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Food and Drug Administration

RegenMedEd: An FDA CBER OTAT Webinar Series

The Critical Role of Patients in Advancing Gene Therapy Treatments for Rare Diseases

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Welcome

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Presentation: Brian O'Mahony, Personal Experience of Hemophilia Gene Therapy

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Chief Executive
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Presentation: Julienne Vaillancourt, CBER Perspective on the Critical Role of Patients in Advancing Gene Therapy Treatments for Rare Diseases

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Q&A/Closing Remarks

PROCEEDINGS

ANNE ROWZEE: Okay, I'm starting to see our participants roll in. I'm going to go ahead and get started. Hello everyone. Thank you all for joining today's webinar on the critical role of patients in advancing gene therapy treatments for rare diseases. Today's webinar is hosted by the Office of Tissues and Advanced Therapies, or OTAT for short, within the Center for Biologics Evaluation and Research at the U.S. Food and Drug Administration. My name is Anne Rowzee. I am an Associate Director for Policy at OTAT, and I'll also be your host for today's webinar.

So, before we get started, I'd just like to share a few notes. This webinar is being recorded; the recording and the slides will be posted on FDA's website in the next few weeks. Closed captioning for the event is available in Zoom. We will have some time during today's panel discussion for questions. If you have a question for our panelists, please type your question directly in the Q&A box in Zoom. Regarding questions, please note, we are unable to answer questions about specific medical conditions or diagnoses, but we encourage you to discuss those questions directly with your health care team. We also understand that folks may have a lot of questions about the status of specific investigational products or drug applications. However, there are laws that FDA must follow that limit the information we can provide about investigational products. We do appreciate your questions and comments, and we'll do our best to address as many as we can during our one-hour time frame. Finally, please use the chat box if you want to share a general comment with everyone or if you are experiencing technical difficulties; someone will assist you.

Okay, so today's webinar is the second in OTAT's webinar series called RegenMedEd. The goal of our webinar series is to bring together patients and advocates, caregivers, and other stakeholders to discuss regenerative medicine therapies, including gene and cell therapies, as well as to explore opportunities for FDA patients and their advocates to work together to help advance these important products. Today's RegenMedEd webinar is also OTAT's own small contribution to the celebration of Rare Disease Day, which, as many of you know, was last week. Rare Disease Day is an international day of awareness for the 300 million people living with a rare disease worldwide. It's also a celebration of their individuality, perseverance, and their bravery. While there is still much to be learned, we do know that around 80% of rare diseases are caused by a single gene defect, and this is what makes the field of regenerative medicine, and gene therapy in particular, so promising for the treatment of rare diseases. Gene therapies to treat rare diseases caused by single gene defects could mean improvements in health outcomes, in quality of life, and in disease management for patients and their families. There are currently two FDA-approved gene therapies for single gene disorders, and we anticipate many more approvals in the coming years, because right now, we just checked the numbers, and OTAT has 975 active Investigational New Drug applications for gene therapy treatment; 975 investigational products, so a lot of potential.

But I'd like to take a second to just emphasize that none of the scientific progress would be possible without the patients who participate in clinical research; patients who enroll in clinical trials are brave. I've often heard OTAT's office director Dr. Wilson Bryan say that patients are

heroes, and he even said in our first webinar that we owe patients a great debt for choosing to participate in clinical research and helping to bring forward products to treat rare diseases. Rare disease patients, by definition, are a precious resource for advancing clinical research in their disease area. They deserve high quality development programs that produce safe and effective and high-quality medical products. We understand that the decision to participate in a clinical trial is not easy, and we thank parents, their family—patients, excuse me—their families, and caregivers for their help in advancing the field of regenerative medicine and for helping to bring new treatments to people who need them.

So, with that, I am really excited to introduce our panelists for today's discussion. First up, we're joined by Debbie Drell. Debbie is the Director of Membership Services at the National Organization for Rare Disorders, or NORD. NORD is a national nonprofit patient advocacy organization dedicated to improving the lives of the roughly 25 million Americans who live with a rare disease. In her role, Debbie oversees NORD's membership programs supporting the collective and individual needs of rare disease patient organizations, patients, and advocates through education, research, advocacy, and mentorship. Debbie is also a caregiver for her sister, who has a rare lung disease.

We will then next hear from Brian O'Mahony, who we were introduced to through Debbie, so thanks, Debbie, for that introduction. Brian is the Chief Executive of the Irish Haemophilia Society, which is a charity representing people with hemophilia, von Willebrand disease, and other inherited bleeding disorders. In his role, Brian leads the society, prepares policies and plans for the organization, and oversees the implementation of the strategic plan. Brian previously served as president of the European Haemophilia Consortium and the World Federation of Hemophilia. Brian also has hemophilia and participated in the gene therapy clinical trial, and we're going to hear about his experience as a patient in a clinical trial in a little bit.

Finally, we'll hear from Captain Julienne Vaillancourt. Julie is a captain in the U.S. Public Health Service Commissioned Corps and also serves as a Rare Disease Liaison and Policy Advisor in the Center for Biologics Evaluation and Research at the FDA. In her role, Julie coordinates CBER's rare disease program, which supports the development of products for patients with rare diseases. Julie also works with rare disease experts throughout the FDA to advance patient engagement and patient-focused medical product development. Thanks everybody for joining us today. I'm actually now going to pass it over to Debbie to talk about her experience as a caregiver and an advocate.

DEBBIE DRELL: Thank you so much, Anne. I am honored to be able to speak on this panel and to more than 300 patients and caregivers and advocates on the subject of the courage of patients participating in research. I have nothing to disclose except for the love of my sister, which I think is hilarious to say. I work at NORD, and it's a labor of love. I came into the rare disease space seeking a cure for my sister, anything to make her life better, in 1998. She's my big sister. She was 28 years old when she was diagnosed with a rare life-threatening heart and lung condition called pulmonary hypertension, and doctors told her she had less than two years to

live, so she wasn't going to live to see her 30th birthday. What we didn't know was that the past 12 years prior to her diagnosis, there were patients who were looking for each other; they found NORD. Then NORD helped them find each other. So there were—there wasn't anything in the 80s for pulmonary hypertension; the patients weren't connected, there was no Internet, and they wrote letters to NORD. NORD helped patients find each other; the very first sort of kitchen table meeting of patients was in the early 90s, and they formed the Pulmonary Hypertension Association. That organization led fundraisers, they connected the community, they connected researchers with the community, and researchers asked the patients, "Hey, when you do this big conference, the largest gathering of pulmonary hypertension patients, can we draw blood? Can we come and set up a research room?" And the physician who led the research effort at that conference collaboratively collected more blood that day than he had his entire year prior, because it was the largest gathering of patients, and because there was trust between the patients and the physician-researchers, patients signed up willingly, and it was incredible, that conference and subsequent conferences, all of the patient activities, the nonprofit organization.

That all led to the development of one drug that was FDA approved the year my sister was diagnosed. My sister did not die; the drug saved her life. We took for granted that there were people involved in generating research, in working collaboratively, both patients, caregivers, and the researchers, a disease that kills within two years 50% of patients who are undiagnosed, and it's a disease that was diagnosed in autopsy. We didn't know any of that; we just knew, hey, there's a drug that's approved, and we were grateful. We were so grateful we just didn't know, we took it for granted, so it's important, I think, telling the story that the heroes before my sister were those that gave their blood, those that filled out surveys and questionnaires, those that made the sacrifice of their time. The disease is very limiting of their energy, and there's only so much they can do and so, you know, you all, this rare disease community saved my sister's life. I worked at the Pulmonary Hypertension Association for 14 years before then moving on to work for NORD, and I've been at NORD for five years, and I will say that, even though I work at NORD, I feel like, you know, maybe there's a bias— "they work at NORD" — but even before that, I knew that NORD was the reason that patients were able to get together. And my job at NORD, I feel like I'm giving it back helping nonprofit organizations get to the point where they can collaborate, if they're not already doing so, collaborate with researchers or be the researchers leading drug development so that more people, like my sister, you know, I came in, with one sister. My family grew when I came into pulmonary hypertension. It grew to, you know, the 30,000 people with PH; those all became my brothers and sisters. Then I worked at NORD; now it's 30 million Americans, you know, what a big family I have. And I tell this story because rare disease, they just happened, and it's a global story now. It's a global family, and in telling my sister's story, and my sister doing advocacy, we're able to continue to help support others. Next slide, please.

So, my sister, it took her 12 years to get diagnosed. One in 13 people are undiagnosed; this chart, this infographic, is sort of the navigation. It looks gnarly because it is, you know, there's so many different paths to diagnosis. Patients have to see multiple physicians, they have to learn about genetic testing, or they learn about it along the way, you know, we don't know

about a rare disease unless and when it impacts us, and so there's a power in telling your story and an understanding that it does take a while to get diagnosed and, oftentimes, the disease is way more advanced, because now it is a disease that cannot be ignored when, early on, the symptoms may be common. So, my sister's story, she talked to other patients. She learned googling. Unfortunately, it's not the best way of learning, but it is what was available to her through social media, talking to her doctors and specialists, and then she found a nonprofit organization and really got involved and engaged. Next slide, please.

So, I say all of this leading up to, you know, how do you get involved in research? Well, I think, oftentimes people go through the stages of grief in their diagnosis. Once you're diagnosed, there's a new normal. There's your life, change your lifespan, what you thought your future was going to look like. Everything changes, and it was true for my sister. And part of the healing and getting involved in research can involve telling your story. Write your story, so that you can tell it to yourself, so you can look at it. Tell it to others; tell it to people you trust. Tell your story, and connect with your nonprofit organization, if there is one. Share your story with local media.

You know, with Rare Disease Day, that power, because 30 million Americans and 300 million people around the world, we're all telling our stories. That helps identify other people, cut the diagnosis cycle, you know, let people know what your symptoms were. Talk about how you got diagnosed. And if you're involved in research, tell that story, too; that's a story people aren't aware of. If I had known that I could, you know, give my information, and participate in research, I would have done it immediately, but I didn't know that that was a possibility. I thought writing a letter to Congress was the thing to do. So, you know, highly encourage you to tell your story, share it with the world, and NORD has resources on our website on how to write an effective speech, on how to tell your story. We have these resources in Spanish as well. Next slide, please.

And I'll put it in the chat afterwards, a link to finding a nonprofit, to getting involved locally, to telling your story, so we do have some links for resources there. And, you know, through the stages of grief, when you're telling your story, there's another way of telling your story. You tell it through medical research, which, you know, whether that's telling it through a natural history study, which collects data from the time you're diagnosed through the progression of your life; through other registries; through clinical trials, which tests new drugs or medical devices to make sure that they're safe and effective, you're telling your story to medical research. It takes time, it takes effort, but you're saving lives when you do that. It informs best practices in patient care, it helps understand what you want in a treatment and how it affects you. It impacts what you're willing to risk. It impacts, you know, how the disease affects you can help, in the natural history, can help you, can help the collective community for future clinical trials. And then I just want to mention, NORD has a partnership with Critical Path Institute and received funding from FDA to create the Rare Disease Cures Accelerator Data Analytics Platform. So, if you participate in a registry with one rare disease, imagine what it would be like if all the rare diseases, all 7,000 rare diseases, had these registries looking at diagnosis, through your life, all of this data, and then pooling it all together, how are we going to accelerate cures unless we bring it all together? Imagine the power of having all of these united databases in a

neutral independent integrative way where researchers, organizations, industry can tap in and see across these rare diseases, you know, commonalities, cross-disease analysis, bringing more treatments to market in a more efficient way, if we collaborate collectively. We can do that, and NORD's role is really helping people set up registries, helping nonprofits form, helping registries come together in this rare disease cures accelerator platform, which helps really collect all of the data in one place. And data sharing is the future and participating in one study is a step towards helping us find more cures for the 95% of rare diseases that don't have treatments.

I am so grateful my sister is alive. She is alive because of people before her who participated in studies and because of nonprofits who led the way in doing things like collecting blood at conferences, so I thank you so much—I think I'm out of time—and I really appreciate the opportunity of sharing my sister's story with all of you. Thank you.

ANNE ROWZEE: Thank you, Debbie. Thank you so much for sharing your story with us. I'm now going to pass the mic over to Brian to talk about his experience participating in a gene therapy clinical trial.

BRIAN O'MAHONY: Thank you. So I'm going to talk about my personal experience of participating in a gene therapy clinical trial. I have a long family history of hemophilia. I had four uncles with hemophilia, three brothers with hemophilia, two of whom I never met, because they died in childhood from bleeding. Next slide, please.

These are my disclosures. Next slide, please.

So my treatment history, it goes right from the era of my childhood, where I had no treatment, many, many bleeds and joints and muscles and nosebleeds with consequent joint damage and need for joint surgery later in life, to the plasma, then plasma-derived factor concentrates, then a recombinant synthetic factor IX concentrate, then a clinical trial with another recombinant nine, then an extended half-life factor IX and, finally, at the age of 62, a gene therapy. Next slide, please.

So, my expectations going into the clinical trial, in fact, were—I was part of the CoreHEM process, which looked at the outcomes that we really wanted to see from a technical trial, and these are real outcomes. That really framed my own thoughts, so I want, ideally, I want to see duration of expression of at least 10 years. I hope for factor expression of 20 to 60%; I was less than 1% before the trial. I hope to see less chronic pain in my damaged joints, freedom from the burden of having to give regular intravenous injections and reduced time dealing with my personal hemophilia, an annual bleed rate at zero or close to zero, factor use only required for surgery or major trauma, and an increased physical activity level. Having said that, I was fully aware that these are my expectations or my hopes, but I also had to prepare myself mentally for a range of different outcomes. Next slide, please.

So, my concerns going into the trial, I was concerned about delivering information transaminitis being missed, in fact, resulting in the loss of expression, which can happen. Also, transaminitis, if it's spotted, would need to be treated with medium- to long-term steroid use; that was a concern. There was a theoretical risk of cancer from insertion of mutagenesis and also the risk of losing the expression that you may achieve during the trial. Next slide, please.

So my rationale. Before the trial, my treatment was very good. I was being treated with extended half-life factor IX prophylaxis intravenously once every 10 days. My venous access is not great; it's okay. My annual bleed rate was quite low at zero to one. I had a knee replacement in 2018, and I had braces and joint damage in a number of joints with a degree of chronic pain. And obviously my rationale included what I said earlier but also, frankly, I wanted to try life without severe hemophilia. Life is not a helicopter ride; you get one go-around, and I wanted to see what it was like without severe hemophilia. I was eligible for one trial, having looked at three. And also, on account of my age at the time of infusion, and by the time we got around to a licensed gene therapy, I may not meet the age requirements for that. And also, as the leader of the organization in our country, and we've been talking about clinical trials for several years, and we had several companies over, and we kept talking about participating in trials, frankly, I thought I should lead and maybe lead the way on this in Ireland. Next slide, please.

So basically, you know, that point of going for gene therapy was the culmination of all of my life with hemophilia of 38 years at that point in time of walking in the area of hemophilia, and this really to me was the logical next step. Next slide.

And this is my gene therapy infusion on the day in question. I look very relaxed there, I think, and that there are the two research nurses, but there was a whole crash team around there as well, just in case anything went wrong which, thankfully, it didn't. Next slide, please.

So, my outcome to date. I achieved good factor expression. I'd hoped for somewhere between 20 and 60%, and I've been around the 40 to 50% mark, most of the time. I had some variability in my expression after the first year. But I've remained close to or near the lower end of the normal range. I'm now at two years post gene therapy; I had no requirement for steroids. Chronic pain has decreased in my target joints. Now, some of that may be due to the gene therapy, but frankly some is also due to the 24—the two years on from my knee replacement, and that does tend to help. My annual bleed rate has been zero after two years. I have only required treatment for a biopsy and also a steroid injection into my back. And I've had no treatment requirement, despite two traumas. Now, I've had no spontaneous bleeds, but also I've had a couple of traumas, including the day on the photograph here. I went up to Dublin Mountains with my wife and children for a walk, and I was climbing over a low stone wall, and I slipped and fell about two feet on some rocks and I didn't get a bleed, which was amazing. That, 100% in the past, that would have required treatment. Next slide, please.

The schedule of visits in the first three months was challenging, but this was not unexpected, and clearly, when you went to a clinical trial, you really do have to realize and commit to the

extent of the commitment before and because the schedule of visits was quite lengthy. It was once a week for the first three months, then once a month, and then, once every six months. But there were a lot of visits; it took a lot of time. There—I had no treatment-related adverse events, apart from iron deficiency because, in fact, if you look here at this photograph, this was the number of drugs taken on a weekly basis, so it actually has amounted to the equivalent of donating a unit of blood every month, which nobody would do, obviously, so I actually did get some iron deficiency from the blood draws over the first three months. I'm fitter and healthier due to gene therapy, but also due to changes in my lifestyle and, frankly, due to a decrease in constant travel due to the pandemic. The pandemic started two weeks out from my gene therapy, so whereas I had been thinking fretfully about how to fit all the visits into my busy schedule, that problem was solved for me by the simple expedient of a global pandemic. In 2019, I traveled on 44 occasions outside Ireland, had 44 trips abroad, and in 2020 I had one. And 2021 I had two, so clearly the more constant lifestyle also helped with us. Next slide, please.

So, my outcome to date, a definite degree of mental freedom. I don't have planned treatments around activities or travel. Freedom from regular intravenous injections; my veins have recovered. I feel no loss of identity; I still have hemophilia. But the freedom from hemophilia is less for me, given the fact that I work about 50 hours a week in hemophilia. Next slide, please.

And I've also used my gene therapy to promote awareness of hemophilia and hemophilia gene therapy in Ireland, which I think will be useful to us when we're looking for this to be reimbursed as an option for people with hemophilia. I don't think it would be universally adapted, but I would like it to be an option, but I think it does need a shared decision making and very, very well-informed patient population. Thank you very much.

ANNE ROWZEE: Oh, wonderful. Thank you so much for telling us about your experience, and that visual of the blood draws is really striking, so I think it helps folks understand the commitment to participate in trials such as these. I'm now going to pass it over to Julie, and she is going to share CBER's perspective on the critical role of patients and advancing good therapy treatments for rare diseases. Julie?

JULIENNE VAILLANCOURT: Hello everyone. Thank you so much. It is such an honor to be part of this panel and to be here today, and I want to share the sentiments expressed by Anne that I have so much gratitude toward all of you patients and caregivers who participate in clinical research in whatever way you participate. You really are brave, and you are just doing so much. It's such a gift for all of us advancing these very important products, so thanks. And again, it's an honor to be on this panel with Debbie and Brian, and I just really appreciate the opportunity once again. So next slide, please.

So, you did hear about our center, CBER, the Center for Biologics Evaluation and Research, in FDA, a bit in the beginning by Anne, and I just want to emphasize that we're one of several centers at FDA, so as you can see on this slide, we have many more centers. Most are familiar with the Center for Drug Evaluation and Research, and we work quite collaboratively with

CDER, the Center for Drug Evaluation and Research, as well as with the Center for Devices and Radiological Health, which is CDRH, and with offices in the Office of the Commissioner, such as the Office of New Drug Products. I'll go over that a little bit more in a few minutes, and again, there's many other centers. Next slide, please.

And here is an organizational chart of our center, of CBER, and CBER's director is Dr. Peter Marks. Our deputy director is Dr. Celia Witten. And I work in the office of the center director, again as CBER's rare disease liaison, and our Office of Tissues and Advanced Therapies is the office that regulates gene therapies. However, there's a lot of collaboration and reliance on several other offices when reviews are done and when products are regulated. So, there's almost like a matrix approach. When one office regulates and reviews a product under their jurisdiction, because they rely again on others, so the Office of Tissues and Advanced Therapies will have reviewers on review teams that are from the Office of Biostatistics and Pharmacovigilance, as well as reviewers from the Office of Compliance, and our outreach is coordinated mostly through our Office of Communication, Outreach, and Development, and they also serve as a resource for questions, so we do a lot of collaborative work in the center. Next slide, please.

This is the mission statement for our rare disease program in CBER, and our center is committed to facilitating and advancing the development and timely approval of safe and effective biologics to improve the lives of children and adults with rare diseases. Next slide, please.

CBER collaborates with many rare disease partners across the agency to support many diverse activities, and I alluded to this a bit already. We are heavily involved in patient engagement, and we coordinate with the Office of Patient Affairs and the Office of Commissioner in regard to patient engagement, as well as with the Center for Drug Evaluation and Research, or CDER, and other parts of the agency, typically when we participate in a patient-focused drug development meeting or patient listening session. We are there with reviewers and other staff from these other parts of the FDA. Once a year, we develop a training for FDA reviewers, and that is led by the Center for Drugs rare disease team, but CBER staff are heavily involved in developing that training. And it is a day-long training, and we typically have CBER case studies, and we address cross-cutting issues, but we also bring some of our experience from CBER just to share with others, because so many of these issues are common issues. And we collaborate on stakeholder outreach. We also have mechanisms for consultative and collaborative review in our products, and this is pretty common in gene therapy development. I'll give you an example. Anne mentioned that we have two approved gene therapies. One is for retinal—inherited retinal dystrophy, Luxturna, and part of the review team—well, the review team included an ophthalmologist from the Center for Drugs, and, you know, that's an example of how we collaborate and utilize expertise and resources from across the agency, and there are many more examples in that regard. And we typically collaborate on cross-cutting issues. We also develop guidance collaboratively with the Center for Drugs, the Center for Devices. Anne mentioned FDA Rare Disease Day, which took place last week. The planning of that is led by the Office of New Drug Products, but the planning committee brings together representatives from

across the whole agency, including CBER, and I hope all of you, if not most of you, had a chance to participate, and it's still available online, there's a webcast of that. And there were panels representing each center, and the CBER panel focused on gene therapy for neurocognitive diseases in children. And then, of course, we have special projects. Next slide, please.

So, we collaborate with our external stakeholders as well to advance development of products for rare diseases, and some recent examples include our Bespoke Gene Therapy Consortium collaborative, which is a new program that is being led by NIH and it's—although it is again a collaborative effort, we are a partner, along with NIH and with the Foundation for NIH and several private and public organizations. And the whole idea behind this program is to streamline adeno-associated virus manufacturing and regulatory frameworks. It's to increase the accessibility of gene therapies for rare diseases that otherwise may not be developed, because there's lack of incentive and interest sometimes, so by streamlining these approaches, we can make them more—make these therapies available for the people who need them most. We also have supported NORD to develop and to conduct a natural history study—with a natural history study of metachromatic leukodystrophy called the HOME study, which is intended to serve as a template for other natural history studies that would provide regulatory-grade data that would help to support development of new products for rare diseases. We also have supported IBM to develop an app that patients can use to enter and upload patient data that can be, that can be—patient preference data that might be used to support product development. It's been used in the HOME study, and it will be available for more public use. Next slide, please.

And I do want to emphasize that, although we've been talking about clinical trials today and the role of patients in clinical trials, there are many, many other opportunities for patients to engage and to contribute to the development of products for rare diseases. Patients or caregivers may participate in a natural history study, a patient registry. Those along with the clinical trial, as we heard from Brian, involve a lot more intense participation, but then there are opportunities that may not require such a commitment, such as patient listening sessions, participation in patient-focused drug development meetings. You may be invited to participate in a review division meeting. You may be invited by a sponsor to meet with FDA and provide your experience so that reviewers can listen. There are public meetings where you may serve as a panelist or a speaker, such as today. And also, we have the Patient Representative Program, which is out of the Office of the Commissioner at FDA, where patients need to fill out applications, which can be a lengthy process, but then they become special government employees and may be called upon to serve in a variety of ways. So you can see that there are many, many ways that you can participate and contribute. Next slide, please.

So, I just want to take a few moments to kind of talk about where clinical trials fit in with product approval and development and the role of FDA. This is a high-level nutshell summary. So, when a company—which we refer to as a sponsor or could be a gene therapy developer, we use different terms, but the regulatory term is sponsor—when the sponsor of a clinical trial to be conducted in the U.S.—we'll need to—let me back track. The sponsor of the clinical trial must submit an application to us at FDA, and it's referred to as an Investigational New Drug

application or an IND. And we review it, and we have a 30-day clock, and then after we've reviewed it, we inform the sponsor that either their trial may proceed or, if we've identified deficiencies that raise concern and that we want identified, we would put the trial on hold and then, once they are addressed, we may allow the trial to proceed. And this IND, or Investigational New Drug, application contains a lot of different types of information, including a protocol for the proposed clinical trial, information about how the product is made and how it needs certain standards, and how it's tested, and data from animal studies to support safety of the trial of the product—I'm sorry—going into humans. And more data, so it's an application that is dynamic as well once that initial trial is allowed to proceed, more data are submitted and amendments, so it's not just a one-time thing, but it is a mechanism for us to monitor and regulate the investigational product during its course of development. And if that initial proposed study is allowed to proceed after our initial review and, as time goes by, and that study is completed, the results are obtained and are shared with us, subsequent studies may be conducted, and we review those as well under the same IND. And then, when there's enough data that's been collected about the product, about the investigational product, and the sponsors had lots of interactions during this whole process with us and it's felt that the data from the sponsor's perspective adequately demonstrate the safety and effectiveness, and they'll submit the package to us. Now, of course, that package also has to have manufacturing data to ensure that it's meeting our high standards for manufacturing quality, product quality.

And then that application is called a Biologics License Application, or BLA, so again, all the results of the clinical trials are in that application, and it's a lot of data. It includes case report forms, all the lab values, safety reports, everything, and our reviewers review it very, very carefully. Next slide, please.

And here is a quote from our IND regulations, and I'm going to read it. "FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects." I can't emphasize how we always put safety first. That is at the heart of what we do. It's the base of our history as an agency, so we always have the patient safety and rights in mind when reviewing data, when reviewing study protocols before a study starts, before it's allowed to proceed. Next slide, please.

Again, as Anne said and Brian and Debbie, so eloquently and gratefully, gene therapy clinical trial participation is really so important. We have a lot of gratitude, and patients are brave, and it truly is such a gift, and I want to make you all realize that. From our perspective at FDA, we realize that the decision to participate or not to participate is truly a big decision that takes into consideration many, many factors. And it's an individual decision; it's a decision that you as a patient or you as a caregiver make. And you have to weigh out many pros and cons, and the best way to make that decision is to be as informed as possible. And it is your prerogative, and we respect the fact that you should be asking lots of questions and you should discuss your concerns. You want to strive to be as informed as possible so that you make the best decision for you and you feel good about that decision. And I loved listening to Brian talk about his journey and also seeing the slide where he talked about what his hopes were and then what he thought, you know, some of the risks might be, and those are the pros and cons and what you

hope to get out of the trial and what you recognize as risk, but you can only make those decisions and those considerations by doing some research, by asking questions.

And again, we in the whole community and at FDA, we are so grateful, and we recognize that when you participate in a trial, you're contributing to the knowledge base about use of this investigational gene therapy product to treat your rare disease, and you're setting the stage and giving of yourself and your time, or of your loved ones' time, to set the stage for those who come after you. And it's so important, and thank you. So with that, move on to the next slide, please.

There's so many resources out there, and Debbie mentioned NORD and patient organizations, and I reiterate that. I'm going to provide a few specific resources. FDA has a For Patients web page, if you go to [FDA.gov/patients](https://www.fda.gov/patients), and we have lots of resources there and links to other resources. Of course, [ClinicalTrials.gov](https://www.clinicaltrials.gov) is a repository for clinical trials conducted around the world. And also, if you've never visited, I would draw your attention to a button they have that says Patients and Families. And that really gives you some good information on navigating [ClinicalTrials.gov](https://www.clinicaltrials.gov), and it provides a glossary and more. It's a good place to start if you've never visited [ClinicalTrials.gov](https://www.clinicaltrials.gov). Medline Plus is another NIH resource, and the National Center for Advancing Translational Sciences, or NCATS, at NIH has an excellent resource called the Genetic and Rare Disease Information Center, or GARD, which has information about several of the 7000-plus rare diseases that have been identified, not all, but several, a good portion. And there's lots of information about the disease itself; it's in English and Spanish, there's links to organizations if they exist, names of specialists, and more. And NCATS also has a toolkit for patient-focused therapy development. And then, as Debbie mentioned, the individual rare disease patient advocacy organizations are an excellent place to start. They're so important, they provide resources support, they'll provide information about clinical trials. I have talked to many parents of children who have been newly diagnosed with a disease that may be incredibly rare and sometimes these organs—there is not an organization, and so, what do you do?

Well, I think listening to Debbie really answered the question, because NORD is like an umbrella organization, and it's a great resource to go to, and there are other such umbrella organizations, in addition to NORD, and if you contact me or Anne or others at FDA, we might put you in touch with certain people we know on the outside or link you even with another patient advocate who has a totally different disease but has years of experience, so last slide, please.

So, I just want to say that, beside all of these resources, if you are up against the wall and you are stumped with the question and can't seem to find an answer to feel free to reach out to me. I'm always happy to talk to patients and patient advocates and help you navigate FDA, but again, I think we do have a wealth of resources, and I hope you will visit them. Thanks so much.

ANNE ROWZEE: Thanks, Julie. I'm going to stop sharing slides right now so we can get all the panelists in view, and I think we've got everybody on and just let those folks unmute as well.

And, you know, we appreciate the questions that have been submitted, so far, both during registration and throughout the webinar today. There's more and more questions than we have time for, unfortunately, but we're going to do our best to answer as many as we can. I'm going to just jump right in and kick this first one to Debbie.

So, in your presentation, you touched upon some of the ways patients with rare diseases can learn about research opportunities and potentially get involved. And what do you think the first step patients can take if they're interested in participating in clinical research?

DEBBIE DRELL: A couple of things, actually. I know you said the first step, but I think asking questions, talking to their family, talking to their medical team, talking to their rare disease nonprofit organization to see if there's a natural history study, and then just, you know, bring all your concerns, bring all your questions, and take your time to make that decision. But know that what you do today echoes for the rest of the community and, actually there's great benefit directly to you if you do get involved.

ANNE ROWZEE: And then I'm moving right now to Brian. Before you joined the gene therapy clinical trial, did you participate in any other kinds of research? Perhaps like a natural history study or a registry study, and if so, could you tell us a little bit about that experience and maybe perhaps how it's different from a gene therapy trial?

BRIAN O'MAHONY: Sure. I took part in a trial for a biosimilar recombinant factor IX about two years before gene therapy, so it basically meant I was getting a product very similar to the one I was already on, but in a higher dose. It was different because the monitoring wasn't as intense and so there weren't as many visits. They certainly left a little bit more blood in my body than the gene therapy trial did. Also, with the gene therapy trial itself, there was also a six-month lead-in period where I stayed in my current therapy, and they evaluate everything. That was very useful because it gave me an additional six months to really—you're in the preparations on then mentally; it gave me six months to really focus my mind on this and decide we're absolutely going to go ahead with this, so I think the lead-ins can be very, very useful.

ANNE ROWZEE: Okay. Interesting. So Julie, we're going to kick one over to you now. Can you tell us a little bit about patient engagement and how that's changed over the years of FDA and, you know, how can patients start up a dialogue with FDA to share some of their experiences?

JULIENNE VAILLANCOURT: Oh, thank you, Anne. Well, FDA's experience with patient engagement or rolling engagement skates back to the 1980s, with the HIV/AIDS crisis when the ACT UP movement was really happening and there was protesters in front of the Parklawn Building where the FDA was located. And eventually, you know, FDA listened, and there was a change in in culture. And it started out slowly with putting patient reps on advisory committee, on advisory committees. And then, after that, more things took off. Prescription Drug User Fee Act started, which ACT UP, you know, in the AIDS activists really helped trigger that and, you know, that has really made a difference over time. And, you know, fast forward to today, we have this incredibly rich robust program of patient engagement, where we have patient-

focused drug development meetings, we have patient listening sessions, as you saw on my slide. It's become a way of life, and FDA is never going to go back. I mean, this is how we do it now, and we're learning every day. We have guidance that we have issued, and we continue to work on additional guidances on methodologies for patient input and more. So it's just—it's exploded, and we continue to learn more.

ANNE ROWZEE: I'm moving back over to Debbie, we have a question about parents, and how can they be involved in driving outcomes for their child's rare disease? At NORD, you know, how have you seen, you know, parents get involved in driving appropriate treatment outcomes or driving progress for their children?

DEBBIE DRELL: Yeah, parents have a huge role in driving progress, whether that's learning about research opportunities and engaging in actually participating in the research or what I found in working at NORD and in rare diseases, parents start nonprofits and formalize the communities, getting a 501(c)(3) designation from the IRS, Treasury Department, which enables them to fund raise and actually start up these natural history studies and research, so they're pioneering their communities, they're driving research, and there's so much that they can do with advocates to helping to find cures.

ANNE ROWZEE: Brian, actually I kind of have something a little bit similar, a question that has come in, and you know, was wondering, what measures did your organization take to educate perspective participants about steps to protect patients during a gene therapy clinical trial, you know, how has your organization through interface with potential trial participants?

BRIAN O'MAHONY: We were very proactive on this, so obviously we produced information material through newsletters and our website, but also when—rather than expecting an individual patient to go in and meet a clinician and discuss a potential clinical trial one to one, we brought them together in very large groups, maybe 20 people at a time, with the clinician, with some technical experts, maybe with the gene therapy company, and had a meeting where they all asked questions and put them out there in the open. And what we found is that type of dialogue means that somebody will ask a question you hadn't thought of, and the answer will give you more information. So that dialogue and community building was very, very useful. And really, I think the education and the information to patients needs to be multifaceted, needs to be comprehensive and comprehensible, but you also need to use the platforms that people use. There's no point in giving, you know, 60-page newsletters to people who want social media, who want an infographic, want a video, so really you have to make sure that you target all the demographics within your patient organization who might be considering gene therapy and get the information to them at the appropriate level of comprehension.

ANNE ROWZEE: Absolutely, yeah, and if I may just stick with you for a second, Brian, and you know, I can, you know, hear how much support the advocacy organization has provided for its constituents, and I'm wondering if maybe you could tell us a little bit more about, you know, your support system, in addition to the advocacy organization and, you know, who that was

throughout the trial experience for you, and what are the valuable ways that they helped to support you during your participation in the trial?

BRIAN O'MAHONY: Well, I think the clinical trial team and the clinical trial research nurses have been really, really helpful and very supportive through the whole trial running the queries and, of course, one of the things people need to realize that during a clinical trial, you actually get better access to health care, because everything is investigators. I think before the trial, I've got a wide circle of friends and acquaintances who were hemophilia experts, technicians, and also expert patients, so I use that network to discuss whether or not it was a good idea for me to think about gene therapy and, frankly, I made sure that I reached out to people who had both sets of opinions, and that's something I would encourage everybody with hemophilia to do is to go into this with your eyes wide open to encourage—don't just listen to people who have one idea, this is a good idea, this is a bad idea. You need to get all frames of opinion, need to understand the benefits and risks, and you really need to manage your expectations because, at this point in time, with hemophilia gene therapy, the outcomes—there's a range of potential outcomes, and if you're not prepared for any one of the range, then you're not prepared.

ANNE ROWZEE: And I'm going to get back over to Julie and to ask a question about patient preference information, and we had a question from an attendee who was wondering what role patients and/or caregiver preference information plays in advancing gene therapy products and how much weight is placed into FDA regulatory decision making or where that comes into play in the development process.

JULIENNE VAILLANCOURT: Okay. First of all, patient preference information is basically what Brian talked about through some of his slides, is looking at what you're desiring as outcomes from participating in a trial and weighing that against what you would consider to be acceptable in terms of risks or other aspects of the trial that may not be necessarily side effects, but you know, they may be inconveniences as well, and you are looking at his preferences and acceptabilities. They can be measured by ranking or by—we hear about them in patient-focused drug development meetings and patient listening sessions; this is the type of information we gather, and we use this to help guide product development. And we encourage companies to also collect this information, because they should be using it to guide product development as well, and what we hear and what our reviewers hear is incredibly helpful when reviewing protocols or other information under an IND in development because it might result in some request for more information or advice or in terms of the trial design, so again, it's very useful information in terms of shaping how a product's development program is designed, whether it's specific clinical trials, and making it hopefully more patient- and caregiver-friendly. And concerning caregivers, we know that for many rare diseases, the caregiver is the proxy; the patient himself or herself or theirselves cannot necessarily communicate, and that caregiver is representing the patient, so the information they provide is incredibly important, and we need to listen. And it's only information they can provide; there are things we would never think of. And it's so valuable, and again, it helps shape element. If a product is developed and doesn't have patient input from the get-go, it could be development of a product in vain because it may not address symptoms or aspects of the disease that really matter to patients, and then it's a

waste of resources and a waste of any patient's time who participated in that trial because patients are our most important resource, so it's so important to engage patients from the very beginning.

ANNE ROWZEE: Debbie, we had an audience question about common concerns and worries that the rare disease community has about gene therapy. I can imagine it's impossible to generate the views of the, you know, entire rare disease community, but are there any common concerns you've heard about the prospects of gene therapy treatment for rare diseases?

DEBBIE DRELL: You know, I think I'd like to actually punt that to Brian because, involved in the Irish Haemophilia Society and himself participating in the trial, I'm sure that he's heard talking to other trial participants in the community some. I'd be curious directly from the community themselves what they've heard.

BRIAN O'MAHONY: Well, you'll have to repeat the question because I was, I was busy answering, I was typing answers to other questions.

ANNE ROWZEE: No, no, that's okay. You know, have you heard sort of common concerns about gene therapy on hemophilia and, you know, I'm almost wondering, you know, versus, you know, given your depth of experience in advocacy work, you know I can imagine that you've heard there may be differences between even the pediatric population versus, you know, an adult population and what those concerns might be, so you may have thoughts on that.

BRIAN O'MAHONY: I mean, in hemophilia, gene therapy is not indicative for a pediatric population because it's targeted at the liver, the liver still developing, so and also the difference with hemophilia is there are other very, very good, very efficacious licensed therapies, so it's not an option at the moment for anybody under the age of 18. And indeed, if you look at that and if you look at people who have pre-existing antibodies to AAV, there's only about 40 to 50% of people with severe hemophilia who might even be eligible for gene therapy. The kind of concerns I'm hearing expressed generally are the ones that I had myself, you know, what about the theoretical risk of cancer, so I think that does point to not just the need for ongoing surveillance but the need for lifelong surveillance and follow-up. And some of the clinical trials talk about a five-year follow-up. My own view, very strongly, is that we need lifetime follow-up. And, frankly, for people with a rare disease like hemophilia where they're used to follow-up a couple of times a year, if you say it, then you won't be followed up once, twice a year for the rest of your life, that has no burden. In fact, I would say the opposite, I would, I think they would be concerned if they weren't being followed up for life. And then the other big concern was the need for, the need for steroids, perhaps the damp down transaminitis, and if steroid use had to be medium to long term, the side effects of the steroid use itself.

ANNE ROWZEE: Thank you. Actually, I'm noticing time. You know, everything got away from me, so embroiled in our discussion, but I just really quickly, let me see if I can, oh my goodness, share my screen again and let's get that going, sorry. You know, so, thank you once again to

everybody—Debbie, Brian, Julie—for answering our questions and sharing your perspectives and experiences. Big thank you to everybody who joined us in the audience today. Those who asked questions during registration process and during today's events on. Before we end, I want to share just a couple quick resources in ways that you can stay informed. You can visit our website, the link is there, as well as sign up for the "What's New at CBER" newsletter. You can follow us on Twitter at @FDACBER. And we also encourage you to use the hashtag #RegenMedEd on social media to share your thoughts on today's events. And let us know if there is information or resources you're interested in seeing from us at future events. Quickly moving on, thanks again to our panelists. Thank you all for attending. We hope you found it useful. The materials from the webinar today will be available within the next few weeks on our website.

I'd like you to stay tuned for more information about OTAT's upcoming regenerative medicine patient engagement workshop; that's going to be in May. And then, this workshop, I noticed we had a lot of questions about natural history studies today. We're actually going to be taking a deep dive into that topic, into the topic of natural history studies. We're going to have a variety of educational sessions and panel discussions on the importance of natural history studies and advancing regenerative medicine therapies. So, thanks everyone again so much for joining us, and I hope you have a great day. Take care. Thank you.