

Prayers were answered. No bacteria were detected. So back to brain surgery, where she would have the port placed on the other side this time, and her infusions would resume 1 week later.

Within the next month, we heard about a physician in California, where we live, looking to also infuse BRINEURA®. To this point, only Nationwide [Children's Hospital] in Ohio was infusing. But the compassionate use space made it feasible for additional sites. We met with the new physician, had Xavier assessed, and made the decision to infuse just 1 1/2 hours from our home in California. No more 8-hour plane rides across the country.

Xavier had his port placed, and he and Maya began infusions at Children's Hospital of Orange County [CHOC] 2 months later. That was 6 years ago. BRINEURA® has slowed down the disease, but we still face decline, and we still worry about acne bacteria in the port, but we have found ways to keep it at bay. We have worked with our medical team to come up with some workable solutions, which includes an at-home regimen involving ultraviolet light application, in addition to our normal cleansing schedule of the scalp.

Overall, our infusions are going pretty well, and we adore our medical team at CHOC. They are like family, and we are ever grateful to BRINEURA®. Next slide, please.

I'm probably the only panel member here who can talk about how her children haven't received gene therapy yet. Believe me, it isn't for lack of trying. After all, this is my third presentation to the FDA within this last year. I came into this rare disease scene about 10 years ago. Many in our Batten community have been on this road even longer. This has been a road full of more losses than wins, and we have seen far too many companies come and go, forced out due to unrealistic regulatory requirements, too stringent or ever-changing

clinical expectations, and companies hence running out of money, and, with an unforgiving financial market, many of them are gone now. They just can't survive.

CLN2 is currently on its third or fourth gene therapy company for the central nervous system. I honestly — I've lost track. This last one seemed the closest to actually going to trial for CNL2 but now has been delayed and on clinical hold. And instead of moving forward with a single patient dose in the U.S. — and believe me, I know; there were many individuals in the U.S. who would have volunteered for this — the gene therapy company thought it had a better chance by dosing a child outside of the U.S., specifically in Brazil. And from what I understand, the child is doing well. Our community heard of this in a press release. I don't have any inside information. And we now are left hanging with what the process might look like now for our community.

Based on our personal history — mine and Maya's and Xavier's — the later-onset individuals won't be the first patients dosed or included in the initial clinical trial. My teenage and adult child will have to wait for the trial to end, and then hope for inclusion into the compassionate use trial of that, and that's a 2-to-3-year wait from the beginning of the first clinical trial. And I have my doubts that Maya will be strong enough by then. Next slide, please.

But if she and Xavier are strong enough, how do we and — how do Beau and I, as parents, guide and tackle informed consent with our children? One of the many reasons we hear about the delay of gene therapy is that there's a belief that parents don't understand or aren't capable of making an informed decision because our judgment is too clouded by the fact that we are desperate to save our children. We, as parents, are put in a position every single day to make extremely difficult decisions. It's all we do, and it is our job. We know our children best.

And I'm reminded of what our neurologist told us the day we heard "Batten" for the first time. "Get a binder," she said. "You will know this disease better than anyone." We make decisions every day that involve informed consent and weighing the risks and benefit of all the things. We make complex medical decisions, educational decisions, social/emotional decisions, mental health decisions. We dole out and administer pharmaceuticals with the skill of a pharmacist. Do we "trach" [place a tracheal tube]? Do we not trach? We are nutritionists and PTs [physical therapists] and OTs [occupational therapists]. We replace feeding tubes, and we tape them up before rushing to the hospital when the neighbor's dog accidently rips it out. That's a true story.

We make these decisions every day, all day long, and we get up the next day, and we do it again, and we oversee the process of our child dying. To help them die a dignified death, we make the decisions, when to stop feeding them and when to stop giving them fluids. So why is it okay to make these decisions about how our child dies but not okay to make decisions about how they can live?

There seems to be so much concern around whether parents are qualified to make the decision to administer gene therapy. And again, I think it is what has been one of the main reasons that gene therapy, at least for CLN2, has had such a difficult time getting approval. There appears to be a pretty huge misconception that parents will make poorly educated decisions, and yes, parents do say — and I'm probably one of them — that we will do anything. But that doesn't mean that we are going to put our children willingly and knowingly in danger.

We approach gene therapy the same way we approach all clinical, all medical decisions. We inform ourselves by relying upon our trusted clinical team, our advisers, our scientists, the FDA's preclinical data, and the intimate knowledge that only a parent has of their medically complex and fragile child. And asking parents who did make the decision to go ahead with gene therapy, they hands-down said they would do it again, and they would include a larger dose and be very open to long-term follow-up. They would do it in a heartbeat, and I also know of a parent who looked at the fine print, assessed her child, and didn't think he would be a good candidate for gene therapy.

And as I said during my presentation a few months ago, the risk of doing something far exceeds the risk of doing nothing. Next slide, please.

So, in closing — this is to the parents and the patients listening now out there — don't be afraid to make that phone call, whether it be to a physician or a pharma executive or a seasoned parent. Don't be afraid to ask questions and to keep pushing for answers. Don't be afraid of someone else's qualifications or the letters they have behind their name. Parents are a critical part of this equation, and until the FDA, pharma, biotech, and researchers are truly working together, many parents will continue to sacrifice the last few years they have left with their children jumping through regulatory hoops, fundraising, lobbying, educating, managing foundations, and partnering with research organizations and pharmaceutical companies.

We will continue to push forward as rare disease parents. That's what we'll do, because the only thing more devastating than not spending the last

precious moments with your child — because you were trying to save their life — is to bury them. It's unnatural — we all know that — to lose a child, and we will go to the end of the earth to stop it from happening.

So don't stop moving the needle forward, parents. Have the hubris to know the extent of your power, know who you are, and you are capable of making change. But at the same time, check your ego at the door and don't forget the parents and patients, clinicians, and children and pharma companies, and biotech, who all got us to this point where we are today. They've done a lot of the heavy lifting.

And to the FDA, thank you for hosting these very important information sessions. I'm extremely appreciative for the opportunity. And as I stated to the FDA a year ago in a private listening session last March, we do need more treatment options, and we need them now. We want more birthdays for our children, birthdays where our kids can eat their cake on their own, not have it fed to them or put in their G-tube [gastrostomy feeding tube]; birthdays where they can hold and eat an ice-cream cone; birthdays where they will be able to see and open their own presents and blow out their own candles, to make their own wishes and have their own dreams.

Little Brody Koslowksi won't have any more birthdays. He passed away on March 25th at the age of 7, holding his favorite toy, Lightning McQueen. In the spirit of Brody and in the words of Lightning McQueen, we need more treatment options "faster than fast" and "quicker than quick." We need a real pathway for treatments with consistent communication between researchers and companies and the FDA, and the critical word here is consistent.

I understand the FDA wants to ensure the utmost safety of our products. So do we parents. We would love a risk-free option. There just isn't one currently. And we, unfortunately, know the risk of doing nothing is death. We need multiple companies working towards treatments both to alleviate symptoms but also to provide long-term relief and cures, but we need these companies to stay in business, to continue to invest in therapies and treatments and cures.

Within the last several years alone, roughly half of the therapies being worked on for Batten disease have been halted, mostly due to lengthy and overly stringent and ever-changing clinical expectations placed on them by the FDA. And whether it be mandatory retesting, using expensive and difficult-to-obtain large animal or dog models, or changing the criteria from pre-IND to IND, these companies could no longer sustain the cost.

And lengthy approval processes have forced many to conduct their clinical trials outside of the U.S. More than 5,000 employees have been laid off from biotech and pharma companies just this year. These companies can't stay in business if they have no product to sell. All this is to say — all this is to say I am still extremely encouraged, and it does give me hope that Peter Marks from CBER is supporting an accelerated path to gene therapy using surrogate endpoints and biomarkers, instead of randomized controlled trials that don't make sense for our population size. This is not a gold standard for our population.

The patient really is his or her best control, but we need it faster than fast and quicker than quick.

I thought it best to wrap up today the way I began: with a few words from Maya.

This is called "Elle Bell" by Maya James. "I hung out with my friend Elle. She was also receiving BRINEURA® infusions in Ohio. Elle lost her ability to walk at around age 4, but she could still scoot on the floor. She would scoot herself all around the living room and land at my feet. She loved my red toenail polish and would poke at my toes with her tiny little fingers. She was beautiful and lovely, and I still can't talk or even think about her without crying. She was funky and full of spirit. My Elle Bell deserved more time on this earth. I will keep her in my mind and in my heart forever."

Thank you for your time today.

MS. JACKLER: Thank you, Suzette, so much. Not unsurprisingly, both you and Bobby have shown us why patients are the experts in your disease, and thank you so much for reading some of Maya's words. It just reminds us, you know, while you are a passionate advocate for your family, you know, you're taking care of real people, and it's really nice how you're conveying their voice to us.

So, as I mentioned, this is part a two-part panel discussion, and we're going to have more panelists lined up and ready to share their gene therapy clinical trial stories and experiences. So right now, we're going to take a short break. We're actually running a little bit ahead of time, and so I'm going to ask folks to return at 12:45, and we'll pick up from there and hear from our two remaining panelists. And then we'll open it up for discussion. So, thank you all, and I know there's — we have a lot to think about during this break. We'll see you soon. Thank you. [Break]

MS. JACKLER: Hi, folks. This is Karen Jackler again. I'm just going to give folks another minute or 2, just in case there was some confusion, because I know the break sign says we're back at 12:50. So if you guys can just hang, I'll be right back with you. Thanks. [Pause]

MS. JACKLER: Hi, all. Welcome back. I'm sorry, I lost a — I lost my notes. [Laughs] So give me just 1 minute while I fumble about for a second here. There we go. All right. All right. Thank you all. Welcome back. Thank you all so much, again, for being here today at our annual Center for Biologics Evaluation and Research, Office of Therapeutic Products, patient engagement workshop, where we're talking all about gene therapy clinical trials.

If you tuned in before the break, you've already heard from two of our panelists, Bobby and Suzette. We have two more panelists we'd like to introduce, who will share their experiences and stories about gene therapy trials. So, our next panelist is Shandra Trantham. Shandra was diagnosed with Friedreich's ataxia in her preteen years. Now, more than a decade later, Shandra is studying to get her PhD in genetics at the Powell Gene Therapy Center at the University of Florida. Shandra, we're so glad you're here today, and we are looking forward to hearing more about your journey, both as a patient and as a researcher.

And our last presenter for today is Jennie Landsman. Jennie is a mother of six. Two of her children are living with Canavan disease, a rare neurological disorder. In 2021, her boys were the first and second patients to participate in a gene therapy clinical trial for Canavan disease. Jennie is not able to join us live today but has recorded a presentation to share with you all. Once again, thank you to our panelists for sharing your stories.

Before I pass it over to Shandra, I want to remind everyone in the audience to submit questions for our panelists in the Q&A box on Zoom, and we'll have some time at the end of the presentations for discussion. And for general comments, please add those in the chat box on Zoom. And now, Shandra, if you're ready, I'm going to pass it over to you. I'm looking forward to hearing from you. Thanks.

MS. SHANDRA TRANTHAM: Thank you for the introduction. Hi, everybody. You can go to the next slide.

So, my first slide was an introduction, but Karen already gave me a really good one, so I'll just reiterate that I'm a patient with FA, which is Friedreich's ataxia. I'm 25 now, but I was diagnosed at age 12. And I'm also doing a PhD in genetics at the University of Florida. And my research area is actually gene

therapy for a different neurological disease than what I have, so I get to know a lot about the ins and out of what gene therapy is and how it's developed and things like that.

And I'm also very active in the FA patient community, so I've gotten the opportunity to speak to a lot of people and hear about different perspectives of parents and patients, ranging from all ages and severity of the disease, different expectations for therapies, and things like that. You can go to the next slide.

So, I wanted to start out today just by telling you a little bit about my story. FA is a rare progressive neuromuscular disease. And so, it's progressive, so at some point in your life, you don't have symptoms yet and you think you're normal, and that's exactly how my journey went.

So, when I was a young child, I was pretty active. I was actually involved in a gymnastics camp that I really enjoyed going to. I loved running around the beach with my friends and just enjoying life. And around age 9, it was actually in that gymnastics camp that I realized that I was having issues with balance that I didn't have before.

At age 9, I was suddenly unable to walk on a balance beam at all. I could barely even stand on it, and that was something that I'd never experienced previously. I actually remember that day, even now — it's like a core memory — because I was so scared and didn't know what was happening, and I didn't want to tell anyone, so I just pretended that I'd gotten hurt so that the instructor wouldn't have me do the balance beam any more that day.

From that moment on, I started to accrue more symptoms as time went on. So, around age 11, I started to experience one of the complications of FA, which is scoliosis, a side-to-side curvature of the spine that can progress to the point of needing surgery.

If you look over at the — in the middle row, that photo on the left is the only photo that I have wearing the back brace that I had for scoliosis surgery, because I absolutely hated it, and I refused to let anyone see me in it, so I would always wear another shirt over the top of it, which I'm sure people were wondering why I had like a flat object under my shirt, but I just avoided all the questions.

And when I was age 12 — next photo — I actually had to have my spine fused. So, it was at age 12 when the scoliosis had progressed to the point of needing surgery that my doctors realized that something was going on and

that there was probably like a deeper reason for everything I was experiencing besides just scoliosis.

And so, they tested me, and I was diagnosed with FA. So, FA is progressive, so since then, I have developed more symptoms, such as difficulty walking. I now use a walker as my primary mobility aid and a scooter when I'm walking my dog or going shopping, things like that. It also can affect my speech, so it's hard for me to talk for a long time, because I get really fatigued. It can affect vision and hearing, but I'm lucky that I don't have those symptoms yet. It can also affect, like, every other voluntary muscle with fine motor control. So, it's hard to do manual tasks.

And one of the things about doing a PhD is that you need to be able to work in a lab and do a lot of fine movements with your hands, and that's something that — I'm lucky I'm able to work with someone who can do those things for me, so that I can still get the education and knowledge of a PhD and then the experience of doing the research by directing someone else to do the fine motor tasks.

Now at age 25, I've been involved in multiple clinical trials for the disease. So — next slide — I did want to talk about just participating in clinical trials in general. I'm sure that many of you who are here today have either participated yourself or had your child participate. But in case you haven't and you're still waiting for a clinical trial, I wanted to share my experience of what it's like.

So, I would immediately — like the first thing that comes to mind when I think about how it feels to join a clinical trial is when I got my first dose of the FDA-approved COVID vaccine, it was like immediate optimism after that nearly a year of being isolated and alone and not knowing what was going on. When I got that vaccine, I felt hopeful for the future, hopeful that I would be able to do things that I had wished that I'd be able to do.

And I would say that living with a rare disease is a very similar experience, where it can be isolating, and you don't know what the future holds. So, when I got that vaccine, that optimism is very similar to how it feels when you sign up for a clinical trial. You're hopeful that this is a drug that may help you get better or may just stop your disease from getting worse. But I wanted to also talk about the other sides of it, because a clinical trial is not an FDA-approved treatment.

So, there are a lot of other factors that are at play when you join a clinical trial. Besides the optimism, there's also a really big-time commitment,

especially if you need to travel to the site for the clinical trial. You also have to accept the chance that you may get a placebo if it's a placebo-controlled trial, and that can be difficult if you commit yourself to a strict regimen of what you're doing in the trial, if you feel like it's not helping you or you may not even be on the drug. But that's a thing that you have to accept when you sign up for the trial, if you're willing to endure that possibility when you do the trial.

You also kind of need to become an expert at navigating all the appointments and things that you need to have, especially if you're in college. I know that one of the clinical trials that I did, you had to be on a very strict diet. And I was a freshman in college at the time, living in a dorm, and I would eat at the dining hall. And so, I'd become an expert in figuring out the polyunsaturated fat content in the items that I was going to be eating to make sure that it added up to an amount that wasn't too high for the drug. I remember having to go up to all the different stations in the dining hall and asking them, "Do you know how much polyunsaturated fat is in this?" And they'd be like, "Uh, I don't know."

And it's just things like that, where you really have to plan your life differently, but it can be worthwhile doing it. So — next slide.

So, that's clinical trials in general. But as we heard earlier, gene therapy clinical trials are different than just normal clinical trials. And so, for this talk, I really wanted to kind of dive into that and how my community is handling that information and the special concerns that come up for gene therapy clinical trials.

For FA specifically, there are multiple gene therapies that are now in development. There's actually a gene therapy for the heart that is now in phase 1 clinical trials. So, this is a gene therapy that just targets the cardiac complications of FA. So, it doesn't target the neuromuscular aspects of the disease, such as, like, the walking issue, speech, vision, anything like that. And then there are multiple other gene therapies that are in development for those aspects of the disease. But those are not in clinical trials yet.

But I just want to talk about in general — sorry — in general what the differences are between standard clinical trial and a gene therapy clinical trial. One second. [Pause] I'm sorry. Sorry. When I talk for a long time, I need water, because my throat starts to get really dry. But for gene therapy in general, there are different aspects that you have to consider.

So, for a normal clinical trial, if a drug has a safety concern, you can just stop taking the drug. You can clear it out of your body and hope that those effects reverse. But when you're doing a gene therapy trial, once you get injected with a gene therapy, it's permanent. So, you have to assess whether the possible safety concerns are worth it for your individual situation.

Gene therapy clinical trials can also be much longer than standard clinical trials for things like small molecule drugs. And so, for example, because the gene therapy is permanent, they have to study that for years and years after you get the injection. So it's not just maybe like a 6-month study or a 3-month study. You're talking about possibly a 5-year-long study or similar to that.

And then you also have to manage your individual therapeutic expectations. What I mean by this is that gene therapy may or may not help a disease, and it may or may not provide different benefits to the people who have different stages of progression.

So obviously, this doesn't apply to all diseases, but for mine, FA is a progressive disease. You might have a patient who can still walk and was just diagnosed like maybe a month ago versus someone that has had FA for 20 years and is in a wheelchair. You have to assess how the proposed benefits might impact you specifically with your disease progression.

You also have to deal with the idea that you may and possibly will definitely be excluded from future trials, and this is because, like I said, gene therapy is permanent. So, it's really hard to, like, test something new in a patient, in a set of patients when maybe a few of those patients have had gene therapy and some of the other ones haven't. So, you don't know if the benefit or side effects that the patients in the trial are experiencing are from the new medicine that they're testing or if it's because of the combination of the gene therapy trial that they did a while ago and then this new medicine. And so, it's likely that people who do gene therapy trials would be excluded from future stuff.

Then you also have to choose the therapeutic target versus the symptom burden. So, this is, again, a thing that won't apply to everyone, but it's really important in FA, since it's multisystem disease. It affects a lot of different things. Like I mentioned, the heart versus the — like the muscles and the nerves and everything — you have to assess whether you want to treat one of those things, if a gene therapy treatment for that thing is available, or if you want to wait and try and treat another thing, or if you want to do a treatment that is supposed to target everything. So, it's kind of a choice

between how you want the gene therapy to be, like, developed for you. Next slide.

So, for the rest of my talk, I want to focus on how the FA community is reacting to gene therapy clinical trials. And so, like I said before, I've been able to meet a lot of people with FA and speak with others about how they feel about the idea of gene therapy and their burden of disease. For FA specifically, the first point that I want to make is that people with FA are used to having to travel to get care.

And so, because FA's a rare disease, to see a specialist, maybe you don't live in the same location as a doctor, or maybe there's not even one that's like an hour away. You might have to fly to see a specialist. And a lot of people with FA are used to that. But that's something important for a gene therapy clinical trial, because there's not going to be, like, an unlimited number of locations that you can go on and get — do this trial.

And then, further, the follow-up for safety is for as long you need to follow up. Because it's permanent, you would have to travel continually for several years back to the site for the follow-up appointments. And this is something that I don't think the FA community specifically is concerned about, because we are used to having to travel for our care.

Then I also wanted to talk about, just in general, I think, from my discussions with the FA community, people are really hopeful and have high expectations for gene therapy's ability to help them. So, this gene therapy may or may not help, like, as much as people expect. But we don't know, because it's never been tried in a human specifically, and there's no data on it. So, we don't know how it's going to work, but I just know from my discussions that people have high expectations for it.

Then I also wanted to talk about how people are uncertain about the treatment target. So, I mentioned how gene therapy can target different things, different symptoms and areas, depending on how it's developed and how it's administered. For FA, people may have, like, a different perspective of their disease burden based on the symptoms that they experience. So, I must struggle with my ability to walk, but I have a friend who's a similar age to me that has a much more severe disease score. She's been in a wheelchair for over a decade.

But for her, she doesn't really care about walking. It's more about the ability to speak, because she is unable to communicate with others because her ability to talk is so impacted that most people cannot understand what she is

saying. I know her very well, and so I would estimate that I can understand like maybe 60 percent of what she is saying. But it's mostly me anticipating what is being said than actually being able to hear her.

And she has shared with me how that is so hard for her and isolating, because walking is not something that can connect you with the world, but being able to talk and be heard and listened to is something that really impacts how you interact with people.

And then I also have a friend who actually passed away last year who had severe issues with speech and vision — sorry — with vision and hearing. And he had a similar perspective to my other friend: that he felt really isolated from the world because he was not able to hear what people were saying or even see them.

And so — he was also in a wheelchair, but he told me that he doesn't care if he would ever be able to walk again; he just wants to interact with the world. And so, for different people, the most burdensome symptom really depends on what stage of disease that you're at.

Then I also wanted to talk about how there's a lot of other issues that specifically impact FA and maybe other neurological diseases here. So, there is the unwillingness to do a sham surgery.

And what that is, is when they are testing a gene therapy that maybe is targeted to a specific region of the brain, they're going to want to test and make sure that any complications that are arising are not from the procedure itself but actually from the gene therapy. And so, they may do sham surgeries, where they pretend to inject something and put the patient through surgery, so that they don't know whether they had it or not, to test and see if there's a reaction in just the placebo group or overall, and if so, like, how that would affect the ability to move the drug forward.

And so, I know, for the FA community specifically, there's a lot of issues with going under anesthesia and enduring the hard process of having surgery. And so that's something for us that we're not willing to accept as gene therapies are developed. But like I said, there are no gene therapies in clinical trials yet with our neurological symptoms. So we don't know if that is going to be an issue or not. But we like to advocate that we would not be willing to accept that, in case those companies and the FDA are listening and can hear our concerns.

And lastly, I wanted to speak about how there's significant urgency in joining these trials, especially to include child patients in these trials, as this is a childhood-onset disease. And so obviously, with a clinical trial, the desire is to test these things in adults first, before you move it to children. But there is a concern that by the time people got to adulthood, they may lose function that could be saved by gene therapy if it was effective. And so, there's a lot of urgency in getting these things moved forward.

And then I also just wanted to talk about the ways that patient advocacy organizations are helping us move in the direction of gene therapy clinical trials. And I wanted to say this just for anyone on the call who might be representing a patient advocacy organization. So, I wanted to speak specifically about FARA, which is the Friedreich's Ataxia Research Alliance.

So FARA has been doing a lot of work for years to try and push us forward to the point that we're at now, where there are gene therapy clinical trials and there are more in development. Gene therapy is an unfamiliar topic for many. And so FARA has really pushed helping educate patients in the community about gene therapy and just FA in general by actually creating gene therapy module videos for the disease and also just little animation videos that have been posted monthly for, I think, about 2 1/2 years now that have helped introduce people to different aspects of the disease and hopefully are improving literacy among the patients and the community.

Apart from the education side, FARA has also had a natural history study that has been collecting data for years on the natural progression of this disease. And this has really helped people or drug companies developing projects for clinical trials decide how they need to measure the effect of the drug and things like that.

And FARA has also funded efforts for new ways for [using] biomarkers to understand how the disease is progressing. And these methods and the natural history study have actually led us to our first approved drug, which was approved on February 28th of this year, which was Rare Disease Day, and that was only possible because there was a large dataset available from the natural history trials that have been going on. And this has allowed additional data to be collected and compared to the natural course of the disease, and that helped create enough evidence that got our drug approved. So that's very exciting.

And then just in general, FARA as well as several other groups, including UF [University of Florida], have been doing survey-type studies to try and

understand the community perspective on gene therapy. And this will actually help us to better understand how the community feels and to create better education to prepare people for these gene therapy trials.

So that's pretty much all I want to say. But thank you so much for having me.

MS. JACKLER: Shandra, thank you so much. That was amazing. I think you were talking in sort of several layers there, your personal experience and then also your experience as part of the advocate community to bring, you know, new therapies to bear. And I think that was really, really, really interesting. And I hope that generates a lot of questions.

So, as I mentioned earlier, Jennie Landsman wasn't able to make it today. But she has kindly shared a presentation of her experience with gene therapy clinical trials, and we're going to share that recording with you now. And I'll see you on the other side. Thanks.

MS. JENNIE LANDSMAN: My name is Jennie Landsman, and I am the mother to Benny and Josh Landsman, who have a rare disease. I'm also a mom to four other healthy siblings. So, Benny and Josh — Benny's now 6 years old, and Josh is 5. Ben was born after a totally normal pregnancy. He had a normal birth. It was a beautiful birth, and after he was born, I felt like I had to be really quiet, that he was such an easy and awesome baby. He was just great. He was happy. He was, you know, very social.

At about 6 months old, I had my sister over, who is an OT, not a pediatric OT, but she just made a comment. She said, you know, "Does he always need this much head support?" And it kind of sparked this thought in my head, and I started noticing his development, not that I hadn't noticed it before. He was, you know, doing things as he should, but he had never gotten to the stage of being able to sit up and hold his head up on his own.

And sort of from that point, at 6 months, is when he just stopped developing. I had spoken to my pediatrician about it. He didn't think that he was really outside the window of normal for his age. But I ended up seeing a neurologist that month for an opinion. He thought maybe he needed a little PT and he'd be fine. I'm going to fast-forward a bit, that we ended up seeing a developmental pediatrician, ophthalmologist group.

And then, the third neurologist, finally, he sent us to a geneticist. He had found a spike of NAA [N-acetylaspartic acid] in his urine, which is a sign for Canavan disease, not much else. So, I took him, and at that point I had a 2-week-old Josh, and I brought Josh along to Benny's appointment. I knew it

was something serious because the neurologist had called me and left a message early in the morning when he got those urine results and said, “I have an appointment for you today for a geneticist.”

And like just getting an appointment that day and that urgency made me realize, you know, something big was happening. We went to go see the geneticist that day, and she told us about Canavan disease. And you know, we said, “Are you sure that’s what it is?” And she said, you know, “We’re going to test for it, but there’s nothing else that it could be, and we need to test Josh, too, because there’s a 1 in 4 chance that he has it.” We tested both boys.

Exactly 2 weeks later, both boys were diagnosed with Canavan disease. Josh was a month old at that point, and Ben was, you know, 13 1/2 months. It was like — you know, our world ended, really, that day and in that moment. The geneticist, who was very kind and took a lot of time with us and, you know, tried to give this news as gently as possible — I don’t think that there’s any way you can – but she said, you know, “Just go home and make them comfortable,” which is, you know, a death sentence.

We had a pamphlet in our hands that day that said, you know, kids with Canavan disease live 3 to 10 years. And we saw pictures in the pamphlet of kids, and — excuse my very crude, you know, perception of what they looked like at the time — but they looked kind of like vegetables to me, you know, not cognitively there, staring off into space. You could see that they had no physical or motor function. It was really hard, and I just fell into this deep, dark hole for a few weeks.

It was actually Benny who got me out of it. I was sitting with him one day, tears streaming down my face. I was putting him to bed, and I was just singing him our bedtime song, crying, and Ben started laughing. And he just looked at me, and he was laughing his happy little laugh. And I just had this moment when I thought, you know — I was sitting there thinking, like, how many more times am I going to get to sing this song to him? Is it like 1 more time? Is it 10 more times? Is it 10 years’ worth of times? I just felt like every day I was waiting for the last day. And something switched, and I decided, you know, these are going to be the only memories that we have, and whatever they have, whether it be 1 day or 10 years’ worth, we’re going to make each moment the best moment that we can and make it something to remember, because I didn’t want what little time he had on this earth for this happy little boy to be the memories of his mother crying, and then all my memories would be of these sad moments waiting for the end to be instead of

living life. And it took a lot of work, and it still takes work to always be in the moment and enjoy every moment with them, but that's what we do.

So, I ended up not taking what that geneticist said that day and staying home and making them feel comfortable, although I do hope that they're comfortable. I didn't sleep for weeks. Neither did my husband. And we just scoured the Internet. We found probably all the different types of research that had been done on Canavan disease. And we ended up finding two researchers who were working on Canavan disease, one that had been working on it for, you know, over 2 decades, Dr. Paola Leone, and then we found Dr. Gao. And we — I ended up connecting to families with children with Canavan disease, and I ended up connecting directly to both researchers.

I spoke to them, and I was able to have some hope with Dr. Leone that she would be able to maybe do a compassionate use trial for the boys for Canavan disease for gene therapy. She had just completed her most recent findings and published them. And we were going with that. I thought that it would be kind of like a 6-month-to-9-month thing to get it all together and they would get the treatment. I'm going to fast-forward.

It was not something that we could do as a compassionate use study. We needed to do a full trial, like a pharmaceutical company, except we were just, you know, a family. And so, we opened up a foundation called Cure Canavan Fund. We were raising money. We ended up — you know, the boys became very popular on social media. I have no fundraising background. I was a yoga teacher and martial arts teacher before that. I had a studio. My husband had a wine store.

We ended up closing our, you know, small businesses and did this full time, fundraising, and we ended up raising close to $6 million. And it took about 4 1/2 years to get the trial underway and do all the studies needed, and the productions and the data. It was a pretty intense 4 1/2 years. I think I aged about 20 years in those 4 years so that we could start this trial. So, Ben was the first child that was going to be treated.

In the meantime, in those years we, you know, always thought about what the treatment could mean for them. When we first started working at doing gene therapy for them and the idea of it and the way that the disease progresses so rapidly, we thought that if Ben reached, you know, age 2 before we had it ready, we probably wouldn't want to treat him after age 2. That was just some number we had in our mind because we thought that kids by age 2 are so degenerated by then that it would be prolonging, you know, suffering for him.

By the time he reached age 2, we realized that it was not — he was physically very healthy and a very happy boy, and he was still learning. And — but we kind of kept having these check-ins every so often. You know, as our 6 months became a year, a year and a half, you know, as things took a long time to do, sometimes we had conversations where we thought maybe God put us on this path to help other children and not our own, because we didn't know when it was going to happen. We didn't know the timeline. Things always seemed to be taking longer than we thought they would. And we weren't sure if it would still be the right thing for our kids, and we just had to take it one day at a time. Thank God, by the time the treatment was ready, Benny was in great health, cognitively, physically, emotionally. There was a cut-off made for the treatment of age 5 at that time, and he really just made it. He had his treatment in April, and his birthday was in June, where he turned 5, so just by 2 months. And I'm glad that we were able to do it for him.

So, I'm going to show you some pictures so you can see a little bit about the — what the boys are like. One thing that we always wanted to make sure they were just a full part of life. So, you know, since we were always planning, we had switched from planning for end-of-life to planning for them to live a full life and just, you know, doing the best that we can in every moment. We really focus on therapies and keeping them strong and making them a part of all our family life.

So, let's show some photos. So, we always took the boys swimming. They both love, love the water. We got these cool head supports that they could [use to] really swim around and kick around in the water. They went to school, even though it was really nerve-racking to send them to school, and I had to make sure they had good nursing care. This is them going to preschool.

And this is us on a little bike that my — he's 2 over here. This is — and that's Josh up there. You know, even if they can't do things on their own, it's helping them to do them. [Plays video]

MS. LANDSMAN: [On video] Isn't that so funny? Oh, my goodness. Josh has the most — biggest smile — [inaudible]. [Video ends]

MS. LANDSMAN: And so, the boys were going to have their treatment then, and Ben was the first child, and it was, you know, frightening. We got to the hospital, I think, the first day we were there, and we had met with Dr. Lober, who was the neurosurgeon.

So, this gene therapy treatment, because it's a brain-based disorder, and it's some — because the brain is not producing an essential enzyme — so leukodystrophy — we wanted the gene to get to the brain, where the enzyme is produced. The research had shown that directly injecting the treatment to the brain was the best way to really get it there and get it past the blood-brain barrier, unlike, you know, some other treatments that can be done through an IV. So, it really needed neurosurgery.

The informed consent that we had to do probably took 4 hours, I'm thinking. The whole day was really a blur, you know. And having brain surgery is a huge risk, and it's a huge risk for a child who, you know, is a bit fragile, who has low muscle tone and doesn't breathe as well as everybody else and, you know, has aspiration risk. So, it was really hard. It was a hard day, and on the other side of that coin really was the very early death that would happen. You know, that was a known. That was known, that that would happen. So, we really — it didn't feel like a risk. It felt like a huge risk and also not a risk. It was a huge risk putting them under and going into surgery that day. And then, on the other side of it, you know, with a fatal disease with a fast progression, it didn't feel like we had a choice. Obviously, we did have a choice. We chose very hard and worked really hard for that choice to have this treatment.

But we really, really wanted it for our boys, and we saw how much they were the furthest thing from those pictures I saw early on and that my early assessment of the Canavan kids being vegetables. They had — they have personalities, and they have wants and desires and likes and dislikes. So, we spent the first day doing a lot of testing.

And I skipped over one big part, which was getting our family there. You know, we were doing this treatment in Dayton, Ohio, where there was a neurosurgeon who was comfortable doing this and where we were able to get approval from the hospital and everyone was on board for it.

You know, not everybody wants to take the risk of doing an experimental treatment in their hospital, so that was also a challenge. But just getting there — we are a large family. At that time, we were a family of five. Now we're a of — sorry, five children, so a family of seven. Now we're a family of eight. So, traveling there and just bringing all their equipment and their wheelchairs and their feeding pumps — they're G-tube–fed — and their supplies and medications and helpers. We rented a 15-passenger van and drove the 12 hours from Brooklyn, New York, to Dayton, Ohio. It was quite a trip. We rented a house there, so we would have space for us and our caregivers that

we needed to bring with us. And we also reached out to the community there, and we were able to have some extra caregivers. Some college kids were able to help us when both my husband and I were in the hospital and we needed extra hands.

We were actually kind of lucky in the sense that it was still during a time when school was on Zoom because of COVID. So, my middle schooler was able to not miss any school, even though we lived in Ohio for an extended period of time. That was one upshot of COVID there, but it was intense, packing up our whole life, basically, to go and move to another state for, you know — we had planned on a month, but we ended up being there for a bit longer.

So, we went — Ben went in for surgery that day. You know, I really prepared for him maybe not coming out of surgery. That was something on my mind. It was very heavy. He went into surgery at — you know, first he had some MRIs taken, which took a couple hours, and then into surgery. He went under anesthesia at around 7 a.m. that morning, and he didn't come out of surgery until about 4 p.m. It was a really, really long day, a lot of praying.

Ben is such a wonderful, happy, happy kid. He's a very good patient. So, yeah, back to our photos: Here's Ben that day in the hospital. Here's before surgery. He's all ready. And here he is after surgery. You know, he was — he needed some morphine. He was in pain. There were wonderful service dogs that — you know, this was the ICU floor dog. This was actually, I see — this was not right after surgery, but this was after we came back to Ohio, so after he had his surgery and he woke up. We stayed for a few weeks. We went back home, and we were going to come back in 2 months for Josh's surgery. But Ben had some complications. His wound wasn't closing properly, and we ended up having to take an Angel Flight for an emergency [return] to Ohio. So, you know, there were some complications with the surgery. They ended up changing the way that they closed the surgical wounds, because kids with Canavan disease are different than typical pediatric patients, because they tend to have higher pressure and higher cerebrospinal fluid pressure. So that was pushing the wound open.

After that, they used caps to close the skull where they had formed the injection site after his surgery, and they saw that it was having difficulty staying closed. You know, it was a little bit traumatic for me. When we came back with Josh, we drove again. We ended up planning on staying longer just so that then we saw — you know, we wanted to make sure that he was good and that he would have enough recovery time. So, we had booked our Airbnb

for longer so we wouldn't have any last-minute things come up. We ended up staying that whole summer.

And Josh had a bit of a harder time postsurgery than Benny. He's a more anxious child in general — not as easygoing and, you know, has more stranger anxiety. Here is Josh when he came out of surgery. So, he's still intubated here. [Plays video] That's his grandma talking to him.

WOMAN'S VOICE: [From video] Can you feel it in your throat? [Inaudible] Can you swallow? [Inaudible]

MS. LANDSMAN: So, it is difficult seeing your kids, you know, go under anesthesia and have brain surgery, wake up from it. Josh — you know, had PTSD [posttraumatic stress disorder] from [going to] hospitals after that. So anytime I had to go to an appointment with him, it was a really big deal.

The next time we went to a follow-up appointment with him, not at that time but 6 months later, when we came for his 6-month follow-up, we actually came into the hospital. And as soon as we came out of the elevator, and he had a seizure from the stress and the anxiety. And it took a lot of work emotionally with him to get over that PTSD. And we do a lot of prep work for him now every time he has any doctor's appointment, which is very often, you know.

The boys have a lot of specialists. So, it's difficult. With the boys, you know, since we've had the treatment, I have thought about that treatment and what they have as a — that they're kind of recovering from brain injury. So, the gene therapy really did stop that degeneration that they had going on before. It used to be, you know, little by little, I'd see things chip away from them, things that they were able to do not be able to do one day. You know, suddenly a day would come, and I'd be like, since when did it take Josh an hour to finish his bottle? You know, it used to be 15 minutes, a normal amount of time, and then it just got longer and longer and longer. Little things like that, you know. When did it become so difficult for them to hold a toy, or that they keep dropping it again and again? And you know, I'd just always be seeing these little losses.

Since they've had the treatment, the first change that I saw in both of them was an improvement in their vision. Both of them are legally blind. They do have some vision.

They have cortical vision impairment, which means that the connection between their eye is healthy, but the connection between the eye and the

brain is very spotty. So sometimes it's like they're seeing. Sometimes they are seeing, and sometimes they aren't. It's, you know — you can stand in front of them, and it's like they have to work to turn it on. So, if they are kind of tired that day, they just may not be seeing, because it's too hard for them to look. And sometimes it just might not be working that day.

After treatment, Ben, for the first time in his life, a few weeks after, was tracking me as I walked across the room. And I was like, what? And I just kept walking back and forth to watch him track me, you know, one of those baby milestones that he never reached. Josh, you know — Josh's vision was much poorer than Benny's before treatment, and it has, you know, improved immensely. Both boys can now use their eyes together. They used to have divergence, where one eye would go one way and the other the other way. They'd really be using only one eye at a time. And now they're using both of their eyes at a time, which, you know, really makes them — it improves their quality of life. They're able to engage with people, see what's going on around them. Most importantly, they're both able to use their eye gaze devices much better. They both use computers with an eye tracker on it that can track their eyes, and they can use their eye as if it were a mouse, so that they can then have speech, you know, so kind of like Stephen Hawking, the famous scientist, used.

And you know, I — with that, it's like they have so much thought. And one thing I always think about and try to remind people is that the disease that they have is a white matter disease. So, it affects their motor function. White matter is, you know, what sends those messages, your thoughts to your body. You know, I think I want to pick something up, and then I tell my hand to go pick it up. Without white matter, you can't do that. But you have those thoughts. So, their gray matter is intact, and being able to use the Tobii [eye-tracking system] lets them get out all of those trapped thoughts, everything that's trapped in their bodies out. I can have conversations with them. One of the first really open-ended questions that Benny answered me on his Tobii when — and this was before the treatment — I said Benny, you know, how is the snow outside today, because we had gone out in the snow. And it took him some time, but he scanned all his words, and he said it was cold, wet, and quiet, you know. Those were his observations. They have a lot of thoughts inside of them.

I'll show you Ben using his Tobii, and I hope that you can hear everything he's saying — on his birthday, saying a speech or making a little speech. So, this is him in school at his birthday party, last — his last birthday, when he turned 6.

BENNY: [From video] I'm Ben. I am 6 years old. I can do it. [I'm hungry.] This is fun. See you later, alligator.

MS. LANDSMAN: Yeah. So, we continue to treat the boys as if they are recovering from a brain injury, and that means 7 times a week they have physical therapy, occupational therapy. We have speech therapy every day. And they work really, really, really hard. Both boys had never spoken a word before. You know, since treatment, Josh started to really try and talk and kept trying. And I ended up finding a specialist who, you know, really works with kids with neurological disorders, and he started to have some words.

So now he has like five words where he had zero before. He can say, "Mama," if he wants, which is just, you know, unbelievable. And Ben — Ben has been — his interest has been in walking. All he wants to do is walk.

I'm going to show you some photos of him so you can really get a sense of what it was like for him before and after. But we have Ben — this is before treatment. This is Ben walking in his walker. He really needed all those supports to really hold him up. He's not holding up his own weight. There's like a bicycle seat under him that holds up his weight. [Plays video]

That was a big deal for him, being able to bring a foot forward. This was him a little bit after treatment. This is last year. You see it takes two people to help him. I'm going to fast-forward a little, so a lot less support but two people. [Plays video]

FEMALE VOICE: [From video] Ben, where are you going? You need to look up. I'm moving it, Ben. You can't see it.

MS. LANDSMAN: And this is Ben less than a month ago. [Plays video] So you can see that that improvement keeps on happening, which is just, you know, a beautiful thing, and the boys are motivated to keep doing more. And we work really hard as a family to, you know, keep them involved and included in everything, even, you know, things that they wouldn't necessarily be able to do on their own. This was a fun day. [Plays video]

Sometimes people are like, "Oh, my God, you have six kids. How do you take care of Benny and Josh and them?" And it's really hard, but there's something beautiful about having other kids to interact with them and also remind me what kids want to do. I don't think I would have thought of going — I wouldn't have thought of going on the slide on my own, but my 3-year-old wants to go again and again. I think I went 10 or 15 times with Ben, carrying him up and around over and over again. That's how I get my workout. But you

know, Ben loved every single round, and I wouldn't have gone again and again and again if I didn't have that kid voice telling me, "Let's do it again and again."

[Plays video] Here we are playing Connect 4, getting everyone included.

MS. LANDSMAN: [On video.] So, take a piece.

CHILD'S VOICE: Okay.

MS. LANDSMAN: Benny, he's going to get another piece from you.

CHILD'S VOICE: Okay. I think I —

MS. LANDSMAN: We just really try and have fun and be as normal as we can. In general, the kids are very happy. Happy kids. [Plays video of children laughing] I always — you know, when I need some uplifting, their laughter and just their personalities really, you know, lighten things up for me. They're incredible kids, and we're continuing with the — with, you know, seeing the improvements from the gene therapy.

And we're still going back, at this point, every year for follow-up tests. And you know, the follow-up tests are MRIs, blood work, EEGs, gross motor function tests, a Mullen exam, which is like an IQ test. That's been pretty incredible, just to watch the changes. Before the treatment, we got about a half hour into the test. Usually you just stop when, you know, the kids stop answering questions. They just can't answer anymore. This last visit, at their 2-year follow-up, we got to the end of the test. So that was pretty incredible, to be able to do the full test, to the end, which meant that they were able to answer the questions from the whole exam, — showing in a lot of areas being at age level intellectually. That's something that they never would have been able to express before. So, I'm just so grateful for being able to have been part of the trial, being able to have been able to facilitate it, being able to watch the other families.

And I don't take it lightly that it's a surgery. You know, I get a lot of calls from different families that reach out to me to ask me how it was, what it's like, what do I see in my kids. And you know, it's a scary and difficult thing to go through, and you know, we're on the other side of it, but it's pretty heavy. I always tell families exactly what it was like to go through it all, you know, all the difficulties, things that one might not think of, like Josh was constipated for, you know, over a month afterwards because of the painkillers, just getting the anesthesia. And all that really was very difficult on his system — you know, things that have a longer-lasting effect, wound care, you know. I've

been very lucky to get to know a lot — the other families that got treated afterwards. A lot of them passed through New York on their stopover flights, and I get to see them when they go for their follow-up appointments as they're flying through to Dayton. Some of them are international patients. So, I've been really lucky to connect with other families and be a part of the community.

In general, Canavan has a nice online community. That's really all that we have. There's nobody usually near any one of us, because it's so rare. I think that that was mostly what I was going to speak about today. I'm happy to answer some questions, if there are any.

MS. JACKLER: Yeah. Well, I have a couple [questions] for you, Jennie.

MS. LANDSMAN: Sure.

MS. JACKLER: First of all, thank you so much. Your children are a delight.

MS. LANDSMAN: Yeah, they are.

MS. JACKLER: It was so wonderful to see those videos. And I think, clearly, you and your family and Benny and Josh have been through a lot. And you're one of the few that have had to make these decisions about going through a gene therapy trial. And so, I was wondering what advice you would give to other caregivers who might be considering a gene therapy clinical trial for their children. Is there anything you wish you had known before starting the process?

MS. LANDSMAN: Hm. Anything I wish I had known before starting? Get ready to pack up. [Laughs] Be ready to travel. I didn't think a lot about how much traveling it would be. I became a very good packer and a very good traveler from all of this. I think, you know, knowing that maybe would be a little bit less stressful, if you go in knowing like, "Okay, I'm going to be, like — I have to live at the hospital a lot." And you know, get to know your resources at the hospital and around the hospital. It really helped to find there's lots of charity organizations that help with, you know, meals when you're there, meals for your family, you know. You know, Ronald McDonald is a great resource, and there's lots of resources. But that, you know, is something that, you know, if I had that list ready of all the resources and — you know, I learned about Instacart. I was there being able to order groceries while I was in a hospital room and things like that. I guess that it would've been helpful, to know that. And get some good luggage.

MS. JACKLER: All good advice. So, sort of along those lines, you created a lot of support around you. You found support. You found resources. But are there things, from your experience, that you and your family went through with Josh and Benny — but can you think of ways researchers and drug developers can make gene therapy trials easier for patients and families? Maybe they can't, you know, do everything. You know, you certainly created a lot of opportunity and found a lot of resources, but you know, what is — is there something that the developer can do or the researchers can do to make things a bit easier?

MS. LANDSMAN: One thing that I found is I feel like there's a lack of communication in the science community and in that research community, just from what I have seen. I wish that there was some way we could get everyone together to work together, so that then things could move along perhaps even at a faster pace. I know that things are moving very quickly in the gene therapy world and things have been, you know, progressing rapidly, you know, in this generation.

But for families that are really waiting for treatment or watching the research happen, it's not happening fast enough, especially when you have a degenerative disease where, you know, every single day could, you know, be *the* day. It could be the difference between losing a function or losing life. So, I think if there was a better way to collaborate, and I don't know how to do that, but I wish there was some way that you could bring those great minds together, and it was — there was more collaboration. I think that would be really, really beautiful.

I love what's happening right now, where there's that patient advocacy at the FDA. You know, one thing that we did as a family when things were slowing down was that we actually went down and met with the review board at the FDA and spoke to them about our family and spoke to them about Benny and Josh and, you know — and brought our researcher and brought our whole team and really talked about what we planned to do in the trial. I wish there was an easier way to have that communication between researcher and review boards and families. I wish it were easier. It was very, very difficult, and I just think more collaboration would mean better and faster results.

MS. JACKLER: Thank you. Thank you so much for your time and for sharing your journey with us, and especially for your insights. And I think people are going to find that very helpful. Thank you.

MS. LANDSMAN: Thank you so much for making this happen and for all that you do. [From recording] My name is Jennie Landsman.

MS. JACKLER: That was good enough to hear twice, I have to admit. [Laughs] I have heard it twice, and it is an amazing story that sort of provides a lot of information both about the benefits and the risks, which the FDA talks about a lot — benefits and risks. And I think that story really highlighted their experience in gene therapy. So, as you see, I got to squeeze in a couple of questions at the end for Jennie, but now I'm going to have questions with the panel.

Q&A

MS. JACKLER: So, we're going to open up our panel discussion now. So, we could have — here we are — Bobby, Shandra, and Suzette join us. Thank you all again for being here. Let's see if Shandra — give Shandra just a second. Great. Okay, there you are. Great. So, I do have some sort of questions that were developed based on ones that were provided during the registration process, but at the end, we will have some that maybe weren't covered in registration that would have come in during the sessions today.

And while there are far more questions than we have time for, we're going to do our best to answer as many as we can.

So, my first question's for Bobby. So, Bobby, could you tell us how you found out about the clinical trial that you participated in? And would — where would you encourage other patients to go if they are looking to participate in a clinical trial for their disease or condition?

MR. WISEMAN: One of the uniqueness of the bleeding disorders community — we gather typically 2 or 3 times a year for a national meeting, because we have main advocacy organizations at the national level. Then we also have local-level meetings. And I'm making that distinction because there's been a thread of the different disease states presented of connectivity, resources, and being able to quote-unquote "meet."

So, I have to give the context in order to explain how to find out about the clinical trials within the bleeding disorders community, so it gets context. Because of our disease state, we have 146 federally recognized treatment centers across the U.S. Okay. And with that, most of our treatment centers are located at a teaching hospital as well. Most of the pediatric hemophilia treatment programs and bleeding disorder programs are housed within pediatric wings, and there's a [googad] of researchers. Okay. That's the baseline stuff.

Our national organization — so that I'm very clear when I give this answer — receive the money from the CDC [Centers for Disease Control and Prevention], the FDA, several other places, and pharmaceutical partners. Okay. At our annual meetings, there's the exhibit hall, where you can find such wonderful things to [decorate] your fireplace mantel, your boudoir, and your bathroom.

Okay. You can fill in the blanks yourself. Yet you're also able to, at the preconference, hear a lot of the medical research, connect with researchers, clinicians, etc., etc., who are beginning the journeys of gene therapy and different research trials. There's not a short answer to it because of the complexities of our community, both how males and females are affected and the manifestation of the bleeding disorders.

The easiest way, you know, some of us had to go online and find out, you know, [through] clinicaltrials.gov. For those of us who are little seasoned and mature — you know, like a good pot roast, you know, when you season it a bit and a dozen things; the mothers and parents know about that — we know how to make a phone call and talk with people and get the real nitty gritty, because we all know parents and whatnot who've been through these trials and things — that volume of paperwork you will get lost in reading when you want to know A, B, and C.

That's all I need to know right now. That's how we find out about it. And as has been very well stated, it's conversations. That it's — and I'm sorry, I'm going off. I'm sorry. It's not just the trial itself. It's those pieces, as the young mother just stated, the packing the bags, the Instacart stuff. All of that comes in. It's not just the trial itself.

It's the anguish, the getting life ripped up real quick when a phone call comes and says, "We're ready for you now." And you've got to figure out how to shift life quickly. That's that piece. I'm sorry. That wasn't — I will [try not to] digress.

MS. JACKLER: Thanks. And Suzette or Shandra, if you wanted to hop in and then — the other thing I'm wondering about along those lines are sort of what were the risks and benefits that you can considered when you were enrolling? Was there a deciding factor? I mean, Bobby, you sort of mentioned, you know, it's — there's a lot of upheaval, right? You get the call, and you've got to go, but even before that, like, how do you decide?

MR. WISEMAN: It's like 20/20 hindsight. You know, because of having preexisting medical conditions, you know, have the binders of stuff, checks and

balances, all of that. But with this one so new, it was literally, for me, honestly it was — excuse my — it was a hell of a lot of prayer, quite frankly, and a lot of conversation and keeping and going back to my "whoosah" moments and really thinking it out, and saying I need to put this paperwork aside, so I don't get distracted into thinking about it.

Because when I look at all the paperwork and the stuff that has to be done, that could have been a deterrent. And I really just have to say, wait a minute. This came for reasons because of conversation that started, because your treatment center was not going to be enrolled in this study. So, I literally had to look at that. So that's my answer.

MS. JAMES: I don't have an answer for gene therapy trials, but just the trial that we — that Maya and Xavier were a part of — we really rely on our clinical team and our medical team and, you know, preclinical data. I mean, that is something and our "whoosah" moments as well, Bobby, yes. But — because that does play into it. But I'm extremely appreciative for our medical team, both in Ohio and in Orange County, and how they helped us make this informed decision. And they really did. You know, they let us know what the risks were, and the benefits. I think that is how — I think, for us, that's how it played out.

MS. JACKLER: Okay, great. So, Shandra and Suzette, so you're both strong advocates for your disease areas. So, I'd love to ask you a question that was submitted by one of our industry stakeholders, and it's about the best ways to reach rare disease patients for clinical trials. In your experience, how do newly diagnosed patients or caregivers find their way to your organizations? And what advice do you give companies who might approach your organization looking for assistance in recruiting trial participants?

MS. TRANTHAM: Well, I know, for Friedreich's ataxia, I think that we're a very fortunate community because we have FARA [Friedreich's ataxia Research Alliance], the patient organization for FA. And they have been very involved in making sure that there's a way for people in the community to get information about trials and things that are recruiting. So, they actually developed a patient registry. And so, you join that, and then, as a patient, if a trial comes through that's recruiting and you're eligible or you may meet certain eligibility [criteria], they'll email you so that you'd know about the trial. And I think that's a really good way to reach a lot of people. They also have a huge presence on social media, and so a lot of people in the community get the information from the FARA Facebook page and Instagram account. And I just think that makes it a lot easier, being so connected, for industry to reach

out and inform people of trials and help recruit as fast as possible, because that's a huge problem in the rare disease community. There are so few people that may want to do a trial or maybe want to but [not] even be eligible to do a trial.

And then, for your other question about newly diagnosed patients, I think, because, again, like, props to FARA, because FARA is so connected with the community, they have a patient ambassador program, so these patients have monthly meetings and learn about things that are in development, how to interact with the community. They're out there on Facebook and Instagram and everything. And when they see or hear about a patient being diagnosed, they will get them information to connect to FARA.

I literally did that this morning. I saw someone saying that their kid was just diagnosed like a few weeks ago. So, I think that because of FARA, we have the privilege of that. I would strongly encourage any other disease organizations that are listening or patients to even urge their communities to connect more online.

MS. JAMES: Yeah, I'll second that. I mean, you know, our organization is the BDSRA [Batten Disease Support & Research] Foundation, and I would point these folks towards them. We also have several strong family foundations. And there's a big online presence, whether it be Facebook, support groups, or Instagram. You know, I would really point them in that direction.

MS. JACKLER: Fantastic. Thanks. Shandra — oh, no, Bobby, go ahead.

MR. WISEMAN: And I'm chiming in in my capacity as a former rep of a couple organizations within bleeding disorders, that, if I understood you correctly, [you're asking about] connecting pharmaceutical potential research to rare communities. Did I get that right, Mother Karen?

MS. JACKLER: Yeah, they wanted the —

MR. WISEMAN: Okay, I want to be clear. So, here's my response as an individual. Any entity that chooses to connect with a rare disease population in order to do advancement, I would suggest strongly to come in the door with graciousness and to come in with an open heart wanting to learn and honoring the journeys of those communities.

And do not presuppose what the PDR [*Physician's Desk Reference*] says about that community. Look at engaging with that community from all parts of the U.S. before creating the plan of how you choose to engage with that community. Let that community co-create the plan of collaboration with you.

And the reason why I say it that way — there have been many times entities have come into communities trying to fix things and do not take into account the human factor, the personality factor, the struggles that are both good and bad of the best ways from a best-practices ground-level standpoint.

Both ways Mother Shandra and my good God girlfriend down there Suzette said — yeah, I just — you done got a whole — you're my sidekick now — have talked about how communities engage, those pieces, because it's distinctly different when you come in willing to learn and understand versus just the PDR or what a document said that does not have voice. And I'm still missing those LEGO cars [I'm seeing] in the background, Suzette.

[Cross talk]

MS. JACKLER: So that's the patient-focused drug development right there.

So, Shandra, so you have a unique perspective as a researcher and patient. So, how has your role as a researcher changed your perspective on gene therapy and critical trials? Are there any learnings from this experience that you'd share with other patients?

MS. TRANTHAM: This is a bit tricky of a question because, like, obviously, you don't — like gene therapy isn't in trials for my disease. So, we don't fully know or even at all know how it's going to affect people and whether it's going to help the disease or not. We only have data in animals. And so, I think that before I became a researcher, I viewed gene therapy and clinical trials in general maybe differently.

I think I was more so driven by hope than, like, analyzing realistically what might happen and side effects and everything. Obviously, like, being a researcher has not crushed my hope, but it's more so — made me more critical of, like, how a trial is set up, what the possible side effects are, like, how I would choose between trials if there are multiple trials, what I think that the science in both trials — like which one is more, like, exciting in my research opinion.

And I think, like, that's a privilege I have as a scientist, that, like, not everyone is going to be able to look at a clinical trial that way before they join it. So, I think that honestly, like, there's a lot of work that we can do, that industry can do to try and make these aspects of trials in gene therapy more accessible to patients so that they fully understand things better and they know what they're signing up for.

I wanted to specifically say that when you join a clinical trial, they force you to sign an informed consent, which, like, goes through in lay language how you're — like what being in this trial means and any possible side effects that they know about and things like that. So, you get that information while you're in the clinic. But I think that there's kind of a lapse in getting that information before you actually go there. So, before you even decide if you want to participate, it can be hard to fully understand what's expected, because you don't get that informed explanation until you're there.

MS. JAMES: I think that's a really good point, Shandra. I feel like for many of us, when we're dealing with informed consent, or when we are anticipating, like our Batten community has for so long, and so many companies that were almost there and then aren't in business any longer. We never really feel like we get the full story. You know, you don't get the full story until you're signing on the dotted line, right? And that's what's really tricky, because we — you know, patient organizations, professional organizations, we could be, I think, utilized in a much better way, in a much more powerful way if we did have more knowledge. I realize that that can be opening up a can of worms maybe sometimes, but everything is [held] so close to the vest, you know, unless you have an in, which many of us have figured out how to do, it's hard to get the full story.

MR. WISEMAN: And I would agree with that, and that clutching it to the vest — and Shandra, you're correct — that when starting the paperwork versus when actually starting whatever the treatment or therapy, there's a lapse, and then when you're in that clinic space, it's like, here, read this, read this, sign this, sign this. For me, it's like an overload. It's like, okay, I have to do this, put a pen to paper on this for the next things to happen, and not fully really processed it, you know, because it's that distinct difference between the thought of the trial, getting cleared to get into the trial. Now you're in the pretrial visits. Here's all this other stuff you have to do. Now here's informed consent again. This is all what this means. And it's a blur. I've got adult "squirrel" ADD [attention deficit disorder] modes. After an hour and a half, 2 hours, I'm — my brain — I'm like — it's like it's too much. It's overload, because, you know, I'm reading about it now, and then it's like, now here's this. But what does this really mean? And to your point, Suzette, who has that information that can support a patient through the process when they get there, you know, and where it's just not a normal doctor visit? Okay. Back to you. Yeah. Sorry.

MS. JAMES: I feel fortunate that in both of our instances with, you know, both sets of clinicians that we worked with, we did feel like, you know, we were getting

the full story. But up until that point, until it gets to that point, you know, it's hard. It's hard to figure that out.

MR. WISEMAN: Yeah. And especially the bleeding disorders community-wide, because it's so new, who has that clutch of information of what is it really like? Because for so many years, we've heard the cure, the cure. But even with the gene [therapy] — okay, before we sidetrack each other, because we could keep going. We could keep going. [Laughter.]

MS. JACKLER: Well, actually, one of the questions I had was about the informed consent process, and what that looked like. And so maybe, to follow that up, it's like, were you ever consulted on the design of a trial, and if so, how? Did it include things like informed consent or any other part of the trial, and what it might look like.

MR. WISEMAN: Yes and no. When I say that, I was asked to be the international patient representative for clinical trials in the hemophilia community, and at that time, worldwide, they made it very clear, the global hemophilia bleeding disorders community. So, there were representatives from the medical community, psychosocial, etc., etc., and I was selected as the patient voice. So, we went through all this stuff, the standard quality of life questionnaires that were to be involved in the study. And some of the study-specific questionnaires brought up some challenges and concerns around them, both in terms of who was eligible to participate and the wording of some of the questions, which had an implication around some other stuff. I'll leave it at that for now. Then also, I did have some discussions with them from the social determinants of health standpoint. What if someone doesn't have transportation to get to wherever the thing is at? What if someone works at night, and they have to come during the day? So, from that piece, on an international level, yes.

What I have found for many of the trials in the U.S. bleeding disorders community, there's not really patient involvement in the design until there's the implementation of whatever the trial is, be it for a new product or what have you. There's not that true collaboration piece of all the players at the table, where there is the collaboration piece in the discussion of what is needed. Does that make sense, or do you want me to clarify it? So that there is discussion at our annual meetings at our local level. This is what the community needs or what the community would like. Here's why. Educational resources or what have you. However, the collaboration of designing a trial or what will go into a new whatever, there's a disconnect. Those that are able to fund a trial, develop a trial, do that in essence behind closed doors, per se.

Then when it's ready to receive participants into the trial, then it's all that "we need to get people in it." It's like, wait a minute. How long have you been working on this? That's that disconnect where it's like, if there was more of a connection, then I believe that there would be more interest within the bleeding disorders community to participate because then it's more transparent and more inclusive, as opposed to exclusive.

MS. JACKLER: So maybe — so what I'm hearing is maybe you get questions about how do we get you to come to a trial and stay in a trial, but not so much about what should this trial measure. Is that what you are expressing?

MR. WISEMAN: What the trial measures and how it's being conducted, those things, or development of a new product, that there's active engagement in that piece at all levels of community, but not the other way around.

MS. JACKLER: Okay. Suzette or Shandra, any experience in folks coming to your communities about clinical trials?

MS. JAMES: I don't. Shandra might. But I mean, every — you know, I would say the majority of individuals within the Batten community — we just want a trial.

MS. JACKLER: Yeah. Of course.

MS. JAMES: I mean, not a poorly done trial, not a poorly executed — you know, we want a great trial. But we need to get to that point. We're not even at that point and had the rug pulled out from under us so many times that, you know, this is a question that I would love to be able to answer, but —

MR. WISEMAN: And that — I have learned so much from Suzette in this time we've presented and last time that I had never heard of this challenge at all. And to have to hear parents have to make a decision on how their child lives or dies or not, and the tomfoolery – I've said it – around that nothing is done from a preventive standpoint from the powers that can be. But we can make something new if you've got seasonal allergies. Okay? Really quick. When there — the human life and value is more important than an ROI [return on investment], or some car, or some corporate office, when lives are at stake, and it only is consequential to the powers that be, or whomever, is when it comes in their backyard. It is sad to me. I'm sorry. It's so sad to me. I'm having to repeat the same thing over and over and again to advocate for our children and our young adults and our adults to get appropriate health care in systems that are supposed to work, that there are more barriers and challenges, as opposed to more balloons of celebration and roadways of hope. I'm sorry. I was trying to be good. I'm sorry. Okay. I'm sorry.

MS. JACKLER: Bobby, you're as real as they get, for sure. But you know, as somebody who's been through a gene therapy trial, you know that there's a lot of follow-up, and you've been going through follow-up. Can you talk to us about what that's been like for you?

MR. WISEMAN: Yes, I am — Karen, I love you dearly, Karen, because you've been — you are one of the people who can rein me in, because you know about my social justice side. Actually, my five-year anniversary is June of this year, of being on the trial that I'm on. Then I officially go to phase 2, which is, they're going to follow me for another 5 years. That's in order to have long-term data. Okay?

Now, bullet point 1: two 3-hour visits after the first getting the gene therapy piece, lab work, all that stuff, answering at least a good 30 pages of questionnaires, true/false, scales to 1 to 10. Okay? Basically, that was a period of 2 to 3 months. Then it went down to every other week. Then it kept transitioning down and down, filling out the same questionnaires that I filled out the first time and the second time, and we have a number of week visits, how they break it out. I think by visit number 48, something like that, I'm like, "I don't want to fill out nothing else. It's the same questionnaire. I don't have no new meds. Y'all would know I have new meds. I have to tell you, and I've got to go to the emergency room if I had to. Don't keep asking me the same questions." Okay?

Now, this particular trial I was in, they gave us a diary to fill out. Remember, y'all — some of y'all, because some of us who are 19 and above, like myself, that — remember the PalmPilots? They gave us a PalmPilot to fill out if you're bleeding. Y'all, I'm on gene therapy; you all know what my levels look like. And daily I had to put in if I bled or not. Think about my brain going, "I'm not bleeding, but I've got to answer if I am bleeding, or not. But you're giving me something that's supposed to cure something." Okay? Tomfoolery! Anyway. So, then we progress forward. Now, magically, then they come up and say, partway through, almost halfway through the study, "We need a sample to see if the vector has sloughed off." Now, I am going to say it as delicately as I know how. They needed to check seminal fluids to see if the AAV vector is sloughing off, in order, you know, birth control and all that stuff. Okay? Now, when the research nurse asked me for a sample, me being me after all this lab work and everything, they gave me a PDF for everything. Everything underneath the sun. I say, can you please give me a PDF to collect a sample. Yes, I did. Because, at this point, and I was being flippant and serious, I'm like, I didn't want anything to contaminate the sample. I'm like, baby oil? Y'all understand what I'm saying, okay? I was being serious

with them. And I said, “Okay, not a problem.” So, they got the first sample. Now mind you, I’m now 51, so minus 5 years, okay? The first one was okay. Here of late there has been huge discussion around sample 2 and 3. And at one point I said to them, “Dear hearts, y’all are forgetting I am still a grown individual that’s living life. So, for you to email me the night before my visit you need a sample, ahem, that might be challenging some days, because” — some of the men that might be on here can understand what I’m saying; I’m being very good about this part here — “that just does not happen all the time, you know.” And so, then I ended up getting into a conversation with the research people. I said, “Some of the stuff you all are asking for is unrealistic, the timeline, and not honoring that I also have a life and work and school and family. I don’t mind the questionnaires. They get done when they get done. That — you know I’m not bleeding because you did not hear that from my doctor. So, some of the stuff you are asking for is not honoring the fidelity of the study, number one, and it’s not honoring the fidelity of the relationship between patient and doctor, because as soon as I tell him what’s going on, he’s going to tell you anyway.” So, then the question becomes, when is too much paperwork too much, in my opinion, that fine balancing line? I’m like, y’all, if we are 5 years in, all the paperwork is the same. The lab work is the same. That balance and that give-and-take. Yes, it’s an arduous process. Yes, I relocated from one state to another, so there is all this coordination and then back. Would I do it again? I don’t know. Because — I don’t know. I was knocked out of a study for the pulmonary and arterial side because of this gene therapy.

MS. JACKLER: Well, I think this sort of brings me to — another really big question I have, which is, what can researchers and drug developers do to make gene trials easier for patients? I mean, you sort of talked about the — it was — there’s a lot of paperwork and it’s not clear to you how, in the follow-up phase, how this sort of relates back to the study questions. And so that is one thing. But are there other things that can help make gene therapy trials easier? Or Suzette, I know you haven’t had the opportunity to do that yet, but just sort of thinking ahead of what you know about — and as Bobby said and sort of a general theme that I’ve heard is, like, you’re trying to live life as well. You have personal goals to meet. Your kids have goals you’re trying to, you know, get them through. You’re trying to live a normal life and enjoy things. So how can we make things easier for patients and honor that idea that you’re not just patients, you’re people?

MR. WISEMAN: Accessibility. And what I mean by that — I’m sorry. Having that — having stuff available to find out from the Internet is great. But if someone

doesn't have a computer to be able to go to clinical trial [clinicaltrials.gov], wherever it's located, or know how to find that, there's a disconnect; that if there's a community that has well over 200,000 people in it, there is access to things for those communities. If your communities don't have those large numbers, which generate other things, you don't have the accessibility to things. It's called accessibility to calmness, so that as a parent, you're calm that you can see your kid grow. As a parent, you have accessibility to relief that there's stuff to help your child, that — because not only, you know, as Suzette and Shandra have put it, and the ones that are caring for our rare kids, is those medical teams who are also in the support of trying to get things to happen. But it just does not exist, because our numbers individually are small, and to make it easier, I would say, are the folks that get out of the equation of what is rare and not rare, and come to the equation of what is life. And if we're really talking about trying to have life and live life, make it happen. If we can mobilize people together to get things fixed overnight for this, that, and the other, a hurricane, a flood, whatever, why not the same energy and effort to save our babies? Why not the same energy and effort to take relief off of parents for them having to see the stresses their child is going through? Why not put energy into assisting the medical teams who're trying to make this happen. It doesn't make sense to me to have to move a family across country for a treatment of a couple months, or all these back-and-forth plane trips. What's with that?

MS. JACKLER: So, tell me about that, Suzette. Tell me about that.

MS. JAMES: Well, I mean, exactly. We did fly back, and it was the compassionate use part of the trial, right; it wasn't the initial part. We did fly back and forth for 6 months, and we would have continued to do that and probably would have moved, honestly. We would have moved, had Dr. Wong at CHOC not set up a compassionate use portion here in California. It would — and I think this is another question that might be coming, so I might be dovetailing to it. But you know, I realize that there is a small "n" [sample size] already with patient population, but I know, such as in Europe and elsewhere, the children — they have far more children in their trials than we do. They start with 20 or 25, and we have 5. Right? So, I think that — you know, as in some other diseases, as you were talking before, there may be difficulty in finding patients to do these trials. I might be speaking out of turn, but I don't believe you're going to have that issue with the Batten community. Yes, we are a very small number in population, right?

That brings me to the next point, which is, you know, expanding just beyond one phenotype, because that seems to be what is really done now. They

home in on a certain age. I understand, in part, why that is done, but we need to address that. I mean, it has just happened recently, where there is a gene therapy trial happening in the U.K. and should be here, but you have to be under 7 in order to receive gene therapy to the eye. And so, you know, some other forms of Batten, like CLN1, they have multiple phenotypes underneath their larger umbrella that they include in trials. We don't do that always. And I think, you know, expanding that [age range] will expand access and potentially, you know, allow us to set up things geographically so that maybe you don't have to fly 6 hours. Right? I mean, the worst part was when Beau — when it was Beau's turn to travel with Maya, he would have to know where in the airport there were family bathrooms, because Maya's a teenage girl, and he would have to go in too — and find it. He knew every place, every airport. You know, we typically had one or two that we would go through, right, hubs, and he would know where the family bathrooms are. But — you know, I don't know if I answered your question, but I do think expansion is needed. Expansion.

MS. JACKLER: Expansion. Yes. Great answer.

MS. TRANTHAM: Sorry.

MS. JACKLER: No, Shandra, please.

MS. TRANTHAM: I was going to say I think patient-focused drug development really does make it easier. This is kind of going back a little to what you asked before, but I think patient input on the design of the trials is a really important thing. I have done four clinical trials previously and have not been ever asked whether something is a reasonable thing to ask for or whether is this, like, too much in the design of the trial. But I am actually starting a clinical trial next week, and they have asked me multiple times over the last couple of months in developing the trial, like, "Is this outcome measure, like a muscle biopsy, something that you would be willing or other people with FA would be willing to do in the trial, or is this procedure too complicated for us to expect patients to do on their own?" Things like that. And I think that that's been a really great experience, and I want to see more of that in, like, all the trials that are developed. And I think that just makes it easier for patients to participate, because then, like, the trial is already designed to be as accessible to patients as possible so they don't have to deal with those challenges once they're already in the trial.

MS. JACKLER: Shandra, I am going to switch gears just a tiny bit because I want to spend the last few minutes we have on questions that were coming in while

you guys were speaking today. So, one question I have — and I'll start with Shandra, and then, Suzette and Bobby, please chime in if you have anything to add. What specific factors would [help] you choose to participate in a gene therapy clinical trial instead of a small molecule therapy clinical trial, or vice versa?

MS. TRANTHAM: So that's going to be very specific to FA, but I'll answer it as best as I can, just in general. But for me, personally, knowing that a small molecule is something that you can start and stop if it doesn't work as well, or you can try something else, but with gene therapy it is like one and done. You can't get another gene therapy if that one didn't work for you. You can't then go on to try other small molecule drugs in trials because once you've done gene therapy, you'd be excluded from other clinical trials. So for me personally, I would — I could hold a gene therapy trial to a very, very high standard, and I wouldn't choose to participate in a gene therapy trial until there's probably already some data on other patients on how it affects my disease, which, I know, like, some people have to do it, but maybe other people have more urgency because their disease is more progressed. But from my personal standpoint, I would just be very, very picky on waiting for gene therapy until it's to my standards. And I would do, like, small molecules first.

MS. JACKLER: Suzette, any thoughts on gene therapy versus small molecule?

MS. JAMES: I mean, I think Shandra has said it best. It's really a difference in the urgency, right? I mean that — to me, that's a really very specific and individual decision, and it's based upon where you are in your health. It's based upon the normal progression of your disease and whether you can wait. That's — you know, that's unfortunately what many people within the Batten community are facing, you know. We can't — and especially if you look at the history, the statistics that I gave earlier, with these companies going out of business because they can't get things approved. We don't have anything. I mean, we thought we were doing great just a year ago, and, you know, the landscape looks very different right now.

So, I think it is a very different perspective when you've actually received something, and when you've been waiting for 10 years. And you've been getting infusions for 6 years, where you're there twice a month for 8 hours at a time, and you're getting a brain infusion that is, you know, a blessing, and we are very thankful, but it is also really hard on some of the kids. Maya has been looking at that, you know, for 6 years. And right now, there's nothing in sight, and we kept telling ourselves every 2 years there was going to be gene

therapy, or something else, small molecule, this, that. It just hasn't. So yeah, I just think it's a really individual decision based upon where you are healthwise, and the severity of your disease, for sure.

MS. JACKLER: And Bobby?

MR. WISEMAN: I echo that, because in the bleeding disorders community, we have some challenges. And something that hit my brain as both Shandra and Suzette were talking, treating protocols pre-1970 was cryoprecipitate, or fresh frozen plasma, which was a long, arduous process, and debilitating, to say the least. And so to be able to sit here and see the vast difference of change in our community in the 50 years, 60 years almost, and that — to hear that some of the challenges of we need something, we keep hearing there is something, and it's not there, and that question of quality of life, what is the big point to be?

That — and I'm sitting here balancing because, I'm a mama's boy. Let me just be transparent with this. And to hear Suzette's story, to hear Jennie's story, and Shandra's story, Shandra, the impact that you're doing with the young women and your community, the force that you are, these two mothers here who've got multiple children and are calmly talking about their story, they're calmly talking about how to make sure their kids are staying alive, they're calmly talking about how they have to make decisions of not only peace for their children, but for others in the community who they are connected to, the impact of that. And when the question comes to what's the choice we make, there is no answer to it, and there is no option to choose from. I'm not trying to be funny, but there is no option. The option is I'm trying to choose life for my children. That's all I can choose right now.

MS. JACKLER: Yeah. This is, I mean, I can see the emotion on the panel here, and these decisions are fraught. They're not easy. And I think what you guys have done has really helped us understand a lot of what goes into the decision making, and it's — and it's hard. It's easy and it's hard at the same time.

Actually, I think we're out of time. I think this has been wonderful, and, before I hand it over to Anne, I want to personally thank you all for sharing your stories. I know it's not easy. But what — when you do share, you help others, and I really, really appreciate that. So, thank you so much. So, Anne, I am going to hand it off to you now.

DR. ROWZEE: Okay. Great. Thanks, Karen. And I hope our panelists have been able to, between giving answers and listening to the presentation, have been able to take a moment and look at the chat and see all the outpouring of

support and gratitude that is coming from our audience today and just the appreciation for you all taking so much time to prepare, spend half of a day with us when we know you have very pressing priorities, but also just, you know, being completely open and just really baring what these journeys have been for you and what it's meant.

And I think that it definitely takes strength of character that not everybody possesses. So, I just wanted to take a moment to add my thanks to what you're seeing in the chat and what Karen had said already. We've been really grateful to have this opportunity to connect, to learn more about your experiences. And what I think what you could learn from the conversation today is there's a lot of commonalities across the experiences with clinical trials, gene therapy trials, small molecule therapies, something in between enzymes and other types of biologic products. So, I hope that folks can take some lessons learned, and I think we saw that in the chat, too, of folks who perhaps are representing industry partners who are showing they are trying to make improvements, and they're trying to make things like informed consent more interactive. You'll see some folks out there trying to say, you know, "We're working on it, and we're making some steps forward."

So, I think, you know, as you saw my earlier comments, my opening comments, we really wanted this to be interactive, and we are seeing that from the questions that have come in and from the conversation in the chat. I'll stop, because I know we are running out of time. But just a big thank-you to everybody who presented today and who, you know, listened online and shared their thoughts. Just a final thank-you to everyone who helped plan today's event: our colleagues at OTP, Dr. Sherafat, Karen from CBER, and the Office of Patient Affairs. We truly appreciate your support in helping shape this discussion. I'm also excited to share, in the next coming months, OTP will be providing more educational resources and hosting more events about topics related to regenerative medicine, so please stay tuned for those announcements.

We have two more events scheduled later this month, including a town hall on gene therapy, chemistry, manufacturing, and controls on April 25 — thank you; sorry; slide change — and a public listening session on postapproval safety and efficacy data on cell and gene therapy products. That is on April 27. Those events will be held virtually again. Registration is free, and you can find those links on fda.gov.

You know, please stay up to date with these events. I think it will be the next slide. You can visit the CBER website. You can sign up for what is new at

CBER. Yes, thank you. You can follow us on Twitter at @FDACBER. And again, we are encouraging folks to use the hashtag #RegenMedEd on social media to share your thoughts about today's event. Let us know what information and resources you are interested in seeing from us in the future. And the last slide. Oh, maybe that was the last slide.

Thanks, everyone, for continuing to work together, and have a great day. Take care now.

[END RECORDING]