FDA Rare Disease Day 2021

Moderated by Dr. Lewis Fermaglich

Friday, March 5, 2021

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Virtual - DC

Food & Drug Administration (FDA)

Washington, DC 20001

Reported by: Carl Hellandsjo (by videoconference)

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A P P E A R A N C E S

List of Attendees:

Janet Maynard, MD, MHS, Director, Office of Orphan Products Development (OOPD) FDA

Lewis Fermaglich, MD, MHA, Acting Senior Clinical Advisor, OOPD, FDA

Katherine Needleman, PhD, Director, Clinical Trials and Natural History Grant Program, OOPD, FDA

Amy Abernethy, MD, PhD, Principal Deputy Commissioner of Food and Drugs, Acting Chief Information Officer, FDA

Susan McCune, MD, Director, Office of Pediatric Therapeutics, FDA

Robert Kroslowitz, President and CEO of Berlin Heart Inc.

Frank McCormack, MD, Professor of Medicine; Director, Division of Pulmonary, Critical Care, and Sleep Medicine, University of Cincinnati

Vasum Peiris, MD, MPH, Chief Medical Officer and Director – Pediatrics and Special Populations, Center for Devices and Radiological Health (CDRH), FDA

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A P P E A R A N C E S (CONT'D)

List of Attendees:

Sally Seymour, MD, Director, Division of Pulmonology, Allergy, and Critical Care (DPACC), Center for Drug Evaluation and Research (CDER), FDA

Robyn Bent, RN, MS, CAPT, U.S. Public Health Service, Director, CDER PFDD Program, FDA

Wen-Hann Tan, BMBS, Attending Physician, Division of Genetics and Genomics, Associate Professor of Pediatrics, Harvard Medical School

Amanda Moore, CEO of the Angelman Syndrome Foundation

Martin Ho, MS, Associate Director of Science for Patient Inputs and Real-World Patient Evidence, Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research (CBER), FDA

Andrea Furia-Helms, MPH, Director, Office of Patient Affairs, Office of Clinical Policy and Programs, FDA

Janet Woodcock, MD, Acting Commissioner of FDA

M. Khair ElZarrad, PhD, MPH, Deputy Director, Office of Medical Policy, CDER, FDA

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A P P E A R A N C E S (CONT'D)

List of Attendees:

Rachel Sher, JD, MPH, Vice President, Policy and Regulatory Affairs, National Organization for Rare Disorders (NORD)

Nicholas E. Johnson, MD, Associate Professor, Vice Chair of Research, Neuromuscular Division Chief, Department of Neurology, Virginia Commonwealth University

Christine Mueller, DO, Medical Officer, Office of Orphan Products Development, FDA

Christopher P. Austin, MD, Director, National Center for Advancing Translational Sciences

Erika Torjusen, MD, MHS, Director, Pediatric Device Consortia and Rare Pediatric Disease and Humanitarian Use Device Designation Programs, OOPD, FDA

Peter Marks, MD, PhD, Director, CBER, FDA

Jeffrey Shuren, MD, JD, Director, CDRH, FDA

Patrizia Cavazzoni, MD, Acting Director, CDER, FDA

Catherine Park, Project Management Officer, OOPD

Dale Sanders, public commentor

Jennifer Ostrom, Health Tree Foundation

A P P E A R A N C E S (CONT'D)

List of Attendees:

Eric Hartman, Choroideremia Research Foundation (CRF)

Jason Colquitt, Across Healthcare

Dean Suhr, MLD Foundation

Brian Smith, public commentor

Sophia Zilber, public commentor

Parvathy Krishnan, public commentor

Mary McGowen, Foundation for Sarcoidosis Research

Christina Brundage, public commentor

Qais Abu Ali, MD

Mary Faxas, public commentor

C O N T E N T S

C O N T E N T S (CONT'D)

C O N T E N T S (CONT'D)

P R O C E E D I N G S

DR. MAYNARD: Good morning, and welcome to this virtual public meeting, FDA Rare Disease Day 2021. It is an exciting time in the development of rare disease treatments with new innovations and advancements.

My name is Janet Maynard, and it is my privilege to serve as the director of the Office of Orphan Products Development at FDA. The mission of the Office of Orphan Products Development is to advance the evaluation and development of products, including drugs, biologics, devices, and medical foods, that demonstrate promise for the diagnosis and treatment of rare diseases or conditions.

A key aspect of supporting this mission is collaboration. This collaboration is seen both within FDA and in FDA's work with others. Within FDA, the Office of Orphan Products Development works closely with the medical product Centers. These Centers facilitate development of drugs, biologics, and devices, and have facilitated important advancements for rare diseases. In addition, FDA works

with other rare disease stakeholders, including NIH, pharmaceutical and device companies, and patients and their families. Today's meeting is one example of that type of collaboration.

Another key aspect of this collaboration is coming together to work towards our common goal of the development of treatments for rare diseases. A year ago, many of us in the rare disease community came together to recognize Rare Disease Day. We at FDA were so appreciative of that opportunity to engage directly with you, at FDA Rare Disease Day 2020.

Over the last year, the rare disease community, including people with rare diseases and their families, have been profoundly impacted by COVID-19. The broad impacts of the COVID-19 pandemic have been seen in many ways, such as accessing medical care, participating in clinical trials, and bringing together stakeholders.

Today, as we recognize Rare Disease Day 2021, we are coming together in a virtual format to continue our momentum in rare disease product

development. An FDA cross-agency group has worked tirelessly to plan this meeting. And I would like to recognize and thank all the individuals who helped plan this meeting. And also thank all our meeting participants. While we would like to be together in -person, we are thankful for this opportunity to engage through a virtual format. Like many things over the last year, we have adapted to the new challenges, and continue to support rare disease product development.

Many of the staff at FDA who work on issues related to rare diseases are participating in this meeting. Usually, you would see these individuals throughout the day. Please know that these individuals are here supporting the meeting and listening to your questions and comments. Here is a picture of some of the staff in the Office of Orphan Products Development, and individuals from FDA who helped plan today's meeting.

We come together today in a virtual format to celebrate the work that has been done and consider strategies to facilitate the development of treatments for rare diseases. This meeting will

include examples of rare disease product development programs, such as studies funded by the Orphan Products Grants Program, to illustrate types of challenges faced and strategies used to address them. It is important to remember that patients and families are the focus of our work to facilitate the development of rare disease treatments.

As a rheumatologist, I have had the honor of caring for many patients with rare diseases. As is common in rare diseases, many of my patients had long diagnostic odysseys that spanned years, or even decades. Some patients would arrive in clinic with U-Haul boxes of medical records. Determining a diagnosis is one important step, as is considering potential treatment options.

For Rare Disease Day 2021, building on FDA's programs and initiatives aimed at promoting inclusion of the patient voice, we captured brief stories from the rare disease community in the FDA rare disease photo and video project. I encourage you to listen to these videos, and to also share your own stories and perspectives.

Today's meeting offers us the opportunity to share strategies to support rare disease product development. And thank you for being part of this meeting.

In closing, over the last year, we have faced challenges as a rare disease community. As we look forward, we are encouraged by the innovation and strength we have seen. Thank you for participating today, and I look forward to a productive meeting.

Now, I would like to introduce -- Lewis Fermaglich --

DR. FERMAGLICH: Thank you, Janet. I am honored to be acting as your master of ceremonies for this momentous day, FDA Rare Disease Day 2021. The virtual setting presents a unique challenge to pull off an engaging and informative conference. But as MC, it is actually -- it actually makes my job easier. I do not need to remind you to silence cell phones, the locations of the restrooms, how to order lunches, Wi-Fi passwords, or anything like that. If you do not know your Wi-Fi password, ask your kid. I am sure they know by now.

As a bit of background on me, my name is Lewis Fermaglich, and I am the acting senior clinical advisor in the Office of Orphan Products Development, or OOPD. Prior to coming to FDA, I was a general pediatrician for 10 years. Over my time in practice I spent the majority of my time doing well child checks, giving anticipatory guidance, and treating mild illnesses. I took care of an Olympic swimmer, a chess champion, and a variety of smiling, drooling babies, goofy, playful kids, and brooding adolescents. And I considered it a privilege to do so.

But during my clinical career, I always found myself drawn to kids and families affected by rare diseases. The siblings with a rare form of esophageal constriction, the newborn with stroke and seizures, the family struggling with a new diagnosis of a genetic syndrome. These patients and families elicited a passion in me that motivated me to be a better doctor.

I am still in touch with many of these families, and it is their stories that fuel my interest in my current job. I am so lucky to get to

work with rare disease patients and families again, to collaborate, listen, and play even a small role in finding effective treatments for these diseases.

The speakers and moderators I will be introducing you to today share this passion for facilitating the development of treatments for patients with rare diseases. And I will tell you about some of their stories throughout the day. Today's agenda is packed with brilliant speakers that will hopefully offer different stakeholder perspectives on challenges and solutions in rare disease product development.

The morning session will kick off with Dr. Kathy Needleman, reporting on the successful Orphan Products Clinical Trials, and Natural History Grants Programs run out of our office. Following Dr. Needleman's talk, Dr. Amy Abernethy, the Principal Deputy Commissioner of Food and Drugs, will offer her perspective on rare disease product development as both an oncologist and FDA's Chief Information Officer. After Dr. Abernethy, we will dive into our first panel, focused on partnerships and

collaboration, within the rare disease product development ecosystem. Our second panel will address the importance of patient engagement, and specifically include a discussion of the immense potential of natural history studies in rare disease product development.

After lunch, we are honored to have live virtual remarks from the current acting FDA Commissioner, Dr. Janet Woodcock. Our first afternoon panel, we will discuss strategies that have allowed researchers to continue to support rare disease product development during the disruptive and unprecedented COVID-19 pandemic. Our final panel of the day includes the Center directors. And we are all excited to hear directly from the leaders that shape the regulatory decisions for the products that are being developed to treat rare diseases.

After the last panel in the afternoon, we will have an open public comment period. To participate in that, you would have needed to sign up prior to the meeting. Participation is on a first-come first-served basis. Speakers will each have two minutes

to speak. After the open public period, Dr. Maynard will provide closing remarks.

As for the rules of engagement for today's meeting, we encourage all individuals to contribute to the dialog, and we appreciate the opportunity to hear your perspectives. The view expressed are personal opinions. You can ask a question by clicking the, "Ask a question," icon, or by emailing OOPDorphanevents@FDA.HHS.gov. And we will try to respond to them as many of them as time permits.

For transparency purposes, when you are sharing a comment, we ask that you please disclose if you are affiliated with an organization or if you have any significant financial interest in rare disease medical product development. A public docket will be open until April 2nd to submit comments. We highly encourage you to so. A webcast recording and a transcription of the meeting will be available on the FDA meeting website following the conference. Evaluation forms will be e-mailed to you following the meeting.

After the meeting ends today, there will be additional opportunities to interact with the FDA. The Office of Orphan Products Development and the Office of Patient Affairs are here, and want to stay in contact with you, whether it is helping you stay connected with other activities at FDA or addressing any future questions you might have. This slide contains our contact information. Additionally, for media inquiries, please contact our press officer, Jeremy Kahn. If you have any questions or are interested in speaking with FDA about this meeting, please connect with Jeremy. Also, if you choose to Tweet about today's meeting, please use hashtag #FDArare2021 -- that is right.

All right. Let's start the program. First up we have Dr. Kathy Needleman, director of OOPD's Clinical Trials and Natural History Grants Program. She has dedicated much of her time at FDA focused on orphan product development, starting in the review divisions in the Center for Biologics Evaluation and Research, or CBER, and the Center for Drug Evaluation and Research, or CDER, and continuing

in OOPD.

Serving as the director of the Orphan Products Grants Program has allowed her to use her background interest and passion in rare disease research. She works closely with project officers, researchers, patients, and organizations, to advance promising medical products for rare diseases or conditions, to market approval, to increase publications of significant findings in the scientific literature, and to oversee the responsible use of federal funds.

Dr. Needleman?

DR. NEEDLEMAN: Hi, everyone. And thanks, Lewis, for the introduction. It is so great to be here today to celebrate Rare Disease Day. Of course, I wish we could all be here in person, but I am happy to see so many of you have joined virtually today. Next slide.

I am excited about today. We have some great panels planned for you, as you have heard from Dr. Maynard. We have many current and former orphan product grantees on the agenda that will be

discussing their experiences with you, as well as strategies to facilitate the development of treatments for rare diseases, along with many FDA staff that focus on these areas. They are excited to showcase that for you today.

Although many of you are likely familiar with FDA grant programs, I am here today as the director of the Orphan Products Grants Program and to give you some background and information about the program, which has impacted several of the speakers today. First, I will start with a brief background about our office. Then, talk about the Clinical Trials, as well as the Natural History Grants Programs that are administrated by the orphan products office. And conclude with COVID-19 impacts on the program and studies. Hopefully, this will give you a foundation to what we do, and who we fund. Next slide.

To start, the Office of Orphan Products Development, or OOPD as it is often referred to, has the mission to promote the development of drugs, devices, biologics, and medical foods for patients with rare diseases and special populations. OOPD has

several programs to provide incentives for rare disease product developments. Specifically, we have three designation programs that are listed here, that provide and focus on incentives for drugs, biologics, and devices.

We also administer three grant programs. Specifically, Clinical Trials Grants Program, the Natural History Grants Program, as well as the Pediatric Device Consortia Grants Program. I am going to focus my talk today on two of these, specifically Clinical Trials, and Natural History Studies Grants Programs. Next slide.

The Orphan Products Grants Program was established back in 1983 to defray the cost of developing drugs, medical devices, and medical foods for rare disease or conditions. Specifically at that time, there was little interest in investment in rare disease product development, as there was little to gain for many companies to pursue those areas. The program started small but has continued to grow. And the impact continues to affect more and more diseases, patients, as well as products. It is one of several

grant programs that the FDA administers. But, one that has specifically focused on rare disease product development. Orphan Products Grants Program supports both academic- and industry-sponsored research. We also fund domestic, as well as foreign, public and private, and for-profit and non-profit entities. One main criteria to be eligible for the grant program is that the disease being studied must be rare, and that is of which affecting less than 200,000 people in the United States.

This program is a competitive -- but it also a very practical and unique -- program. Specifically, the goals are very practical. We are trying to advance marketing approvals to help get treatments to patients. We also support publications that impact the care for rare disease patients, and support studies that help change guidelines for treatment.

Being in the FDA makes this program unique, in that FDA staff bring various expertise from regulatory product development. And being situated within the FDA allows us to use our relationship with

the Centers to ensure appropriate end clinical study. Grantees work closely with medical product Centers, and we want to ensure that what we find is not only a good research study but focused on drug development that will lead to an indication change or a new approval. Next slide.

Since 1983 we have funded over 2,800 applications, we have provided over 440 million dollars for more than 750 rare disease studies. And we have a very good success rate, where about 95 percent of our funded studies complete projects.

Currently our annual budget is about 17.7 million dollars, which we spend on both the Clinical Trial and the Natural History Grants Programs. The program has been quite successful through the years, leading to over 75 FDA-approved products that were, at least, partially funded through the Orphan Product Grants Program for over 85 indications. In essence, about 10 percent of the funded studies have been used towards approval. Next slide.

Here are some examples of approved

products supported by the program. Some on here are products that you are going to be hearing about today from former grantees that utilized the program. Next slide.

Let's move to some specifics about the Clinical Trial Grants Program. Next slide.

As I mentioned, this was established back in 1983 to help provide incentives to researchers to study treatments for diseases that had little interest in investment. Even today, although there is more interest in rare diseases, the majority of rare disease have no treatment options. Orphan Products Grants Program offers funding to help de-risk therapeutic development, so they can become more attractive to potential partners like investors, who will, then, more likely invest into these important treatment options.

The Office of Orphan Products uses about 15 and a half million dollars to fund ongoing and new clinical trials in the Clinical Trials Grants Program. The program provides a method of successfully fostering and encouraging the development of new, and

safe, and effective medical devices, medical products for rare diseases and conditions. And it also helps support efficient product development in a timely manner. It supports the clinical development of products for use in rare diseases or conditions where no current therapy exists, or the proposed product will be superior than the existing therapy. OOPD typically is funding anywhere between 60 and 85 ongoing grant projects at any one time. Next slide.

This slide shows you a breakdown of what types of products we support. As you can see, the majority of the products are supported by OOPD grants are for drugs, about a quarter are for biologics. And we also support device and medical food trials, as well, as you can see in the percentages in the slide. Next slide.

Most of Orphan Products Grants support phase two clinical trials. We do support about a quarter of phase one trials, that have a phase one component. As well as about 20 percent that have a phase three component.

Generally, most of our applicants are

academic researchers who have great ideas paired with clinical observations, that use this for product development and drug discovery. But we see many of these academics also have collaborations with companies, either at the time of their application, or during the grant at some point.

We also support companies, as well. And you can see we score about 25 percent of our funding goes to companies. And these tend to be smaller companies focusing on rare disease research.

Our goal is product development for rare diseases and utilizing various expertise assists in this goal. Next slide.

We currently have a clinical trial RFA that has a receipt date in October 2021. We just had our receipt date in October 2020 award cycle. The purpose of this funding opportunity is to fund well controlled studies in support of a new indication or change in labeling of products to address unmet needs in rare diseases. The focus is efficiency innovation, as well as impact. We included added focus this year on leveraging patient input and infrastructure, as

well as financial resources.

In addition, we added a new piece to the proposal this year to focus on innovation. Applicants were encouraged to submit an optional stand-alone innovative demonstration project proposal in addition to the application, that could be used as a model for future drug development in one of the following areas: innovative collaborations, innovative patient recruitment and retention strategies, or innovative methods for using data simulation and modeling. Next slide.

Now, I am going to focus on the Natural History Grants Program and provide some background. Next slide.

This is a newer program to our office and was launched in 2016 after hearing a great need for good quality natural history studies in rare diseases, and continually seeing specific aims added to our Clinical Trials Grants applications that lacked the needed funding, as well as focus. Its intent was to support drug development for rare diseases in an increased understanding of impact in courses of rare

diseases. The budget for these studies is about two million dollars per year. And OOPD supports studies that advanced rare disease medical product development through characterization of a natural history of rare diseases, identification of genotypic as well as phenotypic sub-calculations, and the development or validation of clinical outcome measures and biomarkers and containment diagnostics.

We had another receipt date in 2018 for the Natural History Grants Program, with a focus on efficient and innovative natural history studies that included patient and caregiver perspectives. From those two receipt dates we were able to find eight natural history studies. Next slide.

The studies are listed here, as you can see. In 2017 we worked with NIH to co-fund two of the six studies that we were able to support that year. And you can see all the studies that we supported from the beginning when we started the program through the last receipt date we had. Next slide.

We took a look at our applications -- our last round of applications, to get an idea how to

further improve the impact of our program. We saw that the applications were being submitted mostly by academics, as you can see. And you can see the breakdown of the main goals of the applications in the bar chart, to the right of the slide. Disease progression and biomarker development were the main goals for the majority of the applications we were seeing. And all of these goals, as well as the other listed on the slide, are great focus areas in line with what we wanted to see for that particular RFA. However, we wanted to be sure we were using our funds in the best and most efficient way for rare disease drug development. Next slide.

So we developed a new RFA that was just posted in February of 2021, right before Rare Disease Day. It is currently on our website, as well as available on grants.gov. The next receipt date will be in February 2022. And the purpose is to support efficient and innovative natural history studies that advance medical product development and rare diseases or conditions with unmet medical needs.

The focus on this RFA is efficiency

innovation, impact, as well as data, quality and interpretability, leveraging patient input, infrastructure, financial resources, and future use of data. We focus this time on data quality, as this data is highly important for the use in regulatory development. In addition, encouraging efficiency, innovation, and leveraging financial resources and infrastructures are all important to ensure that the funds can go as far as they are able, and helps to ensure that the study has a good foundation to be successful and useful in future product development. Next slide.

So now, I am going to turn to talking about the impacts of COVID-19, and the impacts it has had on the studies we have funded, as well as the program. Next slide.

When the pandemic began last March -- unbelievably, already a year ago -- we started hearing from many of our grantees about issues with their study progress, and issues with the study in general. OOPD began tracking these issues and collecting data to see what issues and resolutions

were occurring. Some of the items we started collecting are listed here; from study suspension, to virtual capabilities, different types of protocol amendments, monitoring that was being changed, a plethora of things that were happening to our studies and to all studies that were ongoing at that time. Next slide.

We found about that from our 71 currently funded grants, at that time -- so there were 63 clinical trial grants and 8 natural history studies at the time -- 79 percent were -- of those studies -- were impacted in some way by the pandemic. You can see the areas listed here on the slide. The major impact, of course, was enrollment delays. With sites being closed to studies, travel being shut down around the world, this was an inevitable issue. But other major impacts included study suspensions with unknown times to resume, protocol modifications that were needed to adjust to virtual -- different virtual environments that had not been used before, as well as other needed study changes that were taking place to try to continue that study moving forward.

Additionally -- other things are addition of virtual capabilities and travel issues. And we saw study completion delays that were occurring, and also being projected for the study. And there were product delivery issues that needed to be addressed. There were changes in monitoring practices that needed to be made. And there were changes in informed consent forms as the studies' changes were being made throughout this time. Next slide.

So OOPD wanted to assist in what ways it could to address these issues. We have begun the Orphan Grants Unite Initiative earlier in 2020, prior to the pandemic. This initiative's intent was to provide a forum for our grantees to share experiences and challenges, to support common solutions in rare disease research. It also was developed so we could provide information of interest for our rare disease researchers. The plan was to meet periodically, using internal and external speakers, and include our clinical trial and natural history grantees. The hope was to have this forum so researchers can share issues, address them using expertise of others, and

ultimately to help improve rare disease clinical trial and natural history studies.

We had two Unite meetings planned for 2020, as a pilot for the initiative. But we ended up having three meetings, with the last two meetings focused specifically on COVID-19 issues. These meetings allowed researchers to come together and discuss immediate issues that they were facing during the pandemic. The researchers come from all over the country, the world, and their experiences, although different by institution, had many common themes. Helping find solutions, learning from what others had done in terms of things, like, enrollment, and virtual abilities, product delivery and other challenges to address these issues. It was a great success for the workgroup. And it was a great success for the program, as well as for the grantees that came together. Many advices were taken. And a workgroup was actually formed from it to further evaluate and document these items with the intent to publish a paper on lessons learned in rare disease research. Next slide.

In addition to the Unite response, as I just mentioned, there were other ways that OOPD wanted to help. So OOPD continued to allow for flexibility for the funded studies, as well as for future funding.

OOPD also offered administrative supplements to address unexpected increases in costs in these ongoing trials. We saw several ideas that would help these ongoing studies, and be successful, as well as provide the ability to complete the trial. Examples included supportive additional personnel in lab studies, and cost for a less centralized testing due to travel restrictions. Also, additional computation informatics and telecommunication costs that were needed because of the necessity to care for patients remotely as well as costs to support cloud-based imaging platforms, and IRB and additional startup fees for new studies added to counterbalance the waves we were seeing with the COVID outbreaks around the country.

We plan to continue these impacts as this landscape changes over time, including as the vaccines roll out. Next slide.

So looking ahead, I mentioned our two RFA's, our clinical trial and our natural history studies, which will focus on efficiency and innovation, but also on leveraging funding and patient input. We will also be looking and evaluating additional metrics to evaluate the success of the program. And we will be continuing additional collaboration with our grantees either through Unite or through other means. Next slide.

In summary, there have been several changes to the RFA to increase impact, promote innovation, and learn from the past. We continue to re-evaluate impact after RFA's. And we continue to bring our grantees together with the FDA, and work with other funders to help support rare disease product development. Next slide.

In conclusion, OOPD has been successful in contributing to product approvals for rare diseases and leading to thousands of publications, regulatory decisions, and standard-of-care changes. There is a high need for high-quality clinical data, as well as natural history data for rare diseases. And OOPD

continues to make changes to the grants programs to increase this impact. A large need remains for funding in the rare disease space. And we need to work together to bring products to rare disease patients. Next slide.

Thank you, all. And here is some contact information for our office. I look forward to hearing from our panels today to discuss these important topics in rare disease. And I hope you all enjoy the rest of the program today. Thank you.

Thanks, Lewis.

DR. FERMAGLICH: Thanks, Dr. Needleman. Up next, we have a special guest to deliver opening remarks. Dr. Amy Abernethy is an oncologist and internationally recognized clinical data expert and clinical researcher. As the Principal Deputy Commissioner of Food and Drugs, Dr. Abernethy helps oversee FDA's day-to-day functioning, and directs special and high priority crosscutting initiatives that impact the regulation of drugs, medical devices, tobacco and food. As acting Chief Information Officer she oversees FDA's data and technical vision and its

execution.

Dr. Abernethy?

DR. ABERNETHY: So, hi. And thank you very much for having me today. I am honored to be with you, again, here for Rare Disease Day. At FDA this is a very important day for us, as I know it is a very important day for all of you.

As reflecting on the opportunity to give comments today, and it happened to be that I was also putting away holiday cards -- and I was putting away the cards and ran into a little note from a friend of mine. It is a picture of him and his wife and their new baby, and told about all of the good holiday cheer, with also a sad face for hashtag 2020. And I thought about how I got to know him.

About 2008-2009 we had both been called from Durham, North Carolina to Washington. I was a professor of medicine at Duke. And he was, actually, a recent Duke graduate. He told me that he was working in one of the labs at Duke, and I was curious about what he was working on. And he said, "My tumor." And over the time of when we were giving talks together

in Washington, I learned a lot about his story, including having a rare cancer, flying all over the country to try and find surgeons that might understand his cancer, wanting to participate in clinical studies and registries, but not having really the access to such studies, and the fact that there were, really, very few labs in the country working on this problem. But he had found one at Duke.

Over the course of that period of time, this, at the time, young -- and he is now -- you know, a decade or more older -- remarkable person sitting next to me, really galvanized, for his particular disease, chordoma, a remarkable journey. They developed a national registry program, tumor banks. They not only developed the scientific underpinning, but basically sparked the science that led to clinical trials and evaluating new drug options. They developed a patient community and a peer support network, and patient navigation activities all through a foundation -- a vision -- and a community working together.

The other thing I remember sitting and talking to him about one very cold, sunny day, outside

in New York City, was that figuring this out for that rare disease could not just be the end of the story. That ultimately, in trying to figure this out for a rare cancer like chordoma, they needed to template the process to create common road maps so that other rare disease areas could also learn and benefit from the work. Basically, be able to repeat the playbook on how to build a tumor bank. And repeat the playbook on how to build peer networks.

And one of the things that really had struck me about the conversation was that, seeing beyond his story and trying to figure out how to beat and address his own disease, he was actually asking the question, "How do we do this at scale?" And I think that, today as we talk about rare diseases and we think about rare diseases in America and around the world, one of our critical questions together is, how to address rare disease at scale?

So let's step back for a second and talk about rare diseases. As we think about rare diseases in America affects 30 million people in the United States. But, obviously many, many more people

around the world. In cancer -- I am an oncologist -- in cancer care, we often talk about rare disease affecting 30 percent of all of our cancer types. So on one side, rare diseases are rare. On the other side, rare diseases in aggregate are common. The challenge we got is the complexity. There is a commonality to many different rare diseases being the story. But the complexity of difference in underlying causes and underlying biology. Differences in a remarkable, vast array of different approaches to treatment. Incredible differences in symptoms and experiences. And differences that all of you experience as families -- as people who worry about what this going to look like tomorrow. Differences in what the natural history looks like in the overall story.

So part of the story of rare diseases is that of complexity. And so, as part of that challenge, we have to address rare diseases one disease at a time. Chordoma -- the young man's disease that I was talking about before -- is different than, for example, a genetic childhood illness. And we

have to do each of these differently.

However, as we think about the dizzying array of all of the diseases to address, we can also think about the remarkable commonalities of what we can build together -- common infrastructure. I think about, again, that sunny day -- cold day, in New York City, and when he was saying to me, "You know, what we really need to do is take what we have learned to do and template it and create road maps for the future." And I think that, here, today, on Rare Diseases Day, what we are doing is talking about some of the elements of the road map.

One of the things I always think about problems like this, is that hard things are hard, but man oh man are they worthwhile for us to work on them together.

So that, kind of, brings me today's day. You are hearing about a lot of the work that we are doing at FDA. This is a part of our American response to addressing the importance of rare diseases. And it is also a part of our American response that has got worldwide impact. You are going

to hear about a number of programs, including, for example, the grant program that you just heard about. You are going to hear about infrastructure that is being built at FDA to try and scale our internal work so that we can serve as many of you as possible. You are going to hear about our work to support clinical development and accelerate the process of helping companies who are developing innovating products, get them to people who need them, provided that they are appropriately safe and effective. And you are going to hear about the incredible commitment of all of the people at FDA across the rare disease community within our families, to figuring out how we do this better every day.

As a part of the FDA community, as a part of the global community of families, and as a friend who was just sitting there in New York City listening about what the future is going to look like, I say thank you for all that you do, and this is really important work. Hard things are hard, but worthwhile. And on it -- here we go.

DR. FERMAGLICH: Thank you,

Dr. Abernethy. Next up we have our first panel, Rare Disease Partnerships, Collaborations and Scientific Advancements. And our moderator will be Dr. Suzie McCune, the director in the Office of Pediatric Therapeutics, in the Office of the Commissioner at FDA.

As a neonatologist, most of Dr. McCune's patients had what would be considered rare diseases. Her frustration at not having adequate therapies was highlighted for her when a new drug was approved for the treatment of asthma that she thought might be promising for use in a patient with a rare neonatal lung disease, called bronchopulmonary dysplasia, or BPD, based on the mechanism of action. But there was not any data in the neonatal population. Almost 15 years later, a clinical trial was done that showed that the drug was not effective in reducing moderate or severe BPD, despite animal models that there should be a benefit.

As Dr. McCune said, "We struggle with this issue all the time in neonatology. The failure of clinical trials. We need to better define the study

populations, the study endpoints, and the trial designs, so that we can provide better care for our neonatal patients."

Dr. McCune?

DR. MCCUNE: Thank you, so much, Dr. Fermaglich, for that very kind introduction and a reminder of my neonatology background. And I really miss taking care of all of those patients. I am very honored to be a moderator today for Rare Disease Day 2021.

I want to welcome everyone to the first panel of the day. And as Dr. Fermaglich mentioned, I am Susan McCune, and the director of the Office of Pediatric Therapeutics, in the Office of the Commissioner at the FDA. For the next -- almost an hour, we are going to be focusing on rare disease partnerships, collaborations, and scientific advancements.

The goal of the session is to provide perspectives on successful partnerships to support rare disease product development. Our speakers will outline the importance of working with rare disease

stakeholders to ensure that scientific advancements support the development of rare disease products.

I am going to introduce all of the -- and I -- the original goal of our session -- sorry I skipped over that -- is to provide perspectives on successful partnerships to support rare disease product development.

I am going to, first, introduce all the panelists. And then, we will have presentations by Mr. Kroslowitz and Dr. McCormack. The presentations will then be followed by a general panel discussion with all the panel members.

So let me first introduce our guest panel of experts. First, Mr. Kroslowitz is the president and CEO of Berlin Heart Inc. Next, we will hear from Dr. Frank McCormack, who is a professor of medicine, director of the Division of Pulmonary Critical Care and Sleep Medicine at the University of Cincinnati. And then, after these two presentations, Mr. Kroslowitz and Dr. McCormack will be joined on the panel by Dr. Vasum Peiris, who is the Chief Medical Officer and Director of Pediatrics and Special

Populations in the Center for Devices and Radiologic Health, or CDRH, at the FDA, and Dr. Sally Seymour, who is the director of the Division of Pulmonology, Allergy, and Critical Care, or DPACC -- D-P-A-C-C -- in the Center for Drug Evaluation and Research, CDER, at the FDA.

As we are going along, I would ask that all of our folks that are watching today think about any questions that you have for the panel and send those along to us so that we can address those during the panel discussion.

So let's get going. Mr. Kroslowitz, the floor is yours.

MR. KROSLOWITZ: Thank you, Susan, for the kind introduction. And good morning. Are my slides up? Hello?

DR. MCCUNE: I am sorry. I think maybe the question was to me. Yes. We can see your slides. Thank you very much.

MR. KROSLOWITZ: Oh. Okay. Sorry. I cannot. Okay.

I would like to thank the organizers

for inviting me to participate today. Next slide, please.

While preparing for this presentation, I thought I should be sure about the definition of a rare disease, which I found is mostly based on prevalence. In the U.S., a rare disease is defined as a disease or condition that affects fewer than 200,000 individuals. And in Japan, is any disease that affects fewer than 50,000 individuals. The definition, however, that most aligns with the title of this conference -- Rare Disease Partnerships, Collaborations, and Scientific Advancements -- comes from the European Union, who defines a rare disease as any life threatening or chronically debilitating disease, which are of such low prevalence that special combined efforts -- or in other words, partnerships and collaborations -- are needed to address them. Next slide, please.

Berlin Heart is a company that produces and markets innovative systems for cardiac support. With our EXCOR adult and pediatric ventricular assist device systems, we are the only company in the world

offering durable mechanical circulatory support systems to support patients of every age and size, from newborns to adults. In the U.S. we focus our efforts on the pediatric system, which is intended to provide mechanical circulatory support as a bridge to cardiac transplantation for pediatric patients with rare forms of heart failure. We support approximately 500 of these patients annual worldwide. Next slide, please.

The true global incidence and prevalence of heart failure in children is difficult to estimate, due to the lack -- as with other rare diseases -- of standard definition. The most common causes of heart failure in the pediatric population are congenital heart diseases, which affect 25 to 75 percent of children with heart failure, and cardiomyopathies, predominantly dilated cardiomyopathy. The reported incidents of heart failure in children is up to 7.4 per 100,000, with heart failure-related hospitalizations occurring in 11 to 14,000 children annually in the U.S. Next slide, please.

Treatment of this disease comes at significant cost, with the average cost for admission for a child with heart failure, reaching $180,000. A staggering number when compared to the cost of admission for acute appendicitis, a much less severe and easily addressed condition. For children who require more invasive therapies to treat their heart failure, costs can exceed $700,000 per admission, depending on the length of stay. A recent analysis by one of the leading children's hospitals suggests that total cost for pediatric heart failure in the U.S. is nearly one billion dollars annually. Next slide, please.

Nearly all of these children with heart failure will eventually need one or more medical devices, including stents, pacemakers, implantable defibrillators, or VADs. Here, we see a pacemaker that, while appropriate in size for the smaller patients, is not approved for them. For children with heart failure, innovation exists, however, incentives do not. In the end, cardiac transplantation is the end game for nearly all of these patients. Next slide,

please.

However, while the number of children listed for transplant over this nearly 20-year period has grown significantly, the number of children actually being transplanted has remained steady during the same time period. With this being the case, the development and approval of devices to sustain children with rare disease in their families is critical.

But why would any innovator embark on a process that requires such a significant effort with an uncertain return on investment? For many medical device innovators, it just does not make business sense to enter what is perceived to be a small market. The approval timeline for Berlin Hearts Pediatric VADs system spans a 20-year period, beginning with a HUD request in 2000, and a completion of the PMA post-approval surveillance just last year. While we were fortunate to benefit greatly from one of the FDA Orphan Product Grants early on, our long-term success has been made all possible only by our perseverance and the philanthropic mission of our investor.

For Berlin -- next slide, please.

For Berlin Heart, the perseverance paid off for both the company and the patients that we treat. This was demonstrated in a paper published in 2015, by David Morales, who showed that after the availability of Berlin Heart's pediatric VAD in the U.S., the situation for the most critically ill children with heart failure improved greatly. Despite an increase in the number of patients with the most urgent status listed for cardiac transplant, there was more than a 50 percent reduction in transplant wait list mortality for pediatric patients who were supported with an assist device while waiting for a donor organ to be found. Additionally, children supported with a VAD were four times more likely to survive the transplant. Next slide, please.

Yet, with the continuing and growing need for additional medical devices for children with heart failure and other rare diseases, progress is described as slow. The HDE regulatory pathway, which was developed to encourage the development and approval of medical devices for small populations with

rare diseases, lifted the pediatric HDE profit restrictions in 2007, to further encourage the development and approval of pediatric specific devices. However, since that time, only six pediatric specific HDE approvals have been granted. I would argue that we need to design programs that really work for children with rare diseases. Next slide, please.

The fundamental challenges of pediatric medical device development were verified at a public FDA meeting in 2018, when 76 percent of the attendees reported return on investment as the dominant barrier to entering the market. Low development incentives, limited market access, no guaranteed reimbursement, regulatory complexity, and evidence generation challenges were the most common factors reported influencing the potential return on investments. Next slide, please.

When presenting the feedback from this meeting, one of my co-panelists, Dr. Vasum Peiris, challenged us with this statement, "Imagine a world in which children had access to innovative medical devices at the same time as everyone else, a world

where medical devices are designed and evaluated for their unique needs, a world with the right ecosystem that supports explorers and innovators to engage, sustain, and innovate in the pediatric medical device market." This world really does not exist. It probably seems as close to getting to Mars or trying to populate Mars. I think we can get there. We just have to take the right steps. Next slide, please.

Not only did Vasum come to us with a challenge, he came to us with a plan for a national ecosystem for pediatric medical devices. The system of hospitals for innovations and pediatric medical devices, or SHIP-MD. Next slide, please.

SHIP-MD is designed as a framework for innovation in pediatric medical device development with a vision to increase and accelerate safe and effective device development by focusing on innovation for children. With all stakeholders at the table, including regulators, reimbursement specialist, innovators, industry investors, the medical community, and the hospitals that serve these children, we hope to develop a shared, transparent, public/private

sector solution, with a transformative and collaborative strategic approach to foster a robust pediatric medical device ecosystem that will be primed to de-risk and accelerate medical device development for children, and address the dominant barrier to entering the pediatric medical device market by developing innovative solutions. Next slide, please.

Focused on creating a safe environment for innovation, the foundation of SHIP-MD will be a dynamic, adaptive, and sustainable evidence-generating infrastructure, made of qualified hospitals with the necessary expertise and experience to safely evaluate novel technologies for children. Engaging the expert review of these novel technologies and exploring the potential for novel regulatory pathways. Next slide, please.

Companies developing pediatric medical devices that improve care options for children may apply to engage the many potential benefits of SHIP-MD. Whether it is a standardized single contract to access the qualified hospital network, collaborative development of a clinical trial that

efficiently achieves regulatory and reimbursement endpoints, integrated single IRB review, or strategic engagement with regulatory and reimbursement organizations, SHIP-MD will simplify, streamline, and improve the pediatric medical device development process by aggregating incentives, eliminating barriers, and transforming traditional business thinking related to pediatric device development. Next slide please.

SHIP-MD will be guided by those who understand pediatric medicine, pediatric device development, and the care of children. Together we will create an ecosystem that inspires innovators for the benefit of our children. Imagine a world in which children have access to innovative medical devices at the same time as everyone else. This world really doesn't exist. It probably seems as close to getting to Mars. I am sure we can get there, as we have now started to take the right steps.

Thank you, very much.

DR. MCCUNE: Thank you very much, Mr. Kroslowitz, for an excellent talk, and for kicking

us off in terms of consortia efforts. And next, we will hear from Dr. McCormack.

Dr. McCormack?

DR. MCCORMACK: Thank you, Dr. McCune. And thank you for inviting me to be part of this wonderful day.

Today I am going to be talking about partnerships that have led to an effective treatment for LAM, a rare lung disease. Next slide, please.

LAM is also known as lymphangioleiomyomatosis. And that is a 24-letter word that I will only say once. This is a progressive, low grade, metastasizing neoplasm of young women that is characterized by smooth muscle cell infiltration and cystic destruction of lung tissue. And these extra pulmonary cells that move to the lung have activating mutations and tuberous sclerosis genes. Now, that is a lot of description for what is essentially a form of emphysema in young women. Next slide, please.

The average age of diagnosis for LAM is 35 years. But patients have been reported in age ranges from three to 85. And it occurs in women much

more frequently than men. The rate in decline in lung function is typically about three to five percent per year. And the disease course is such that 10 years after symptom onset, 55 percent of patients are breathless, 20 percent are on oxygen, and 10 percent of patients are deceased. The median survival varies in the literature between eight and a half and 29 years, depending on how the patients are ascertained. Either in hospital environments or population-based studies. And there is no cure.

These images depict a young woman who was perfectly healthy until she discovered she was pregnant by a home pregnancy dipstick test, and the next day suffered a pneumothorax, or collapsed lung that persisted throughout her entire pregnancy. In fact, she developed a contralateral -- or a pneumothorax on the other side a few days later, after the first one. And they did not heal. These holes in the lung did not heal until this term infant was born.

Her lung function had deteriorated so much over the course of the pregnancy that she required a lung transplant about a year after

delivering her daughter. And she is shown, here, on the bottom picture, a little bit cushingoid from prednisone treatment for her transplant, along with her three-year-old daughter. Next slide, please.

The LAM foundation was an organization that was founded in 1995 by a family in Cincinnati, a music teacher and a football coach and history teacher at Princeton High School whose daughter was discovered to have LAM at the age of 22. And over the course of the last 25 years, this organization has raised almost 30 million dollars and devoted 17 million dollars to research. And this is a disease that affects only about five women per million. The foundation has registered about 3,000 patients. And this small group of individuals has raised this enormous sum.

You can see in the bottom, one of the conferences that has been held for LAM every year in Cincinnati with support from the NHLBI, which usually attracts about 150 LAM patients, and about 150 investigators and scientists. It is a very unique meeting where science is discussed in great depth. Patients are welcome at those sessions. And the

clinicians and scientists also update the patients in a parallel tract. It provides for a lot of interaction between patients and scientists, and it has been a major motivator. Next slide, please.

So the road map for LAM is the same as it is for many rare diseases. In the beginning, Sue Burns and her husband organized the patients in a way that facilitated research, engaged and motivated scientists. We found ways to fund research. We engaged the NIH and pharma, by traveling to the NIH and requesting a registry. We established -- the gene was discovered for LAM in the early -- or the late 1990's and early 2000's. That led to knowledge about the protein and the pathway involved, and a very promising target. When we had established a pathway for trials, patients volunteered. Pre-clinical studies were done, followed by a pilot trial and a pivotal trial ending in the discovery of an effective therapy, all within about 10 years. Next slide, please.

One very fortunate development was that we were able to achieve -- or receive a grant from NCATS and the NIH to form a rare disease consortium of

clinics around the world that followed patients with LAM and other rare diseases. And, as you can see, in this network we were following, roughly, 3,600 patients with LAM, as well as a number of diseases that also were -- had prevalence well below one in 200,000.

The principal investigator of this grant was Dr. Trapnell, and I was the Co-PI. And Dr. Lisa Young and Nishant Gupta were also major co-investigators and PI's on this grant. Next slide, please.

Around 2000, the mutations that were responsible for tuberous sclerosis were discovered. And then, soon thereafter, they were linked to LAM. These occur on chromosomes nine and 16. The functions of these genes were not apparent at first. But in parallel experiments done in a laboratory in San Francisco, it was determined that these genes control the size of cells in the fly eye. And subsequently, were also found to control cell growth and cell movement. And that focused our attention on the -- signaling pathway in this disease. Next slide, please.

So at this time, we had an organized patient population and a very promising target. We approached pharma and were told that there really was not enough of a market to consider conducting a trial through a pharmaceutical route. So a number of us decided to form a consortium of physician scientists interested in developing a treatment for LAM. There were a total of 13 sites in three countries -- Japan, United States, and Canada -- that engaged physicians, scientists, and experts in quality of life, radiology, pathology, and statistics, to conduct this trial. Next slide, please.

The hub for this trial was the University of Cincinnati. The sites around the United States are shown. Most enrolled less than 10 patients. Cincinnati, NIH, and Osaka enrolled from 10 to 19 patients. But for the most part, the other sites enrolled somewhere between one and seven. The data center was located at the University of South Florida with Jeff Krischer leading. Next slide, please.

And the end result to the trial was for patients who were on placebo, they lost about 11

percent of their lung function in the first year, for patients who took the active agent, sirolimus, in this randomized controlled trial, their lung function did not change over the course of the year. The statistical difference -- this was a highly significant statistical difference.

In the second year, when the drug was withheld, the sirolimus group began to decline at the same rate as the placebo. So it was apparent from this study that sirolimus effectively suppresses lung function decline in LAM, and that it -- for continued benefit, you have to have continued use of the drug. So it is a suppressive therapy, which like we use for hypertension and depression, it does not cure the disease, but while you are taking it, it stabilizes lung function. Next slide, please.

So on the basis of this result, the FDA approved sirolimus for LAM in 2015. And it is now approved in 40 countries, including Japan and the EU, many countries in South America. And roughly, 40 to 50 percent of LAM patients in the United States and Japan are now taking sirolimus. Those are the two countries

where we can get excellent data on current use. Sirolimus is well-tolerated, and lung function stabilization is durable. It has been quite a game-changer for our patient population. Next slide, please.

It is useful just to review the partnerships and the timelines associated with this trial. The genes that were discovered to be mutated to LAM appeared in 2003. We achieved a -- we obtained an FDA IND in 2005. It took us roughly three and a half years to get all the approvals from all sites, and about three and a half years to enroll all patients in the trial. So a total duration of the trial of about -- of over seven years. The result was published in 2011, in the spring. And FDA approval occurred in mid-2015. We had partnerships from the NIH, from NCATS, the FDA Orphan Drugs Program provided us with a very important grant, Pfizer provided the drug and some study funds, the governments of Canada and Japan contributed, the LAM foundation contributed half of their net worth -- about half a million dollars at the time. So it was through these partnerships that this eight and a half

million dollar trial was possible. Next slide, please.

I think it is also useful to review the timeline for FDA approval, because we had a lot of help with this process. So when this trial was published, we approached Pfizer and asked them to consider pursuing an FDA indication. They gave it a lot of thought. They said that it really did not make sense from the patent timeline, or the market size. And they initially declined. But we approached the FDA about submitting a citizen's petition to compel changing of the label, without the need for the company to participate. On the basis of that review, the FDA invited Pfizer to come forward and suggested that they might consider submitting for an indication, because they thought the trial results were compelling enough that they could support that change.

We had a lot of help from the FDA with planning the path to FDA approval with orphan drug designation, breakthrough designation. All suggested by the FDA and submitted with Pfizer as the sponsor.

The NSDA -- or the new drug application as submitted in -- about Christmas day in 2014. And

six months later the FDA approved the drug for the use in LAM. Many approvals followed. It is really shown as the power of what an FDA approval can do for drug approval in other countries. And in many of those countries, there is no access to the drug without government approval. So this provided first time ever access to the drug for patients in Japan, many Asian countries, many South American countries. Next slide, please.

So these are what I view as the six key ingredients that resulted in an FDA approval for sirolimus in LAM. And it begins with the courage and resolve of patients. The patients had the foresight to organize and facilitate and fund research. And then, they lined up for trials.

Funding of excellent research, blind to immediate relevance. The major breakthroughs in this field occurred from research in flies, worms, and rodents, that were not immediately linked to human disease, but which rapidly elucidated molecular targets.

The power of academic health centers.

The expertise, flexibility and resources of multiple major academic health centers made this trial possible.

Altruism of medical care givers, lawyers, Pfizer, and the FDA. Many -- each of these domains donated large amounts of time and efforts.

Advocacy by the LAM Foundation was pivotal. They brought the patient voice to every conference table.

A government regulations act, such as the Rare Disease Act of 2002, provided the infrastructure that made an international investigator initiated trial possible in LAM through NCATS years later. And the infrastructure and guidance we got from the Rare Lung Disease Consortium supported by the NHLBI, NCATS -- and the willingness of multiple agencies to contribute partial support for this trial, including the FDA, governments of Japan and Canada, the LAM Foundation, the Tuberous Sclerosis Alliance. Each of them was willing to contribute in a partial way to make this trial happen. Next slide, please.

So there are many acknowledgments.

NHLBI and NCATS for the rare lung disease consortium with Steve Groff, and now, Chris Austin at the helm. The Miles principal investigators and site teams, the LAM Foundation leaders Sue Burns, and now, Sue Sherman, the Translational Research Trials Office here at Children's Hospital, FDA Pulmonary, Allergy, and Rheumatology Branch, with special help from Sally Seymour and Badrul -- Chowdery -- or Chowdery, FDA Orphan Products -- Kathy Needleman was very helpful with obtaining this grant back over 10 years ago -- people at Pfizer, especially Sandy Seathie [ph] and Elly Katz [ph] who helped us navigate use of this drug in this investigator-initiated trial, and all other sponsors. And next slide.

And the most important acknowledgements are here. So these are the 89 patients who signed up for the Miles Trial. And what you have to realize is every one of these patients knew that this drug was promising, and that they could go to their physician and get a prescription and start taking this drug immediately. But all of them signed up for a two-year course of the trial, during which they knew they may

be declining at the rate of 10 percent per year in their lung function. So it took a lot of courage to stick this trial out to the endpoint. And in the end, it led to a result that will help LAM patients for a long time to come.

So thank you, very much, for your attention.

DR. MCCUNE: Thank you, so much, Dr. McCormack, for an outstanding talk. I would like to invite Dr. Peiris and Dr. Seymour to join Mr. Kroslowitz and Dr. McCormack on screen for our panel discussion.

Thank you, so much, for the background information in the device space on SHIP and in the therapeutic space in the LAM Consortium. I have also been involved over the last five years with the International Neonatal Consortium. So these are all very powerful entities for us to be able to move forward, both in the device space and the therapeutic space. And it is nice to be able to join Dr. Peiris with Mr. Kroslowitz, as was already mentioned in the talk. And Dr. Seymour with Dr. McCormack, as was

mentioned in his talk, as well.

So I am going to open up the discussion. And please, for anyone who is listening, if you have questions for our panel, please submit those and we will follow up with those as we get them.

But my first question for each of you is that, clearly you have all been engaged in very successful consortia efforts -- and as Dr. Abernethy talked about this morning, we need this roadmap to be able to move forward -- and based on your experiences, can you discuss, kind of, the whole entity of consortia? In other words, from start to finish? How do you start or begin a consortium? How do you ensure successful continuation or engagement of that consortium? And then, how do you ensure meaningful deliverables that you all have already pointed out? But how do you continue to deliver those kinds of meaningful deliverables? So I will open it up -- who would like to start?

MR. KROSLOWITZ: Vasum, I think it would be a great place for you to jump in.

DR. MCCUNE: All right. All right.

Dr. Peiris, you are up.

DR. PEIRIS: Thanks, Bob. It is a great question, number one, Suzie. And thank you to all the organizers today for inviting me to the event. And this has been going so well so far.

Starting a collaboration. It is a big process. And there is, obviously, a huge need for us to actually work together and leverage the comparative advantages of so many stakeholders in the ecosystem to be able to address these long-standing public health needs in rare diseases and in pediatrics. With respect to starting SHIP, as Bob eluded to -- I think you provided a quote from me from a presentation that I gave when I was in Houston a few years. And again, the reason that, that is important is because back then, I was trying to develop the plan, clarify the information, and the issue to all the interested stakeholders wherever I was speaking.

After that, we -- you know, we had the public meeting. We went through the issues and clarified the issues during the public meetings. We discussed strategies for overcoming -- or, at least,

mitigating some of those issues during the public meeting. And then, we developed the strategic framework -- the SHIP-MD strategic framework. And once that framework was originally developed, I think vetted that framework amongst a number of different stakeholders across the country to get their feedback from different vantage points -- different perspectives -- from hospitals, from payers, from financers, from industry, and others.

And once we had that feedback from so many, and a representation that this was a good idea to move forwards with, we were then able to get some funding. And then, be able to establish what many have seen recently, which is the leadership of continuing development of the framework in phase one, via C-Path. And hopefully, many of you were able to -- or, at least, some of you were able to join our workshop on the SHIP-MD framework, to get additional broader stakeholder feedback, and continuing vetting the framework to figure out if we need to iterate on it.

That initial step was an initial step. But it is a big step. And the great aspect of this is,

now, we have the majority of stakeholders in the pediatric and small population device space aligned around a message and a strategic path forward. We are not all speaking at it from different angles, because all of those angles are important. We are now bringing all of those perspectives together. We are clarifying a path forward. And now, we are able to take those steps forward, together.

DR. MCCUNE: Thank you, so much, Dr. Peiris. I just would like to follow up with Mr. Kroslowitz as a member of the SHIP and thinking about how this can help in the Berlin Heart Space. How do you view your role and the importance of the SHIP Consortium?

MR. KROSLOWITZ: I mean, I think this is really a very, very important project. This is really important work. And finally, to be able to bring everybody to the table that is really necessary to move the field forward, has been an amazing feat. I think Vasum really deserves tremendous accolades for having to -- having done that, and gotten everybody to the table, and really to move forward with a common

goal, right?

I mean, it is important whenever you are bringing people together to work on a project, or to collaborate, that you set goals that are achievable, and in the end, meaningful. And I think that is exactly what is happening with the SHIP. And I have no doubt that this program will be successful and will be very meaningful. Especially, in the space of pediatric medical device development.

DR. MCCUNE: Thank you very much. Dr. McCormack, I would like to open it up to you in the therapeutic arena. You know, your thoughts in terms of the -- what has made your consortium successful and how you continue that moving forward?

DR. MCCORMACK: I think I -- there are a number of key elements. And it mostly comes down to what -- knowing what motivates people. So what motivates patients, I think, is having a physician who cares about them, and who understands their disease and is -- or is willing to learn about their rare disease. But even more than that, they want hope. And what they may not realize right off the bat is

research is the source of hope for these rare diseases. Sometimes that takes a fair amount of education. But over time, the LAM community became very aware of how important research was to the ultimate success of the drug that is now used in treatment of the disease.

And knowing what motivates federal health agencies. They are all interested in improving the health of their public and being responsive to patients. They like to see progress -- or, at least, the promise of progress. And they want to do good, like many of us.

Knowing what motivates companies. They want to expand knowledge about their product. They want to gain additional indications for their product. They want to do good. There are many people within these companies who donated a lot of their time to make this trial successful.

And knowing what motivates academic physicians. They like developing new expertise. They like doing good. That is why they are physicians in the first place. They like to receive credit when they

have done work. So including people as authors on manuscripts is very important.

These direct interactions that we engineered between patients and physicians was incredibly motivating. And I would encourage any rare disease community to consider including both physicians and patients in conferences together.

But above all, I think, what really motivated progress in LAM was exciting science, and these biologically tractable problems with tremendous clues from nature about the most promising drug and drug targets might be.

So, I think, overall, it is knowing your constituents, knowing what motivates them. And all of these things aligned incredibly well for LAM and we are very fortunate in that regard.

DR. MCCUNE: Thank you, Dr. McCormack. Dr. Seymour, clearly, Dr. McCormack talked about the role of FDA with the LAM community and the LAM Foundation and the LAM Consortium. Can you talk a little bit more about the role of the consortia efforts in this space?

DR. SEYMOUR: Sure. Thank you, Dr. McCune. And thank you to the organizers for inviting me to participate in this panel.

You know, I think the role of FDA in these collaborative efforts can be different, depending upon the stage of development, and how organized the collaborators are. So we can receive submissions -- inquiries from -- you know, individuals, patient organizations, academic investigators, pharmaceutical companies. And each of these can play a role in the process and the collaboration.

Sometimes efforts in a certain disease area, from our perspective, seemed scattered and going in different directions. Maybe, duplication of efforts. Maybe, there is more than one patient group who are working towards the same goal, but duplicating efforts. And sometimes bringing those folks together to combine their efforts would be more efficient. And we may suggest that some of these stakeholders actually work together.

If it is early in development and a

patient group is reaching out to us, we may suggest something like a patient-focused drug development meeting to obtain some feedback from patients, and to try and generate some interest in development of therapeutics in this space.

It may be that there are some academics or sponsors early in the process. And this was the case with Dr. McCormack. And we can provide feedback on the type of data that is necessary to open an IND. And also, feedback on the purposed development program they are proposing, and outline our expectations for a successful application.

So depending on where folks are in the process, FDA can play a different role. But I think we do have an important role in these collaborations, because we have expectations for what is necessary for successful application. We have a lot of clinical trial expertise and can provide feedback on the design, endpoints -- those types of things that are important for the trials. And for sponsors who are submitting applications -- you know, they want information, like, is an advisory committee going to be

necessary? So we can provide all of that feedback to them, depending on where they are in their stage of development.

But I think one of our main roles can be bringing these stakeholders to the table and trying to get them to work together. We also can provide a lot of feedback on all the different resources that FDA offers -- many of which Dr. McCormack mentioned in his presentation.

DR. MCCUNE: Thank you, Dr. Seymour. We have gotten a couple of questions from the audience. And I would like to fold those into a little bit of the discussion, right now. Because you are talking about how to engage stakeholders. And I want to go back to Dr. McCormack for just a second, because I know that you mentioned starting with the LAM foundation. And one of the questions that we have gotten is, "How do foundations work with industry to get to the point of submitting an NDA, and how do you motivate sponsors -- " and this goes to both the device side, as well as the therapeutic side -- "How do you motivate the company sponsors?" You were

speaking of that, Dr. McCormack, a little bit. But I think folks have found some challenges in encouraging industry to be engaged in this space. And do you have thoughts on that?

DR. MCCORMACK: Yes. The LAM Foundation's role in the NDA was not so much to submit it, but to organize the patients in a way that -- in which trials were possible, and to find seed funding for studies that ultimately led to federal funding and larger research discoveries. I would say that most of the foundation -- scientific foundation for the use of sirolimus in LAM was developed with funds that, at least, started with LAM Foundation seed funding.

So pharma becomes interested when the target is biologically plausible and promising, and the patients are organized so that the studies can be done. And I think that, really, the -- until that happens, it is very difficult for pharma to engage.

So rare disease organizations -- rare disease populations have tremendous power to make themselves accessible to progress, to pharma, to science, by organizing, developing seed funding, and

then, engaging in pharma and the FDA and other organizations to move treatments forward.

We were very fortunate that this drug was already approved for another indication, had tremendous interest from the science community behind it because of its role in a central energy pathway in the cell. So there was a lot of horsepower behind this drug before we even got started with the trial. And that is not true for every patient community.

But I think it all starts with becoming organized, funding seed research, and then, doing trials -- making patients accessible for trials.

DR. MCCUNE: Thank you. And Dr. Peiris, I will ask you, sort of, the same question in this space, because I know that you have been very active with the sponsors. And can you talk a little bit about the other stakeholders, including the patient voice, in this space?

DR. PEIRIS: Yeah. There is no doubt, Suzie, the patient voice is critical and fundamental to all of this. All of these efforts that we are trying to move forward on is intended to help patients that

need the care, that need the therapies, the drugs, the biologics, the medical devices. And I -- even at CDRH we have a patient engage in the Patient Science Program, that is specifically encouraging developing tools for sponsors to be able to utilize the patient voice in a more established and quantitative way. Sometimes it is qualitative information that needs to be created into quantitative metric, so that, that can be utilized within the scientific approach that our review viewed to evaluate the product. So patient aspect is critical.

And, Suzie, if you do not mind, just to literally a point about -- I do not create collaboration that are really as effective and as potent as we need. Just to dig a little bit more on that. I know there is a question in the chat around how can federal agencies make a difference in this space. And I think that is an extremely poignant question.

When we think about collaborations, especially similar to what we have been doing with the SHIP-MD framework, we are trying to bring together,

again, multiple stakeholders across the ecosystem -- patients, academics, innovators, industry, financers, reimbursement experts. And I think there is a great role for us to be able to leverage the strengths of a number of different sister federal agencies to really bring that -- those groups together to be able to address some of these long-standing public health areas, where there are needs that are across the device development -- for the -- development spectrum. But and eventually -- more focus on the medical pediatric device development spectrum.

DR. MCCUNE: Thank you, so much. And I -- and there is another question in the chat box, related to the use of placebo arms in trials, and the use of historical controls, and whether consortia can play a role in developing registries and the role of that in clinical trials for rare diseases. I just thought I would throw that out, see if anyone would want to start that discussion.

DR. MCCORMACK: Just say in terms of the Miles Trial, the inclusion of a placebo group was incredibly important for -- I think, for ultimate

approval and acceptance around the world. I was encouraged to design the trial in that way by a former FDA employee named Gene Sullivan. He helped me with trial design all through the trial -- trial design and implementation.

I recognize that is not possible for every patient population, and that it can be difficult -- it can make recruitment difficult, which I think you can see from the slide that showed how few patients were enrolled at most of the sites. So many patients are resistant to the concept of a placebo arm, especially in the face of a promising drug. But it was incredibly impactful in the LAM community. And I am very pleased that we decided to go that route. And I acknowledge that is not possible for every organization -- every patient community.

DR. MCCLUNE: And Dr. Seymour, did you have any thoughts in that arena?

DR. SEYMOUR: Well, I think, Suzie, it depends on what you know about the disease, right? I mean, you have to have an understanding of the natural history of the disease. That is very helpful. And in

some cases, you may not need a placebo control. But I think that would be an exception. But there are cases where the natural history is so clear that it would not necessarily be required to have a placebo control.

But I do think having a rigorous trial design is -- including a placebo control if it is appropriate -- is very helpful in interpretation of the data. Often, we do not have large trials, here. Often, we only have a single trial. So we really need the most robust design we can get to make the best decision for patients. Often, these are lifelong treatments that they are going to be taking. And we have to really have the best information we can to make those benefit/risk decisions for them.

DR. MCCLUNE: And thank you, so much, Dr. Seymour. And as I -- as Dr. Fermaglich pointed out in my story, about what seemed to be a promising drug that finally, when it was studied in the neonatal population, did not demonstrate any benefit, in terms of moderate or severe BPD. But we needed to do the study. And we needed to have the placebo population. And we -- specifically, when you are 15 years out from the

original thought, clearly the standard of care changes. And so trying to be able to look at natural history studies may be a bit more complicated. So I think it is a really important aspect of rare disease trials.

And I will say that we did have another question about the patient voice. We have gotten a little bit into that. But I want to note that our next panel is specifically regarding patient engagement and includes a patient advocacy representative. So we are going to let more of the patient voice conversation go to them.

I am going to -- looks like we have a little bit under 10 minutes, or so. I want to go to the second question that we had, kind of, talked about originally. And that gets into a little bit of what we have been talking about. But collaborative efforts in the rare disease space may require unique approaches. Especially, related to enrollment of small populations, implementation of innovative trial designs, and creative approaches to developing incentives. And we have talked a little bit, today,

about some of the funding issues. And maybe you all can talk about some funding opportunities. And I just want you to discuss your experience in your consortium, and how you have addressed these issues.

So maybe I will start again, back, with Dr. Peiris.

DR. PEIRIS: Sure. Happy to kick it off. A lot, here. As you already -- as the question also outlines. Let me take it from, perhaps, the SHIP-MD framework perspective that we have been working on.

As I mentioned, these types of long standing public health issues, especially -- and I will speak to the pediatric device area. The issue around a -- of medical devices developed for pediatrics has been -- is such a generational issue, that in pediatric medicine, and pediatric interventions and surgery, we train our residents and fellows to be able to utilize the devices off label. We have to alter them, and cut them, change them, reshape them, to be able to work for our patients. And that certainly is very appropriate. Physicians have to

do that. They do that every day.

But it certainly also exposes those pediatric patients to a very different benefit/risk profile than the device was originally designed, evaluated, and approved for. It was not necessarily evaluated in the populations that we may be using.

So in order to begin to overcome these generational issues, number one, we have to help all of our colleagues and everyone that is interested in the space. All the stakeholders recognize, hey, number one, there is an issue here. Number two, what is the solution to that issue, and how do we clarify a clear path forward -- how do we take -- how do we develop the right strategic steps? And then, again, take them together in an aligned manner that can truly begin to overcome some of the systemic issues in a systematic way.

And I think that level of collaboration does take time. But it probably is the method by which we will make the most significant and durable solutions to issues like those for the rare disease, small population, and pediatric device space, and that

can, again, begin to shift the entire arena towards a time similar to what Bob had mentioned, when we can actually get to a point where medical devices and medical technology are being equitably developed for pediatrics. Because that is not occurring at the current time.

So, again, it really is taking those clear and strategic steps, making sure that all stakeholder voices are incorporated and integrated, and then, how do we create, again, the integrative approach across the strengths of all the stakeholders and organizations to be able to overcome some of these systemic barriers.

DR. MCCLUNE: Mr. Kroslowitz, thoughts on some of the innovations that are necessary?

MR. KROSLOWITZ: I think -- you know, all of this that we are talking about on the device space, on the drug space -- right -- the goal for all of us is to improve the care, outcomes, and quality of life for these patients -- right -- with rare diseases. And who is not motivated by that, right? Clinicians are very motivated by that. Hospitals are

motivated by that, right? If you improve the outcomes, there is cost savings for them. If you improve the outcomes for industry -- right -- there is greater revenue generation for them. So I think there is something at the table for everybody. And, again, the closer that we align, and work on these issues together, I think, in the end, really, we will all achieve our goals much faster.

You know, there is another -- again, with the limited number of patients, or populations that we have of patients exposed or presenting with these rare diseases -- right -- it is critical to capture as much data as you possibly can. There is another very important program that the FDA has developed in collaboration with PMDA, the Japanese regulatory authorities, called Harmonization by Doing for Children, where we are looking for creative ways to develop clinical trials that will lead to approval in both the U.S. and in Japan for children with rare diseases.

There is other collaborative efforts in the cardiovascular space that I work very closely

with. A learning network for children with heart failure. And where they brought, again, all the stakeholders to the table -- industry, the medical community, the hospitals, and the patients -- and really, with these collaborative efforts, in my career, I have seen more innovation happen in shorter periods of time, than ever having tried to do something on your own. So I think it is really very important to, sort of, look for ways to be innovative in capturing the number of patients, and collaborating on all of the things we have discussed generating -- infrastructures that make the whole process manageable and much easier.

DR. MCCLUNE: Thank you, Mr. Kroslowitz. And Dr. McCormack, some thoughts on innovation in this space?

DR. MCCORMACK: I think one of the most impactful innovations in this trial was the use of the LAM Foundation to motivate, educate, and recruit patients at every step. I mean, when you have a disease that only affects five women per million, finding them can be difficult. And the Foundation has

a series of publications that goes out to patients, they have a listserv for patients to talk to one another, they engage patients at their annual meeting as I have mentioned before. We talk about the importance of trials, about the importance of placebo groups. And I think those things made LAM successful in their trials.

Now that we have an effective drug, we are thinking hard about what next steps we need to take to -- for the next breakthrough therapy. One of the things that have happened that is very encouraging, is that the Chinese population has mimicked the Rare Lung Disease Consortium in the United States and opened a set of 80 trial sites within China for rare lung disease. And in the end, the best way to make progress in rare lung diseases is to open sites in populations centers where there will be many patients with those rare lung diseases. And efforts, such as those going on in China, will make that more feasible.

As Bob mentioned, we need to develop more innovative trial designs -- adaptive trials that

can answer questions with fewer patients. And we need to figure out how we are going to develop new therapies when we have an effective drug. And with the ethical considerations about doing trials when there is an effective drug already approved. So we are thinking hard about what next steps will be.

But for now, we are refining our approaches to the use of m-Tor inhibitors, trying to find out what the minimal effective doses are of the known approved drug. At the same time testing new combination therapies in small trials around the U.S. and Europe.

DR. MCCLUNE: Thank you, very much, Dr. McCormack. And Dr. Seymour, any last minute, as we are winding up our session?

DR. SEYMOUR: That was well said by Dr. McCormack. I do not have much to add, Suzie. I would just say that -- you know, all of these programs, they are -- each one is different, and often requires some degree of innovation along the way. One area where I think is always a challenge are the endpoints. And I think we need to have better

approaches for capturing patient outcomes.

All roads seem to lead back to the patients when we have conversations with companies about rare disease programs, because established endpoints are always a question. And often, the patient symptoms are one of the best ways to potentially go forward.

But we need to have, I think, a more streamlined -- or better way for companies to develop these patient reported outcomes, so that it is more feasible in a shorter period of time.

DR. MCCLUNE: Well, thank you, so much. I want to thank all of the panel members. And I want o say that I think that the last comment is a great segue into our next panel. We have received a number of questions in the chat. And I am sorry that we were not able to get to them. But we have them all cataloged. And maybe, some of the panels, later in the day, can address some of those issues. So at this point, I am going to toss it back to Dr. Fermaglich. Thank you, so much.

DR. FERMAGLICH: Thank you, Suzie. Thank

you, all. We will take about 10-minute break. Please rejoin us at 10:45 for our next panel.

(off the record)

DR. FERMAGLICH: Welcome back to FDA Rare Disease Day 2021. Our next panel will focus on the importance of patient engagement in rare disease product development, moderated by Robin Bent, director of CDER's Patient Focused Drug Development, or PFDD initiative, an effort to systematically obtain and facilitate the incorporation of meaningful patient input into drug development and regulatory decision making.

Robin has been a pediatric oncology nurse for over 20 years, and still practices on weekends. In an e-mail to me, she said, "The voice of the patient being incorporated into the drug development process is incredibly important to me. While the concept is relevant across all diseases, patient involvement is especially important in conditions that we know less about, because they are just being identified, or because they are just so rare that most of us are unfamiliar with. We need to

partner with patients and their loved ones, so we can better understand risk/benefit, identify targets for therapy, and identify meaningful clinical trial endpoints. We cannot move science forward without input from those directly impacted by the science."

Robin?

MS. BENT: All Right. Thank you, so much, Lewis. And thank you for the opportunity to moderate such an esteemed panel today. I am really looking forward to what we will learn from our panelists.

So just briefly, the goal of this panel, really, is to examine tangible examples of patient engagement in rare disease product development, and to include a discussion on the importance of natural history studies in rare disease product development. Our panelists will provide presentations at the start of the panel, followed by facilitated discussion with the panel members.

I would encourage all of you viewing the meeting to submit your comments by clicking on what I consider, kind of, the thought bubble that you

see in the right corner of your screen.

And so, with that -- because I want to give most of our time to the panelists -- please let me invite the -- our four panelists to turn on their cameras, briefly, for introductions. Great.

So I am happy to introduce Dr. Wen-Hann Tan, attending physician, Division of Genetics and Genomics, associate professor of pediatrics at Harvard Medical School. Dr. Tan, thank you so much for joining us today.

Our next panelist, is Amanda Moore, CEO of the Angelman Syndrome Foundation. Amanda, thank you so much, for taking the time to join our panel today. I know we are going to learn a lot from your experiences.

Our third panelist will be Martin Ho, associate director of science and patient inputs and real-world patient evidence in the Office of Biostatistics and Epidemiology and the Center for Biologics Evaluation and Research, or CBER, here, at the FDA.

And finally, we have Andrea

Furia-Helms, director of the Office of Patient Affairs, Office of Clinical Policy and Programs, here, at the FDA.

So at this point, I would like to invite Dr. Wen-Hann Tan to begin his talk. And the rest of us will mute and turn off our cameras, to avoid distraction. Thank you, so much.

DR. TAN: All right. Can you hear me?

MS. BENT: Yes. We can.

DR. TAN: Great. So thank you, first of all, for the opportunity to speak at this event. And thank you for the FDA for all organizing this wonderful event today.

So I am going to tell you about the importance of natural history studies. And let's make sure I can see my slide.

MS. BENT: If you would like to, you can --

DR. TAN: If I can --

MS. BENT: -- click on the slide that -- where you see it, and pin it, and it will become larger. Can you --

DR. TAN: Okay. Sorry. Just -- let me try -- I can see my slide and it is so small.

MS. BENT: Right. So right click on the slide.

DR. TAN: Ah. There we are. Okay.

MS. BENT: There you go.

DR. TAN: Right. Right. So -- in the interest of time. So next slide.

So natural history study. Well, I think many of you there in this audience probably know what natural history studies is. But just so we are all on the same page, just want to emphasize is a natural history is essentially a long -- observational study conducted over many years to study the natural progression of a condition. Whether that is a rare syndrome, whether it is a common disease, it is -- conceptually it is basically an observational long term study. And participants are typically seen multiple times throughout the study at, sort of, intervals, depending on the study. And it compliments a patient registry.

So it is different from patient

registry in that in natural history study there is an investigator who sees the patients and collects data points, as opposed to a patient registry in which the patients, themselves, would enter those data into, typically, an online database. Next slide.

So why do we care about natural history studies? Well, as many people in the past have mentioned, natural history studies is really, really important for the development for therapeutics products. Particularly in rare disorders. And natural history studies tells us what -- tells us something about the disease. It teaches us about the potential complications of a disease. So when you are conducting a clinical trial and you observe a sudden -- what you may think is an adverse event, you can know from knowledge of the natural history -- you will know whether that is truly an adverse event due to the intervention, or whether it is just a natural part of the disease.

It also helps pharmaceutical companies identify endpoints that can be used in clinical trials. And as Dr. Ameokakis [ph] whom many of you may

know, have previously said, natural history study is really important because it provides you with the data that you can utilize in a drug development program. Next slide.

The other thing about natural history study, I think, some people may not, sort of -- have thought about, is that in addition to collecting and producing data for clinical trials, natural history studies also provide investigators with expertise in the disease. By seeing a ton of patients with the same disorder, you start to learn about the subtleties of the disease. You start to learn about things that are not in the textbooks, not in the literature. So it builds expertise in the investigators.

It also allows us to build infrastructure. Because if you have a natural history study, you will have the personnel, you have the PIs, the investigators, the -- you know, research assistants. And by having an infrastructure in place, it allows you to launch therapeutic trials much more quickly. So when a company comes to you and says, "We want to conduct a trial in this condition," you do not

have to start from scratch building your team. Your team is already there.

The other things about natural history study that is really important and distinct from clinical trials, is that the population that you are studying in the natural history study is usually, by definition, relatively heterogeneous. So you are taking all molecular subtypes, all ages, and it gives you the full spectrum of the condition, as opposed to clinical trials, which are necessarily homogeneous in their makeup. Next slide.

So one of the challenges that we have found in conducting natural history studies -- and we have been doing this since 2006 -- over the last 15 years -- is that -- notwithstanding its importance, it is really hard to draw subjects into -- participants into natural history studies, because everyone wants to be in an intervention trial. No one want to just come in, see a doctor just to -- for observation.

And what we have found is when we conduct the Angelman Syndrome Natural History Study as part of the rare disease clinical research network

from 2006 to 2014 -- every time we had an intervention trial, along -- at the same time as our natural history study, we would have a boost in our enrollment numbers. Because patients will come in, they want to participate in the therapeutic trial. We say, "Well, since you are here, would you mind participating in the natural history study, as well?" And I have never had a patient say no, because they are already here, and they are doing the same thing, and we are just collecting some additional data.

But the consequence of that, however, as you can see, is that the -- at least in our population in the natural history -- in Angelman Syndrome Natural History Study, our data became very skewed to those subjects who were in the therapeutic trial, as well. And you can see that in each group. So this gives you a breakdown of all the participants in the -- Angelman Syndrome Natural History Study that we conducted from 2006 to 2014. And you can see that it was highly skewed towards the younger age group. And that is because during the course of the natural history study we had two therapeutic trials, one

enrolled only first -- the first therapeutic trial was open only to individuals up to age five, and then, the second was for age four to -- so you can see we had an unproportionate of participants in this age group. Next slide.

So we were very fortunate to be funded by the FDA Office of Orphan Products Development in 2017 to relaunch our natural history study. And in this trial we made an active effort to try to recruit older participants. So now you can see that our proportion of older participants has actually increased compared to the previous study.

And it probably also helped, the fact that, again, during this study we had therapeutic trial. One of which was open to both children and adults. So, again, you were able to co-enroll of some of these individuals in our natural history study. Next slide.

So retention is a major issue in natural history study. And I am sure Amanda can talk about this a little more a little later. But essentially, we -- you can see from in the previous

natural history study that we ran from 2006 to 2014 there was a huge drop off from patients who would just have one visits, to those who had two visits. And eventually, even though it was an eight- or nine-year study, we only had a very small number of patients who came in for nine visits. Mostly, just dropped off after the second and third visits. Next slide.

So what can we do to -- you know, increase our recruitment and retention, which is really a major theme of this panel today. So we have been working very closely with two main patient support groups in Angelman Syndrome. So the Angelman Syndrome Foundation, and the Foundation for Angelman Syndrome Therapeutics. We attend all the national conferences, as well as their local events. And I think local events are usually very important. For example, the ASF walk every year that we attend. We source their input into the study design, and, sort of, ask them what would families want to see from this.

We also engage with pharmaceutical companies, because the -- one of the major goals of

our current ongoing natural history study is to generate data that can be used in pharmaceutical trials. So we want to hear from the pharma companies what accommodations they would be interested in.

We also engage with the local physicians and we have started sending out study new letters every three to six months to keep people engaged, that then know what we are doing. Next slide.

So the other thing we are afraid to do is to review some participants' verdict. To say, well you know, if we can make life as easy as possible for this participant, can we, at least, retain them in the study for a longer duration, so that they would not just give up. So what we have done as part of this new revamped natural history study, is to convert some of our -- the question/answer we used to complete in person to an online portal, so that parents can complete this in their own time. We have started to move to a virtual visit. Really, as -- by the COVID pandemic. And we have found a lot of outcome measures can be done through a virtual visit. So with that, we have minimized the amount of time they spend in the

clinic. And we have also allowed patients to come in for follow up through virtual visits, again, because we are trying to capture patients who live all over the country -- and indeed, all over the world -- we want to make this as easy as possible. We also, working with the Angelman Syndrome Foundation clinics to synchronize their visits, so that patients can go and see their doctors for regular visit, and still complete some forms for our research study. And finally, a work in progress right now is to develop home video recordings as a way to capture natural history data.

So these are all the various ways in which we have tried to reduce participant burden and increase retention in our study. Next slide.

So with that, just want to thank all the wonderful people I have worked with, both in the Angelman Syndrome Foundation, the Foundation for Angelman Syndrome Therapeutics, as well as all the parents and caregivers of children with Angelman Syndrome, and all funding sources. Thank you.

MS. BENT: Wonderful. Thank you, so

much, for a really informative presentation. I know we are going to have a lot of questions for you coming up.

But for now, I would like to invite you, Dr. Tan, to mute and turn off your camera. And invite Amanda to turn on her camera as we turn, kind of, the virtual microphone over to her.

Thank you, so much. Go ahead, Amanda.

MS. MOORE: Thank you, so much, Robin. And thank you, Wen-Hann, for that presentation and for your years of service to the foundation.

My name is Amanda Moore. I am incredibly excited to be here today. I am not only the CEO of the Angelman Syndrome Foundation, but more importantly I am a mom to the cute kid that you probably see on your screen on the right there, Jackson, who is five and was diagnosed with Angelman Syndrome at the age of two.

So I am here today -- you can go to the next slide -- to talk a little bit about how the patient engages in the rare disease product development, but also how patient advocacy

organizations can help in that process, as well.

So just a little bit about the foundation -- if you would like to go to the next slide. The mission of the Angelman Syndrome Foundation from the beginning has been to advance the awareness and treatment of Angelman Syndrome. And so a few ways that we have done that are through three pillars. Which is, family support, clinical -- our clinical network, and really investing in research.

And so few things that we have done that we -- I felt was really crucial for the conversation today. And if you can go to the next slide. When it comes to engaging the patient and engaging the patient advocacy organizations in rare disease development, are some of the things listed here in no particular order.

So I think the one that -- important for the patient to think about is how you really get involved in advocacy early on. I think when we talk about treatments -- when we talk about product development, a lot of that also goes for advocating for a lot of these things to happen, whether it is for

newborn screening, whether it is to have individuals join the rare disease caucus, to increase funding for FDA -- whatever it may be, it is really, really important to really give tools for yourself, and for your families that you are supporting, on how to advocate.

So one thing that we did really early on was just create an advocacy taskforce. And these are parents that come together that really want to learn more about how they advocate for their child, but also how they advocate, hopefully -- you know, down the line for access to treatments as we move forward. So that is one thing that we think is really important.

The other thing is how you engage with industry. Especially from a patient advocacy organization perspective. It is really crucial early on to engage with industry. And a few ways that we have done that at the foundation is really from early on getting meetings -- you know, holding monthly meetings with the industry partners in the space to talk about -- you know, to get the parent/caregiver

perspective, to talk about what you are doing at the foundation that can aid in their development. And also, just -- you know, helping them understand -- you know, the burden of disease, and getting them access to the patient experience, I think, is really important.

The other thing that we felt was really important to do, as well, is along with other patient advocacy organizations in the space, like FAST and other organizations coming together to bring industry together to work on creating those essential endpoints and biomarkers. So creating a consortium of individuals to come together to really work towards creating that space -- that non-competitive space, where you can come together and really think about the endpoints and biomarkers that are essential for treatments as you move forward. And so, engaging with industry really early on is essential for the patient advocacy organizations.

Another thing that I think is really essential to think about from the patient advocacy organization part of it, is we early on saw the need

of the clinical care, and how can we ensure that individuals with Angelman Syndrome are receiving the best care possible. And in order to do that, with having the, kind of, long-term goal of being -- if we created these centers of excellence -- or these clinical networks, what we would be able to do is possibly engage experts with industry as we move into clinical trials.

So when clinical trials come, as they have -- as we -- you know, have had happen in the Angelman space, there are these experts in Angelman Syndrome that can work with industry and work with the patients to ensure the best care during those clinical trials. And so we have the 15q Clinic Research Network, which is 20 clinics across the United States, and then, clinics globally, that meet on a monthly basis to talk about patient care, to talk about clinical trials, to give advice to industry on clinical trial design, and the -- you know to understand the disease and the symptoms and how we can support them, and how we can -- and -- you know, increase the best standard of care possible -- has

been a huge asset to the community in that way. But it has also been a really great way for patients to engage, also, with clinicians. And also, to take that knowledge back to teach their clinical teams back at home, if they do not have access to a clinic in their backyard.

And then, I think, another thing that is really important to think about when you are talking about rare diseases is that, a lot of these rare diseases, kind of, overlap when it comes to symptoms. And so, the one thing that we really work on is, how do we collaborate with other like-minded mission-oriented rare disease organizations in the field? How do you come together to really create and work on not duplicating efforts? You know, a lot of these small, rare disease organizations are working with really small budgets. And so, making sure that there are ways that we can support each other and not duplicate efforts, I think, is essential as we more forward when working in the space of product development.

And then, if you could go to the next

slide -- I think, one of the biggest things that a patient can really -- you know, engage with when it comes to rare disease development, is this idea of participating in registries, participating in databases that are essential -- have -- you know, in turn. How do we educate individuals, and how do we ensure that people understand the importance these registries, and their involvement in it.

So the one thing that we did that I think was really important, is that we created a LADDER database. And so, the LADDER database is a database that basically is -- the goal is to link data in the Angelman Syndrome space. So we have a lot of these different data points. So how do we bring all these data points together, and how do we collect clinical data? So all that data that is happening in the clinics, how do we bring all those together to be able expand research and get access to that research?

And so LADDER also works with other important registries within the space -- works with the natural history study data. It works with the Global Angelman Registry data, which is a parent

reported registry, which is crucial to this work, as well. And it, kind of, just acts as a conveyor. So we can clean -- bring in this data, clean it all up, and then, provide it -- you know, get it out to those key stakeholders, whether it is industry, research, or anyone, as quick as possible.

So it is really important for parents to understand even getting on and spending time on those registries, although it may not seem like it is as important as going into a clinical trial and receiving a possible treatment, it is incredibly important for the journey to get us to those -- to that end goal in that line of a possible therapeutic treatment. So the best way that patients can really engage in product development is when they have an opportunity to take part in a registry, or any sort of research study -- they should just on it. So next slide, please.

So you know, overall, I think there is multiple ways. I could talk for a very long time -- but I know we are running out of time already -- on ways that patients can engage, as well as patient

advocacy organizations. I would love to chat with any -- you know, organizations that are out there that are wondering and wanting to dig a little bit deeper on how we do this.

But, thank you so much, for allowing me to be here today to talk about our experience.

MS. BENT: Great. Thanks, so much, Amanda. Thank you for sharing a lot of valuable information. And I think it sounds like, maybe, some lessons learned as you have, kind of, worked through this process.

I would like now, to invite Martin Ho to turn on his camera and his video and begin his presentation. Martin, go ahead.

MR. HO: Thank you, Robin.

MS. BENT: Thanks.

MR. HO: Can you see my slide now?

MS. BENT: We can. Yes.

MR. HO: Okay. Great. Thank you. Good morning, everyone. It is my -- really -- my pleasure to be able to participate in this very meaningful conversation on such an important topic. I am a

statistician by training. And I have been feeling very privileged to be able to participate in a study sponsored by the FDA to address some issues regarding the natural history study. And this study is the Natural History Study of Metachromatic Leukodystrophy Study. And I would like to, first, go over the values -- or difference -- what is the difference between a natural history study and a randomized clinical trial, very briefly, and talk about -- as a statistician, how we -- you know, from a stage of design -- study design to address those issues. Next slide, please.

It is a disclaimer that all the presentations I talk about today, it is only my opinion. Thank you. Next slide.

So I think Dr. Tan has defined natural history study very clearly. So I do not need to repeat that. But I just want to emphasize that the FDA has been required to consider valid scientific evidence or substantial scientific evidence, which, by law, is often defined as the randomized clinical trials. And as NHS, or natural history study, is a study that follow people over time in an observational study

manner that does not involve randomization. So as a result of that -- you know, we are facing a few differences between the two different type of -- these two types of study design.

The first one that we are facing that is the randomized clinical trial is -- you know, can allow us, or protect us against the biases and the confounder. Biases, meaning that if there is some underlying -- you know, factors that determine or affect someone's treatment assignment, then -- you know, it can, basically, affect the outcome. For example, for people who are -- you know, one group would treat -- tend to treat people with a better baseline condition than the others, or something like that.

So the second issue is that for data quality, the randomized clinical trial that is considered by the FDA -- their data auditing and the data -- and their study conduct, actually regulated, versus, the natural history study is not.

And last but not least, the study design of the randomized clinical trial is very

focused. And they only consider a very homogeneous type of patients in the study, so that they can maximize the probability of rejecting their own hypothesis or to, basically -- to declare a win for their study, versus, natural history study is much more broader and have -- tend to have a bit more heterogeneity among patients.

However, these three points is not something that we can -- is something that all of them can be a certain level, mitigated. So therefore, to tackle the -- these three issues, by Center for Biologics and Evaluation and Research has sponsored this Natural History of Metachromatic Leukodystrophy Study, which is a very rare disease with very dire consequences. So therefore, we would like to conduct a natural history study and partner with the National Organization of Rare Disorders to -- basically, to develop a natural history study from scratch. And hopefully, through this process, we will learn about the challenges and the design considerations through learning by doing. And for that, we have developed three different ways to mitigate the problems -- or

the gap between the natural history study and randomized clinical trials.

The first one -- next slide, please. And this is -- all right -- the webpage of the natural history study. And next slide, please.

So here are the three things that we are very proud of to be innovative to tackle -- the issues that I have just discussed. The first one is the data quality issue.

Here, there is a -- prevent -- we wanted to prevent not only the -- obviously, it is not the attribution, but rather it is attrition, and also the missing data. And we know that as a fact it is really -- you know, it is a lot of effort to retain patients, and also to have an equal -- or a good quality of data entry at different points. And as a result, we wanted to reduce the burdens on patients and their caregivers, in terms of inputting data and reporting events. So we are using a site that is designed that -- not only the data entry can be done through the web, and also tablet, but some very important health event that we also have developed an

app on the mobile phone for both Apple and Android for patients and their caregivers to report this data. And more importantly, we are going to -- you know, we are having a very talented and very good with engaging patients -- a study coordinator to walk through the study and the study visit assessment with the caregivers and the patients through the video camera of the app, and of the tablet. And so, hopefully, through that way, we not only be able to achieve the goal of being a siteless study, but also have a more interactive -- you know, engagement between the study coordinator and the caregiver and offer help if we need it.

And then, the second approach -- the second prong of the strategy is to make sure that the study design is high quality and relevant. How we do that is we involve not only the patients -- and we also use our multi-stakeholder approach. We also involve physicians in -- you know, and drug developers, and also, the reviewers at the FDA, to make sure the information that we collect not only essential, but also must be -- you know, must be

collected in a natural history study so that when they are being considered as evidence from the agency's perspective, all the important pieces are there.

As a statistician, speaking from my experience, I have to say that nothing is more frustrating than seeing a good natural history study coming in, but just missing one or two critical pieces of information for us to use it as a comparator, or to consider that as important evidence to inform our decisions. So this multi-stakeholder approach is basically trying to balance on one hand, collecting too much information and increased burden on patients. On the other hand, trying to avoid collecting too little information that render the natural history study data not useful.

And last, but not least, is we are going to use statistic -- some statistical techniques and then -- and to try to mitigate the potential bias and confounders. And there are many different methods. And one of the methods are called matching. But regardless of all these methods, they are all, basically, following a basic simple principal, which

is trying to compare apple with apple. And here, we see are red apples, and green apples. And so -- I mean, the purpose of that is trying to identify the red apples in the natural history study, and the red apples in which is coming from some concurrent randomized control that have a higher ratio treatment than the concurring control group. So hopefully, through that, we can reduce the burden on patients regarding being -- the chance of being enrolled or assigned into the control group.

Thank you.

MS. BENT: Great. Thank you, so much, Martin. And I mean, I think that one of the key take-homes that I am hearing is -- you know, it is important to make sure that we are collecting the right information. So I feel like you just said, "call me," to everybody. Maybe not you directly, though.

So I would like now to turn over to our final presenter today. That is Andrea Furia-Helms, from our Office of Patient Affairs. And Andrea, let's go ahead, and you can take it away. Thanks.

MS. FURIA-HELMS: Thank you, so much,

Robin. Good morning, everyone. I am really honored to be part of today's Rare Disease Day event, and, as well, alongside of the distinguished panelists today. Thank you for joining. Also, I want to thank the Office of Orphan Products Development for allowing us the opportunity to share some ways that FDA involved patient and patient perspectives in the agency's work. Next slide, please.

So I will just start with a quick overview. And then, I want to cover some ways that FDA includes patient and advocate perspectives in the regulatory activities. And then, I have some resources to share with you that you may find helpful. Next slide, please.

So I just want to start with why hearing from patients and caregivers is really important to the agency. What patients and caregivers provide in hearing their stories and experiences, it really gives us an insight on things, like, issues, their needs, and what their priorities are, and what they feel are important to both, not only patients, but even their family members. And listening to

patients and caregivers really provides diverse opinions and experiences, and can shed a lot of light on issues, such as things like risk tolerance, and potential benefit. And, of course, let's not forget, they provide real-world experiences in real everyday settings, which remind us of the human element. So really FDA's work and activities is centered around patients, and it is really at the heart of our activities.

One thing I just want to note, 'cause sometimes people think patient and engagement and including patient experiences in FDA's work is pretty new, it has been going on for quite a while. Over 30 years. It is hard to pinpoint when patient engagement in FDA really began. But there was an increase in engagement at the height of the HIV crisis in the late 1980's. And since that time, it has been so great to see that it has been involving patient stakeholders in our work -- has been increasing and -- continually, and evolving continually, ever since. Next slide, please.

So now, I want to talk about some

patient -- activities for including patient perspective in FDA's work. And I will start with a patient listening session. Next slide, please.

Patient listening sessions are one of the many ways FDA has been expanding patient involvement. And it really encourages communication between FDA staff and the patient community. Now, currently our patient listening sessions are focus on rare diseases, and they are conducted in collaboration with our partner, the National Organization for Rare Disorders -- and as you probably well know, NORD -- a memorandum of understanding. But we also partner and acknowledge that the Reagan-Udall Foundation has been really helpful and supportive for the sessions.

Now, these sessions allow FDA staff to engage with patients, caregivers, and their advocates, to hear directly from them about their experiences living with diseases or caring for a loved one with a disease. And this can really help inform medical product development, as well as other regulatory issues.

So just for an example, listening

sessions provide an understanding of things like, disease and treatment burdens, functionality and impact on daily activities, and really what priorities should be considered when medical products are being developed. But what they also do is, they help educate the review staff. And really help them understand the various diseases and conditions more clearly, and more in depth. And it helps patients and advocates understand FDA's work, just by participating and really interacting with the staff and the types of questions that they are asking. And it also provides a starting point to -- for information early stage research and development.

And we had asked review division staff how they might see this information with patient listening sessions informing the work, and they have cited things, like, informing regulatory decisions, informing guidance development, helping to prepare agenda and topics for a workshop or other public meetings to make sure it is really focused on what is meaningful for patients. And also, there have been other things cited, such as providing a broader

understanding of the range of opinions that patients have, and maybe shaping regulatory thinking surrounding endpoint selections and other instruments for study design. Next slide, please.

So one thing I do want to highlight, is the critical path innovation meeting, or also known as CPIM. And this was developed by the Center for Drug Evaluation and Research. The CPIM is a forum for FDA and stakeholders -- and stakeholders, such as industry, academia, scientists, and patient advocacy groups, as well as government -- to discuss potential scientific advancements in developing products and specifically, drug development. And so, like, issues around methodology, technology, or even a data collection tool.

So these types of meetings, FDA may provide some general advice in -- and to folks that request this type of meeting. And they are usually centered on those items that I discussed -- the methodology, technology and other tools -- and really is all focused to enhance drug development. Now, just to note that the CPIM is not a substitute for formal

other regulatory meetings like the pre-IND, an IND, or an NDA, or the BLA-type meetings. And it is not to provide any in-depth review of data by FDA. And they are not regulatory. And they are not binding, or specific to any particular medical product. Next slide, please.

I will start wrapping up with the following resources on the slides. Next slide, please.

One thing I just want to mention is this resource, that may be useful in helping to inform the design and implementation of natural history studies. The Rare Diseases Natural History Study for Drug Development Guidance can be used to support the development or drugs and biological products for rare diseases. And this guidance describes things like potential issues of a natural history study in all phases of rare disease drug development. And it also highlights strength and weaknesses of various types of natural history studies, data elements, and research plans, and provides the practical framework for the conduct of natural history studies. So we highly encourage you to take a look at this resource. And it

might help in developing a natural history study, or maybe even informing one that is already in progress. Next slide, please.

So this is a bit of a busy, busy slide, which is a good thing, because what it does is demonstrates the various patient-focused activities at FDA. And it is a resource for contacts and links when you are looking to learn about how to engage and become more involved in the patient engagement program and initiatives across FDA. And it is organized by Medical Product Center in the Office of the Commissioner. Next slide, please.

And finally, we know that it is really hard to navigate, sometimes, where to go for the appropriate place to get what you need at FDA. So please feel free to contact us at the Office of Patient Affairs. We are always happy to help.

So thank you for your attention. And I look forward to any questions you may have.

MS. BENT: Wonderful. Thank you, so much, Andrea. And actually, thanks all of you for some really thought-provoking presentations.

I would like to, once again, encourage those of you viewing the meeting to submit your comments through the comment bubble in the bottom right corner of your screen.

But with that, I would like to start off our conversation with, maybe, a question for Dr. Tan or Amanda. We know that clinical trial participation can be burdensome, and that a lot of impacts, including -- and it can have a lot of impacts, including limited diversity of those who are able to participate in the trials. How do you see the information that you learn in natural history studies being incorporated into clinical trials? Does it go beyond better understanding the natural course of disease, to, maybe, informing the design of clinical trials to make them less burdensome, or informing inclusion/exclusion criteria?

DR. TAN: Yeah. I will take that. So, yes. Absolutely. So one of the many reasons for having a natural history study is to allow investigators to test and pilot different outcome measures. And we have actually done that in our current iteration of the

natural history study. We had developed some forms that we thought might be useful. We administered them to the participants who have -- you know, study so far. And we realized, after about a year or two, that particular form -- that particular questionnaire was not very discriminating -- was not particularly useful. So we have abandoned that. So that is an example of where -- you know, moving forward in a future clinical trial, we would not use that.

On the other hand, we have also introduced other measures that we found to be very helpful, and we will recommend that those measures be incorporated into future clinical trials.

MS. MOORE: Well, and if I can add, too, I think --

DR. TAN: -- answer your question?

MS. MOORE: Yeah. If I could add to, I think understanding how even simple things, like traveling with individuals with the rare disease that you are working on, or how anesthesia affects that child, all these things can create a lot of burden on the families when they are participating in the trial

that includes those things. So knowing those things in advance, industry can create clinical trial designs that help eliminate some of that burden. And I think that is really important, as well.

DR. TAN: And the other things about burden is that -- you know, there is obviously traveling to the site that is a major burden. But the other burden actually comes from the duration with which they have to be remaining on the site. So how long does it take to administer a particular assessment. And that is something we are monitoring and measuring as we study. We are learning from it. And we have found that some assessments can be done more efficiently, and therefore, can be incorporated easily. And some have taken more time than we initially anticipated. So -- you know, we have had to modify things. And we will continue to do that.

And it also speaks to why we try to move as many of these assessments as possible to Zoom, to a virtual setting, so that we can do those outside of a standard visit. So we are very conscious of participant burden. And we are doing what we can to

minimize that.

MS. BENT: Great. Thank you. That is really helpful. I do not know if either of my FDA colleagues have any thoughts on that. I -- that was not really a question that, maybe, we focus on. But if -- do you -- does anybody have any other thoughts? Or shall we move to --

MR. HO: This Martin. I just want to add one more thing. When ceased or start of our -- the natural history study, we recognize that one of the primary endpoints of interest in most of the clinical trials -- you know, regulatory submissions are actually not something that would be conducted -- or the assessment would not be conducted in regular medical encounters. So therefore, it is something that is being done in this trial -- and so therefore, is not easily -- or almost impossible for us to get it from a usual real-world evidence -- or real-world data type of situation. So this is something that we are -- we find is very important.

And also, to reflect on -- to echo the previous two speakers, I really find this fascinating

to hear from the patient's and their caregiver's perspective about the clinical protocol and the forms -- the stuff -- the assessment that we need to go through in the usual clinical trials.

And so, I just want -- let me stop, there. And thank you.

MS. BENT: And thank you. I think that, that is a -- that is a really good point, as well.

Let me move onto a question for Amanda. And I know you spoke to this during your presentation. But I wonder if you can talk a little bit more about how patients can be, kind of, instrumental in the rare disease product development. Particularly, as you mentioned your partnering with industry partners. How have you built a relationship with industry partners, and what recommendations do you have for others? And I know during your presentation you spoke to, kind of, your monthly meetings and things like that, where you are keeping your industry partners engaged. But what did that look like in the beginning? How did that -- can you, maybe, speak a little bit to, kind of, how that evolved?

MS. MOORE: Yeah. I think there are two different ways that I have seen it evolve. One, industry will come to us very early on -- pre-clinical, just to want to start engaging in a conversation. They want to understand the burden of the disease. They want to understand the services of the foundation. They want to help and support. And so, early on, they will have -- you know, connected with us.

Or, vice versa. We will hear through the pipeline that an industry partner possibly has Angelman Syndrome as part of their pre-clinical work. So we will reach out to them early on, and say, "We want to be a partner from day one with you. Can we get a call together and work on what that looks like moving forward?" And you know, I think the most important thing is letting them know the resources you have, because you want to make sure that they understand the disease. You want to be able to schedule caregiver monthly -- you know, we have industry who will schedule caregiver monthly calls, where we have caregivers come and just talk about what

it is like to be a caregiver to a child with Angelman Syndrome on all -- in all different ages.

And so, ensuring that, that is happening, I think will -- ensures later on, when they start getting to the clinical trial design, knowing some of those things that are going to be hard on patients, like, traveling, like -- you know, sleep for kids with Angelman Syndrome is sometimes non-existent. So having to stay overnight multiple nights in a hotel to do a trial is hard. Or going under anesthesia, there is issues with that. So understanding that, really early on is crucial for industry and it is crucial that the patient and the patient advocacy organizations have that voice early on.

So really it is very organic at the beginning. Like, let's just meet, let's become friends, and let's -- you know, let's go on this journey together to try to get to the finish line. But also helps us, too, because it educates the patient and the patient advocacy organization on all this product -- you know, drug development process. Because early one, when you are a new organization and a new

rare disease doing clinical trials for the first time, there is a lot of questions that come out from the community. So industry can be a great partner in that.

MS. BENT: Great. Thank you. I will just pause to see if anyone else has anything to add before I move onto another question that we have received through the chat.

MS. FURIA-HELMS: This is Andrea. Can you hear me?

MS. BENT: Yes.

MS. FURIA-HELMS: Okay. I never know if -- when I am unmuted.

So I think, Amanda, you really outlined a lot of the great ways that you have been working in various -- with various partners to get those patient perspectives incorporated. And I think one of the things that you did highlight was, early on. And we have seen, through our work and patient -- where sometimes patients' and caregiver's perspective might have been requested or sought out a little too late, and maybe they have -- would have gone in a different direction. And so, I think, you know, as you outlined

-- I think -- you know, working with academic experts who are conducting the research in the rare disease -- you know, the clinical disease experts, as well. And they may also be conducting clinical trials -- you know, working -- with them closely -- you mentioned, but as you work with industry partners, as well. Especially the ones that have a particular interest in rare disease.

But always remember that FDA has a variety of activities, and initiatives, and programs, now, that you can get involved and really share those perspectives, as well.

MS. BENT: Great. Thank you, Andrea. And that, kind of, ties directly into my next question, that I am, kind of, going to aim towards you, that we received through the chat. And those are -- are patient listening sessions open to the public? If so, how do we get more information on joining in? And I am going to, kind of, tag team that with another question that we got, which is; can you explain the different types of listening sessions for patient engagement, particularly listening sessions versus

patient focused drug development?

MS. FURIA-HELMS: Sure. So to the first question, right now the patient listening sessions are closed sessions. They are informal, and almost like intimate discussions between the FDA staff and the patient community that participate. So -- but, one thing that we do provide is summaries after each patient listening session.

So -- and to get to the other question about the types of listening sessions, there is two types. They can be requested by FDA staff, to really understand and ask questions for a particular sub-population of that particular disease. Or they can be requested by the patient organization, where they feel that they have some information and they want to share their experiences and stories with FDA about -- you know, what is important to them, and how they are managing their disease or condition with usually no -- but sometimes, maybe, very minimal treatment, sort of, things that -- you know, they are trying to manage with what is available to them.

Did I answer all the question? Or there

was another question?

MS. BENT: There was a little bit of a question between patient focused drug development and the listening sessions.

MS. FURIA-HELMS: Yes. So one of the things -- the differences is, because our listening sessions are closed, where the patient focused drug development meetings are open to the public, so anyone can join. And I do not know -- that this is particularly interesting -- of interest to industry as they indicated to us, because they want to know what the conversations are and hear those perspectives and what is important to patients. So that is why we make those summaries available online.

And so I think, also, the patient focused drug development meetings, because they are open to the public, there is a much more representative participation. So ours are usually just to have those intimate conversations. They include probably seven to eight patients and caregivers. Whereas, the patient focused drug development meetings could have hundreds of people, even, as we know, thousands, coming up soon,

so that you can hear from a broad range of perspectives.

And Robin, please chime in, because that is your whole initiative in your programs.

MS. BENT: No. It is great to be on the moderator side, just asking the questions. So, no. That sounds great to me. And thank you for that answer.

I think -- I know we are coming up on the end of the -- end of our time together. But I did want to, maybe, Amanda one more question about harnessing social media networking to promote patient engagement in rare disease product development. I do not -- and obviously, it is open to all of you. But I wonder, Amanda, if you have any thoughts or experiences with that -- any best practices or any thoughts you might have?

MS. MOORE: Yeah. And I will try to make it quick, 'cause I know we have a little bit of time.

Social media is like a whole new world for us when it comes to getting information out about

getting -- you know, signing up for registries, doing research, helping educate families. It is interesting because there is such a wide variety of platforms, too. So you cannot just do Facebook. You have to go across the line in all the different ways on how you are educating.

But I -- what I do think is really important is that, the messaging is able to get out quicker. And I think helping people understand the importance in crafting messages to your audience is important. So working on when you are thinking about the different platforms, what are the audiences that are typically using that platform, and how are you crafting those messages.

So we know that with Facebook, we have a -- quite a wide audience of Angelman Syndrome individuals. But we also know Instagram may be, now, where some of our newly diagnosed people are mostly participating in. So we just have to think about those and how we are crafting the messages. And it is great on getting research opportunities out there.

MS. BENT: Great. Thank you, so much.

And I know we are pretty much out of time. But if anybody had any kind last minute thoughts on that, I would certainly be happy to hear them.

DR. TRAN: Yeah. Can I just add, just reading through the questions that came in presumably from the audience in the chat. I wanted to respond to a couple things very quickly.

One, phase one trials can involve and do involve patients. We are doing in the Angelman world right now. We have two. And we will soon have three first-in-human trials. So that is not restricted to volunteers.

Second thing is, that patients do and can get involved in design of natural history study. When we designed our study, we actually reached out to the patients and the organization and asked them what outcome we should include.

And there were a couple of questions about starting natural history study. I would be happy to field those question from those listeners by e-mail, if they can e-mail me. And FDA can provide them with my e-mail address.

MS. BENT: Wonderful. Wonderful. That is very generous of you. So I would like to take this opportunity to thank all of our panelists for coming today, and really sharing their thoughts and their experiences and their significant knowledge about this. I hope you have a wonderful day. And I will turn this back over to Lewis.

DR. FERMAGLICH: Great. Thank you, all. We understand some viewers have been having some technical issues, viewing the conference, especially the presenter slides. To address these issues, please close your browser and reopen the meeting link with Chrome, which seems to having better results. We apologize for the inconvenience.

We will now take a one-hour break for lunch. Please rejoin us promptly at 12:45 for afternoon remarks from the acting Commissioner of FDA, Dr. Janet Woodcock.

(off the record)

DR. FERMAGLICH: Welcome back to FDA Rare Disease Day 2021. I now have the great honor of introducing our next speaker, Dr. Janet Woodcock,

acting commissioner of FDA.

Dr. Woodcock began her long and distinguished FDA career in 1986 with CDER as director of the Division of Biological Investigational New Drugs. She also served as CDER's acting Deputy Director, and later as director of the Office of Therapeutics Research and Review.

In 1994 Dr. Woodcock was named director of CDER, overseeing the Center's work, that is the world’s gold standard for drug approval and safety. In that position she has held -- she has led many of the FDA's groundbreaking drug initiatives. She also served in other leadership roles at the FDA, including as Deputy Commissioner and Chief Medical Officer.

With the onset of the COVID-19 public health emergency last year, Dr. Woodcock was asked to lend her expertise to Operation Warp Speed, the initiative to develop therapeutics in response to the current pandemic.

Dr. Woodcock was named acting Commissioner of Food and Drugs on January 20, 2021.

Now, everybody knows about

Dr. Woodcock's extensive career at FDA, but before she was overseeing their regulation, she was a practicing physician prescribing medications to treat patients with rare diseases. She relayed to me a story about a patient she treated with a rare autoimmune disorder called Bechet's Disease, which causes inflammation in the blood vessels. After running out of therapeutic options, she recalled trying to get access to a controversial medication called Thalidomide through the agency but was denied. Years later, Dr. Woodcock oversaw the approval of that drug, albeit for a different rare indication, leprosy.

Her years of service to the American public started with the care of individual patients. And that patient-centered approach continues to motivate her up to this day.

So without further ado, Dr. Woodcock.

DR. WOODCOCK: Thank you. I am sorry. I am having a little trouble unmuting myself, here. But I should get back on track in a second.

UNIDENTIFIED SPEAKER: You sound great, Dr. Woodcock.

DR. WOODCOCK: Pardon me?

UNIDENTIFIED SPEAKER: You sound great, Dr. Woodcock.

DR. WOODCOCK: You can hear me. Yeah. I just have to get back to my talk. I am very sorry, folks. There we go. There.

I am very pleased to be with you, today, to mark Rare Disease Day. And thank you for that very kind introduction.

You know, it is, indeed, a time to celebrate the enormous progress that has been made in the treatment of rare diseases. And this is a result of both advances in science -- and this last couple decades it has been particularly fast -- and collaborations among a wide range of stakeholders -- many of whom are part of today's celebration. So -- because with rare diseases, as was just said, it takes a village -- it is a relay race, and we have to hand off to one another.

Even as we celebrate successes in this area, we have to remember that we still face many challenges across the diverse landscape of rare

diseases. There are about 30 million Americans affected by 7,000 known rare diseases. And the vast majority do not -- still do not have approved treatments. Finding answers for treatments can pose enormous scientific challenges, and also be costly.

For example, clinical trials to evaluate the safety and efficacy of medical products in rare diseases can be much harder to plan, and harder to conduct, than with common diseases. Both due to shortage of patients, and their lack of knowledge and uncertainty about the rare disease itself. And these challenges have been exacerbated as a result of the COVID-19 pandemic, which is an enormous urgency, because people with rare diseases are among the most vulnerable to COVID-19.

At the FDA, our mission is to protect and promote the health of all Americans. An essential responsibility, that mission, which we take very seriously, is to find new and better ways of approaching the challenge of rare disease, to lead us to new treatments, and, we hope, cures.

And we oversee a variety of programs

and activities to support this work. One way that people pay a lot of attention to, of course, is our oversight of drug development and review of new drugs. Since the passage of the Orphan Drug Act in 1983, we have approved products for over 950 orphan indications. This number continues to grow with rare disease therapies being developed at a faster pace than ever before.

Last year the agency approved 32 novel drugs and biologics with orphan drug designation. And these groundbreaking approvals included one we just heard about -- the drug to treat certain people with Progeria and Progeroid Laminopathies. Those are rare conditions caused by genetic mutations that lead to premature aging -- and this was a huge landmark approval and development program -- a drug to treat patients with hereditary angioedema, a rare disorder characterized by recurrent episodes of severe swelling most commonly in the limbs, face, intestinal tract, and can be fatal in the airways, and a CAR-T cell therapy to treat adult patients with relapsed or refractory Mantle Cell Lymphoma, which is a rare

cancer and a type of Non-Hodgkin's lymphoma.

So those are approvals. But still, another important part of FDA's work involves the Orphan Drug Rare Pediatric Disease and Humanitarian Use Device Designation Programs. So we have three separate designation programs. Last year, we received a record breaking 284 rare pediatric disease designation requests. That is more than a 330 percent increase from 2019.

The agency also focuses on the development of medical devices. Particularly, efforts to reduce hurdles for the pediatric device market, which is a small market to begin with. And then, even smaller in rare diseases. And that is the specific goal, the strategic framework developed by our Center for Devices and Radiologic Health, or CDRH, called SHIP-MD, which is designed to support medical technology innovation to meet the unique needs of children and small populations.

But a primary focus of all the work we do, but especially in the rare disease space, is to engage patients. Patients are the most important

assets to finding solutions. Their voices, experience and understanding must be integrated into all phases of medical product development. And, really, in rare disease, chronic disease, patients are, really, the biggest experts in their own disease.

Now, one way we do this is through our rare disease patient listening sessions, that is facility by the agency's Patient Affairs staff. We also have an interactive webinar series, called, Orphan Grantees Unite. It connects current orphan product grantees so they can share research goals and stories, and further the development of orphan products along the route to marketing approval. Recent sessions have focused on strategies to support rare disease product development during the COVID-19 pandemic.

Our focus on patient engagement has underscored the importance of our continuing support for research in this area. We have really heard from patients that -- the work that needs to be done. And one example of work we have done is testing and molecular diagnosis -- this has allowed scientists to

pinpoint in some cases, the exact cause of some genetic diseases, which may lead to development of a product tailored to that patient's specific genetic variant.

For example, CBER has started what they call the Bespoke, or Individualized Gene Therapy Consortium. This is intended to advance in development of therapies for rare disease that affect one or a few individuals. And then, these would typically have a genetic basis. The goal of this project is in collaboration with the Foundation for the National Institutes of Health, FNIH, and the National Center for Advancing Translational Sciences, or NCATS, which is at NIH, is to build a standardized and efficient approach for development and delivery of gene therapies in these settings.

So we need a platform for delivering gene therapies that rare disease developers can pick up and use, rather than them starting from scratch and developing a new gene therapy, which is an extremely complex and expensive endeavor.

The FDA also continues to provide a

variety of other funding sources for important research efforts that support various aspects of rare disease product development. For example, our Orphan Products Grants Program helps advance the development of many types of orphan products by supporting both clinical and natural history studies. We recently announced a new request for applications for support of natural history studies in rare diseases. These studies can enable the standardization of data collection, inform interventional trial design, and selection of endpoints, and provide other critical information on the course of disease that can be absolutely essential to actually design interventional trials.

Also, our Center for Biologics Evaluation and Research, CBER, recently awarded a contract to NORD to design and conduct a pilot rare disease natural history study. It could serve as a source of control data for clinical trials of therapies for rare disease in situations when it is not feasible or ethical to enroll and randomize patients to a control arm, and a clinical trial. And

we do encounter these types of situations where we can, perhaps, use a natural history study to construct what is called an external control group.

And the Center for Drugs continues important work with the Critical Path Institute to build the Rare Disease Cures Accelerator Data Analytics Platform, which will provide an integrated database and analytics hub designed to promote the secure sharing of existing patient-level data, because one of the problems we have encountered is that in rare diseases patients are followed at different centers around the world, and unless we can pull this information and get people to collaborate together and share it, we are not going to make the progress we need to make.

So importantly, FDA is really eager to continue our work and collaboration with the rare disease community, to embrace the challenges, and address the significant unmet needs of patients and families living with rare diseases. We are on your side, and we are going to make progress.

And thank you, again, for your

participation today. I think the community push for advocacy for treatment is making all the difference. Thanks, very much.

DR. FERMAGLICH: Thank you, so much, Dr. Woodcock. Our next panel will focus on strategies to facilitate rare disease product development during the COVID-19 pandemic, moderated by Khair ElZarrad, deputy director of the Office of Medial Policy in CDER.

Dr. ElZarrad told me that members of his family were afflicted by a rare disease called idiopathic pulmonary fibrosis, or IPF. He noted that the causes of IPF are not fully understood, and that it has an unpredictable progression pattern. His personal experience helped him see not only the impact of the disease on patients, but the impact on the whole family. He noted, that like other severe rare conditions, the unknowns are many, and patients of families are in great need for more data, research and more tools to handle such diseases. This made me better understand that there is nothing like reliable scientific evidence to guide healthcare providers,

patients, and families, collectively. I lead streams of work around clinical trial design and conduct, and I am constantly thinking of the need for good trials and reliable evidence. This is especially true for rare diseases, where clinical trials and the generation of evidence in general could be challenging.

Dr. ElZarrad?

DR. ELZARRAD: Thank you, very much, for the introduction. I appreciate that. I am, first of all, grateful to be part of this meeting. I have been watching the meetings, and the videos, even during the lunchbreak. And what a reminder, really, to all of us, why we do what we do. You know, we are different tools. But also, a reminder of the importance of good research coming from us all. It is very difficult to follow Dr. Woodcock, of course. But we have an excellent panel for you that will be discussing a critical topic, focused on strategies to facilitate rare disease product involvement during the COVID-19 pandemic.

On the panel today, we have Dr. Rachel

Sher, the vice president of Policy and Regulatory Affairs from the National Organization for Rare Disorders -- NORD. Followed by, Nick Johnson, the associate professor and vice chair of research and the Neuromuscular Division chief at the Department of Neurology, Virginia Commonwealth University. Dr. Christine Mueller, a medical officer at the Office of Orphan Products Development at the FDA. And Chris Austin, the director of the National Center for Advancing Translational Sciences.

We are going to start today by a presentation by Rachel Sher. Followed by a presentation from Nick Johnson. And from there, we are going to gather the panel after that to discuss a few questions. And we welcome your question in the chat, as well.

With that said, Rachel, do you want to take it from there?

MS. SHER: Yes. Thank you. And thank you, so much, for having us here today. NORD is extremely excited about the FDA's Rare Disease Day event, and all the fantastic Rare Disease Day events

that we have had throughout this past week.

If we could go to the first slide. Our world has been forever changed by the shared experience of the COVID-19 pandemic. It is has touched each and every one of us in one way or another. But for the rare disease community there have been unique impacts. And we know this from the thousands of calls for help that have been coming into NORD's offices, and from our community surveys that have helped to uncover the impact of COVID-19 on those living with rare diseases and their loved ones.

Early on, NORD took a multi-pronged approach to addressing the COVID-19 related challenges faced by the rare disease community. We really wanted to hear directly from the community, and to understand the nature and extent of the issues they were experiencing during this time. Part of that community outreach was through our Rare Action Network, which is NORD's grassroots advocacy arm. Our volunteer state ambassadors hosted 128 meetings and events during 2020, which really helped to give us a better understanding of all the challenges that people were

facing in the rare disease community.

And as you see on this slide, the word cloud is populated with things that we heard throughout all of those meetings. And it gives you a really good glimpse of the diversity and type of challenges that the rare disease community was facing. Next slide, please.

Another part of our outreach was conducting two different COVID-19 community surveys. The first was released in April of last year, and the second in June. And a total of 1600 respondents participated in the surveys. Those surveys showed that the community was overwhelmingly concerned and impacted by COVID-19. Well over 90 percent of the participants in both surveys indicated that they were worried and had been impacted to some degree. And the sources of concern and worry varied as 69 percent of the respondents indicated concern about medication shortages and PPE shortages, 32 percent of those surveys had challenges accessing critical medical care and treatment, and 79 percent of the respondents recorded having had a medical appointment cancelled

during the pandemic. Next slide, please.

As the pandemic continues into 2021, the concerns that mark 2020 endure, and new ones have developed. More recently we have heard a major focus on issues including mental health, which have been stemming from the social isolation that has marked our lives for over a year now, concerns about medication and protective equipment persist, as do those associated with long-term financial instability that has occurred for so many.

And although there is so much enthusiasm and excitement around the amazing speed in which we saw not one, but now, three COVID-19 vaccines become available, along with several promising therapeutics, there are so many questions among the rare disease community that have come up. When can I get the vaccine? Is it going to be safe for me, given my particular rare disease? I am a caregiver for someone with a rare disease, can I receive the vaccine too?

In January NORD was honored to host a webinar featuring the FDA and the CDC to help answer

these questions. And that webinar is still available on demand on our website. I encourage everyone to watch it -- the -- everyone we heard from was just so appreciative that FDA and CDC took the time to do that meeting with us. So, many thanks to FDA and CDC for that.

Another persistent concern that was all the focus on the research into COVID-19 vaccines and treatment, which obviously everyone wants, that there will be and has been a lag in research in the rare disease space. Next slide, please.

NORD heard this concern from the community and worked to find out exactly what the impact on rare disease clinical trial work has been during the pandemic. Obviously, even under normal non-pandemic conditions, rare disease trials can be more complex than trials for common diseases and their unique challenges. Patients may be hard to find. Travel may be difficult, depending on the burden of disease. Knowledge gaps persist about disease progression. And others.

NORD completed an informal survey last

year of our corporate counsel members industry partners to understand what it was like, then, during the pandemic, to be conducting these clinical trials in the rare disease space. And of the companies that responded, 58 percent indicated that they had to postpone enrollment for at least one rare disease clinical trial. Only eight percent were able to conduct trials as usual. And 33 percent indicated they had to adapt their trials to remain on course. Forty-five percent of them had already -- or anticipated having to cut some of their R and D budgets as a result of the pandemic.

NORD also hosted a webinar last year, along with IQVIA -- a lot of work compiling -- data around rare disease development during this time period. And you see some of that data presented here. This chart shows that rare disease studies that were in startup and enrolling phases had to make the most adjustments to continue. And they were more likely to have suspended some of their study activities. Clinical site closures, local restrictions, PPE shortages, and safety concerns were all major

challenges at the time this IQVIA data was compiled.

Conversely, studies that were already going on, or in development, were able to continue with more than half of those already going not needing to make significant changes in order to continue.

Luckily, most studies did not have to completely suspend their activities, and they were able to continue with some modifications. And, in fact, almost no trials were put entirely on hold, according to this IQVIA data. Overall, this is, obviously, excellent news for rare disease patients. And we think it really speaks well to how well all stakeholders have worked together during the pandemic. Next slide, please.

At least part of what has allowed so much of this critical trial work to continue has been the increased reliance on telehealth in both routine care settings, and in clinical trial work. Amidst the COVID-19 related destructions to traditional modes of care, telemedicine has really emerged as a way to safely access medical care without exposure to COVID-19. And again, the surveys I mentioned with regard to

telehealth showed that 88 percent of those who responded to our survey and had been offered a telehealth appointment accepted it. Ninety-two percent of those individuals reported that it was a positive experience. And 70 percent said they would want to have the option for a telehealth appointment in the future. Sixty-one percent of those said that if they were going to opt out, they would do so just because they prefer that face-to-face interaction with their providers when it is safe.

Of course the move to telehealth has been a long-sought goal for so many in the rare disease community. This is just not a new concept for them. With geographic dispersion in terms of patients and specialists, many rare disease patients and their families have always had to travel several hours or out of state to access the medical care that they need. Virtual appointments, particularly for rare disease families, have saved time and money, making healthcare more accessible and easier for them to manage their often very complicated conditions.

In the wake of the pandemic NORD has

placed a renewed emphasis on permanently integrated telehealth into our broader healthcare system. Early last year, NORD issued a set of telehealth principles to help guide us in this war. In our virtual COVID-19 discussion groups we held throughout all 50 states over the course of the last year, we gained some key takeaways. One of the most important -- is that patients and provider choice is critical, and we have got to preserve where possible. Next slide, please.

These changes and technological advances, as I mentioned, have also been successfully incorporated into the drug development and clinical trial rounds. The pandemic has revealed new ways to achieve the goal of ensuring clinical trials continue, or simultaneously allowing patients to participate in a safe, and when necessary, remote way. FDA has really risen to the occasion and responded to work with patients and industry and issued timely and really effective guidance that has allowed this work to continue.

Getting to the end of my time, here. I will just wrap up by saying -- you know, NORD is very

excited about these changes that we hope will increase the accessibility of these clinical trials for rare disease patients throughout the ecosystem. And thank you, again, for having us here on this panel.

DR. ELZARRAD: Thank you, so much, Rachel. Very interesting to hear about NORD's activity and getting back to when the patients and clinical trials, as well, and the role of technology. That is very interesting.

Following Rachel, I am going to ask Nick Johnson to please start the presentation. Thank you, Nick.

DR. JOHNSON: Great. Thanks. And I think, really, what I will do is expand on a case study that speaks to a lot of the issues that Rachel brought up, talking about the impact of COVID-19 on a large natural history study, as well as some of the things that we have tried to do on the ground to mitigate that risk. So you can go to the next slide, which is my disclosures. Okay. And then, next slide.

So our study is in adult myotonic dystrophy, which is an autosomal dominant condition.

Essentially affects every organ system in the body. The core symptoms include distal weakness, myotonia, early onset cataracts. But, these are patients that have respiratory failure, cardiac arrhythmias, significant daytime sleepiness and fatigue, irritable bowel symptoms. And as I said, it is a tremendously difficult condition with a number of different symptoms, and a huge unmet need for these patients, without otherwise disease-modifying therapy. Next slide.

And there have been a couple of other smaller natural history studies in myotonic dystrophy. This is data showing, in general, that the rate of change in this slowly progressive condition on the ability to walk, for example, is about five to six percent across the population. But that when we plotted out an individual vector of each patient -- which you can see in the figure on the top right corner -- you can see that there is a collection of patients that really have a rate of progression that is faster than others. And this work, really -- just to give credit -- has been led through the Myotonic

Dystrophy Clinical Research Network, and Charles Thornton at the University of Rochester.

But -- you know, it came to mind that we needed to do a better job of understanding key inclusion/exclusion criteria to better design an effective clinical trial to understand potential disease-modifying therapies for these patients. Next slide.

And so, that led to our current study, which is NDM1, which is to characterize myotonic dystrophy type one severity and disease progression in a large cohort of approximately 700 patients with myotonic dystrophy type one, complete the development of a key biomarker, which is muscle or any alternative splicing events, to understand disease severity. And then, of course, at the end of the day -- as Janet Woodcock said -- our goal is to provide robust natural history data to support drug approval using the FDA's guidance on natural history studies. Next slide.

And we have been tracking fairly well, and we are going reasonably well in terms of our enrollment. And then, like everyone else in the world,

we had -- so before COVID-19 we had nine sites activated, and 150 participants had been enrolled as of February 2020. And here we are about a year later -- but I think everybody remembers March 2020 -- all of our sites halted all enrollment in March 2020. And that was -- it was that way until, at least, July 2020. In July we were able to begin enrollment very slowly, only at five sites. And since that time, really across those nine sites, people have had their sites open, and they have had to close. And so enrollment has been quite halting. And then, several key study endpoints, including spirometry, have been unable to be completed because of infection control issues at the individual sites with the COVID-19.

So we estimated that we financially lost -- or there is an additional cost of $75,000 to the study. Probably more important to us is that we lost five trained clinical research coordinators, two clinical evaluators, and one PI due to institutional funding and prioritization during the COVID-19. Which has been each time you go through another process of retraining, and of course, finding new people. Next

slide.

Here are a few of the things that we have tried to implement to deal with the COVID-19 pandemic in this important natural history study. So we have expanded our visit windows from plus or minus two weeks, to plus or minus two months. We have been able to add travel reimbursement. As Rachel mentioned, this is a significant issue to begin with and with -- twice as significant or more during the COVID-19. Next slide.

We have -- like I think so many others -- have embraced, to the extent we are able to, remote assessments. Particularly, we are able to have participants do their spirometry, which is the key outcome measure that was unable to be completed previously -- or still, really, in person -- by having -- you know, mailing people this remote spirometer with an iPad. We watch them do it at the same time. We do still require in person functional assessments. But we have engaged in several pilots to start to understand remote functional assessments. In neuromuscular disease, the ability to watch somebody

walk and push on their muscles is such an important part. So we are taking the time and care to do this with diligence and ensure that these outcome measures are as reliable as they were previously. And then, of course, we are doing remote evaluator and training to ensure a continued quality. Which we would have normally done every year in person, we are now doing remotely. Next slide.

One of the things, again, from a strategic standpoint, is that we have had to try and build -- or add a number of sites that we are able to enroll. So sites, typically, are able to enroll two to three participants per month in normal times. Our delay due to the COVID-19 means that the original sites will not complete enrollment during the grant period. And so -- you know, we have chose to add two additional U.S. sites, and five E.U. sites. You can see the graph of participant enrollment. And with that addition of sites, we are going to be able to track enrollment faster by -- again, by adding sites. We were able to do this, of course -- adding sites -- because a lot of the activity is remote anyways. So we

can do that during shutdown and from home. And as sites come online -- you know, we will be able to complete study enrollment more quickly. Next slide.

And then, we could not do this -- there is -- you know, beyond the exact loss of -- or additional cost to the original sites -- the ability to add new sites, to retrain evaluators. Each site costs about $125,000. And there are, of course, additional costs for remote assessments. And so we have worked to create a pretty competitive partnership, and to essentially speed therapeutic developments. And ultimately, this will provide earlier access to data, samples, and know-how to -- like I said, to speed the development of treatment for patients.

And so, of course, much thanks and recognition goes to the FDA for -- as the original sponsor of this study, along with the Myotonic Dystrophy Foundation. But we have had three pharmaceutical companies join in sponsoring the study to cover and defray the additional costs and work together to bring multiple different therapeutic

choices to patients. And last slide.

And so with all that, these are the efforts that our study NDM1 has taken to try to mitigate the challenges that we have seen in this natural history study during COVID-19. And of course, even though I am the one here speaking with you, lots of thanks goes to my co-principal investigator, Dr. Charles Thornton, as well as all the different site investigators, which you can see on the map from the United States and Europe, our study team, and of course our sponsored program VCU, who has helped us with pivoting all of these subawards and moving them forward.

Thank you.

DR. ELZARRAD: Thank you, so much, Nick. That was very interesting, actual examples actually of the impact of the pandemic on research. So appreciate that.

I am going to ask Christine and Chris if they can open their camera and join the panel, as well, for us. Hello, everybody. Thank you.

So we have heard quite a bit, now,

about how the pandemic is really impacting our life. But you especially have -- how has your work been impacted by the COVID-19 pandemic? And what changes has it necessitated? I am going to ask Chris to start us with that. You know, you worked at NCATS and NIH and, kind of, that leadership spectrum. How did you see the work being impacted? And maybe you can give us some examples of that.

DR. AUSTIN: Well, thank you. And it is great to be here with you. And thanks to Rachel and Nick for those presentations, 'cause they really encapsulate two very important features that we have noticed are general principals.

And our work with patient groups and researchers, they have also found really considerable disruptions in the work that they have been able to do. As you heard from Nick, most clinical research sites and most laboratories -- we have not talked about that, yet. But most laboratories shut down and did not allow people in their buildings until some time in the summer. And I am fond of saying that though COVID was important -- it is important -- and I

will get to that how that has also affected us -- at NCATS there are 6,999 other diseases that are not taking a vacation because of COVID. And so I have pushed my organization that -- as I think you all know -- is the epicenter of rare diseases research at the NIH -- to keep that work going as much as possible, support our extra -- researchers in every way that we can.

But we also did our own survey through the Rare Disease Clinical Research Network to -- with slightly different questions from the ones that Rachel talked about -- but very, very similar answers. And we, I think, like NORD, are writing that up. And that will be published shortly. And one of the reasons we wanted to do that was that we wanted to understand both the good and the bad from this pandemic. We wanted to understand the direct impact that COVID had, had on rare disease patients. And of course, our primary -- our first concern was that rare disease patients would be disproportionately affected -- infected and affected medically by COVID. Our data, at least, has -- does not suggest that, that is the case.

I think, because we see in those patients that we see in other high-risk patients -- such as those with heart disease and diabetes and others -- is that they have from the beginning gone to increased care to do all the preventative mitigators that we all know so well, now -- social distancing, mask wearing, hand washing, and keeping themselves and their children out of communication or contact with others. And so I think that is probably responsible for a lot of us.

But certainly, the research ground to a halt. And the natural history studies, particularly, as well as interventional studies were interrupted. We have tried, at the NIH, to the degree that we can without additional funding -- to extend grant periods, training periods for trainees, to make up for the six months to a year that all of them had lost. But as you are hearing from Nick, this -- it is not just a matter of time. It is a matter of people, and expertise, and losing people semi-permanently, because they did not have a way to support themselves. So we realize we are going to have some rebuilding to do.

On the other hand, I want to completely

agree with what Rachel said. You know, we have, on behalf of ourselves in innovation and transitional science, and on the behalf of rare disease patients who we work with every single day -- have been arguing that more remote trials and more remote monitoring technologies of the sort that Nick talked about, should be possible.

Human beings, as we know, are loathe to change, however. And as a good friend of mine likes to say, "People do not change when they see the light. They change when they feel the heat." And in this case, the heat was COVID. And I think our challenge, now, as a community is to work with the legal and regulatory communities and the pair communities to try to maintain as many of those authorities as possible.

I was really heartened yesterday to see the announcement from CMS that they are working with the Congress to try to change some of the legislation that prevents this from happening. I think a lot of people do not realize that there are regulations and laws in place which prevent a lot of these things, which, now, are technologically possible. They were

put in place for very good reasons. But I think the time has come to -- where we have shown ourselves we can do this, and we need to continue us.

I guess, the last thing I would say is that -- you know, at NCATS, we have, like most of the National Institutes of Health, have pivoted most of what we do -- not our rare disease forum -- but of course, over the last year, I would say 80 percent of my time and my colleagues' time, here, at NCATS, has been pivoted to COVID-19. And I think that has been the right thing to do. And we have played a major in the response we are now seeing benefits from. But I like to say that this is a time when I think all of us as a community -- the rare disease community, need to push the point that is going to make people uncomfortable. But I think we need to do that. We need to get people out of their comfort zone, have them feel the heat, if you will. Which is that, we as a biological -- biomedical community -- patient community -- society, moved Heaven and Earth to develop diagnostics and therapeutics for COVID-19 in record time. And what that shows is that the

translational system can work -- really can work much faster than it normally does. We have known this is possible at NCATS for a very long time. Of course, it is our mission to do that. And some of it is held back by science. But a lot of it is held back by people issues and funding issues.

And so, I think the time for the community to say in an unabashed way, "Don't we count as much as patients with COVID-19? And if our lives are as valuable as those with COVID-19, then we deserve the same kind of movement of Heaven and Earth that happened with COVID-19" And --

DR. ELZARRAD: Hopefully, all will push us towards being more proactive than reactive.

DR. AUSTIN: Yeah. So that is what we are up to, here.

DR. ELZARRAD: Thank you. Thank you, so much. Christine, continuing with the federal theme, from NIH to FDA, how do you say your office has been impacted in the processes that you have to employ, in general?

DR. MUELLER: Good afternoon, everyone.

I am thankful to be here today. And as Khair mentioned earlier, I am a medical officer in the FDA Office of Orphan Products Development, and a clinical geneticist by training.

We provide grants for clinical trials and natural histories studies to defray the costs of developing drugs, devices, medical biologics and medical foods for rare diseases. We started hearing -- like everyone has mentioned -- concerns about study progress when the COVID-19 pandemic began last March. Early on, we started tracking the issues our studies were having due to the pandemic and how grantees were addressing them, from study suspensions, study completion delays -- as Chris mentioned -- or terminations, changes needed to informed consent, protocol deviations, and study endpoints not being assessed, protocol amendments being needed, monitoring changes being needed, and study sites dropping or needed to be added -- like Nick mentioned in his natural history study -- changes that were needed for product delivery, travel issues patients were having and their caregivers were having, loss of patients due

to disease progression, and budget implications to our grants. Of 71 of our ongoing grants, 63 clinical trials and eight natural history studies, 79 percent had some effect due to the pandemic. Many studies stopped in March enrolling new patients and/or following patients already on study as per protocol at one or more sites, really based often on the effects of the pandemic, geographically, the kind of study being done, and institutional needs -- as Nick mentioned with his study -- related to the pandemic in terms of staffing, and supplies, laboratory necessity or study imaging. And as we all know, enrolling and completing rare disease studies is already challenging on many fronts, including due to small patient populations. Really in working with our grantees during the pandemic, we have been looking at preserving time, invested resources, the effort of participants that have already been enrolled or completed, and completing studies with flexibility in mind, where appropriate. Really, the safety of trial participants and study staff is the most important factor in doing so, by us, and institutionally. And really

limiting potential exposure to COVID-19 and avoiding interference with clinical care for COVID-19. And you know, continuing study activities, perhaps, virtually or in person where feasible when benefits greater than risk for patients, but while still maintaining -- you know, compliance with the clinical practice and minimizing risk to trial integrity.

Early on we also provided our grantees with the FDA guidance on the conduct of clinical trials of medical products during the COVID-19 pandemic, which was issued early in March last year, and has been updated several times, including a question and answer section.

We have encouraged our grantees to consider their circumstance with, really, a focus on the potential impact on study participant safety, like I said before, while minimizing impacts to the integrity of the study, as outlined in the guidance, and in collaboration with us as project officers and their respective FDA medical product centers.

To better help them navigate challenges, we have also had two Grantee Unite

meetings to facilitate discussions between them and the challenges they faced with their studies, and ways they worked to adjust those challenges -- you know, within their institutions and across sites, if they have multiple sites in their studies. The topics that grantees have discussed have been -- you know, included decisions related to where enrollment continued at some sites and not others, what study processes were being done at a distance for current or new enrollees. And how protocol deviations were being changed or managed. We have formed a working group from these discussions with the grantees through the Unite meetings. And we also continue to monitor the impact of the pandemic on our grants as the landscape, as everyone knows, is changing over time, as well.

DR. ELZARRAD: Thank you, for that. Thank you, Christine, highlighted how -- you know, our work -- you have to look at our work and how the function around it happen -- internally as well. And see how we can operate within our organizations. Thank you for that.

Rachel, do you want to add something to

the perspective?

MS. SHER: Yeah. I mean, we started out our year -- and to be clear -- I -- my role at NORD is overseeing all of the policy work that we do. We have different departments at NORD. And all of NORD has been impacted in one way or the other and had to shift. And I will touch on a couple of those areas. But from the policy perspective -- you know, as I mentioned in my presentation -- we completely shifted what we worked on. We started out the year -- you know, anticipating a lot of activity around drug pricing, and the Orphan Drug Act, and things like that, and it just all changed. So we spent a ton of our time in the policy department working on a lot of these changes that were necessary, particularly with respect to telehealth on the care delivery side at the state and federal level. I mean, there has just been a ton of activity. And to echo what Chris said -- I mean, it is incredibly complicated, and there is a lot that needs to go into facilitating the effective use of these remote technologies in care, and, obviously, in the clinical trial ground. So we spent a lot of

time on that.

And then -- you know, just a lot of time helping the rare disease community understand what therapeutics are out there, what vaccines are out there, and the impact on them.

The other shift that we have had to make in the policy realm, is so much of our work had previously been done in person, whether that means going to Capitol Hill to meet with offices there, or through our Rare Action Network, we had in-person events with state legislators all the time. So all of that shifted in a way that -- obviously, you lose a lot through in-person interaction, but the events that we have been able to hold just this past two weeks around Rare Disease Day -- we held dozens of virtual events with state law makers, state policy makers, and our ambassadors in each state, that have gone quite well. So I mean, I think we are making the best of it.

NORD was able to stand up a COVID Assistance Fund, that we have been able to help many, many people in the patient community with that. And a lot of the work that NORD has done, I think, has come

to a forefront, here, during the pandemic, with respect to research. Our IM Rare Registry that Dr. Woodcock mentioned -- you know, I think has been a source of white light, that this is the type of ongoing research that can and has continued throughout the pandemic. You know, patients own these registries and continue to contribute data to them throughout the pandemic.

So lots of changes. And I think that everyone has a lot to learn going forward, that -- you know, in all of these realms that we are working on. But hopefully, in the end, for the better.

DR. ELZARRAD: Thank you, for that. Nick, I am going to ask you to add your perspective from an academic situation. And I want to highlight, too, that we have -- if we would have any questions, please put it in the chat, and we will try our best to incorporate any questions that I see.

Nick?

DR. JOHNSON: Yeah. I think we talked a lot about the challenges. Two bits of silver lining. Number one, my colleagues -- the other investigators

at the site would have had to fly to meet each other -- you know, once every six months or a year. We now see each other routinely, once a month. I think those -- that dialog and, kind of, the richness of the scientific discussion has definitely been a silver lining. And then, just to really emphasis that -- you know, we were definitely caught flat-footed, in terms of our ability to bring outcome measures into a patient's home. But having watched us pilot some of these outcome measures in the home, you get a better sense of true real-world evidence. So I am very optimistic that over time, and with -- you know, increasing reliability and validity data, we will be able to really get a better sense of what actually is important. I mean, we are very good at watching people run down a hallway, but not their hallway. And so -- which is really what is important at the end of the day. So I think there is a lot of benefit coming out of this.

DR. AUSTIN: Yeah. And if I may, I want to add something to Nick -- what Nick just said. As a result of demonstrations on the part of investigators,

like Nick, we have been able to generate enough enthusiasm, here, to come out with what we think is going to be a really -- I will use a non-scientific term -- cool request for proposals, which incorporates not only remote sensing technologies, but what are called haptics, which are what you use in your -- if you have an iWatch -- or Apple watch -- or you have a fit -- something that can track your movements, and even a virtual reality kinds of applications. And that is focused on rare diseases. So it has opened up, for us, a whole area of research that we are really excited about.

I mean, as Nick said, we got a long way to go from a six-minute walk text and watching kids run up and down the hall, to having sophisticated in-person haptics. But that is going to -- that could break open the whole field, particularly for a lot of the neuro-behavioral disorders. I mean, when we do a lot of work with the autism spectrum community -- I think about the Angelman community among them -- where these children have very characteristic behaviors. And if you know what you are looking for, you can say,

"Yes. I recognize that." But trying to write that down, is really difficult, even though a parent can tell you in a second. And so trying to be able to capture those things -- and then, improvement that FDA would take as an outcome measure is really an exciting frontier that we are beginning to start on now. And it is -- I think it would have started. Like a lot of things, it would have happened without COVID. But COVID has really helped.

The other thing I think is really going to be interesting to watch -- and I do not know what -- how this going to turn out -- but like Rachel said -- and you heard from Nick, and from Christine -- the connectedness -- first of all, the social separation has driven us insane. And from -- as the standpoint of human beings. I mean, I think we are built to enjoy interpersonal contact with three dimensional people in the room. On the other hand, the rare disease community, in my view, has in the past suffered from fractiousness, and not being able to have a coherent unified message that, we are a rare disease community. We are all zebras, hence the tie.

And we have more in common than we do separate. And a house divided against itself will fall. A house united can do amazing things, especially when there are 30 million people in that house. And we have seen -- like Rachel has said -- unprecedented numbers of people and repeatedly -- frequency of tying together of communities that would have had to fly to see each other before. And especially rare disease patients. You know, it is hard to get around. Our rare disease celebration -- Rare Disease Day at NIH, that our FDA colleagues participated in -- thank you -- we had 3,000 people attend that. Our previous number total, in-person and online was 1,500. So it was double the number of people we have had in one year.

And so, that is the kind of thing going forward the rare disease community can really benefit from.

DR. ELZARRAD: Well, thank you for that. I think this will be a really good pivot for us to start thinking -- taking that perspective in general, and what areas we can really -- move forward, now in more of an action, kind of, based. What do you

guys see that the main take-away, practically, from this pandemic in the relation to the conduct of clinical trials? Christine, you mentioned, for example, the importance of the integrity of the trial. That clinical trial, for example, will maintain a level of integrity that will provide us with data that we can rely on, regardless of the situation. And I am just wondering what do you guys see as an important aspect we learned from this pandemic? And if so, what we can take forward?

Maybe, starting with you, Christine. You mentioned the guidance the FDA had. And maybe extend on that a little.

DR. MUELLER: Yeah. And I think I will, sort of, tag onto Nick, in saying -- you know, if there is going to be a silver lining to the pandemic, it is really going to be to take what we have learned -- you know, the things that benefit patients, make participation in a clinical study more convenient and efficient in the end, and see how those changes can really be integrated in the studies, even when it is not by necessity, as it has been with the pandemic.

You know, we have said before, enrolling and completing rare disease studies is challenging, really due to the geographic dispersion of patients, the small number of patients, and as well as really disease and caregiver related burdens often associated for the -- with the need to travel. And I think we are hopefully that virtual and remote enrollment and visits, as well as things like the collaborations between multiple study sites, all these systems for data sharing between sites, and local assessments really were appropriate, will help increase -- you know, enrollment, improve study assessments, patients completing studies, and really allow for rare disease clinical trials, overall, to be more efficient in the future.

You know, I guess, one thing to keep in mind is that as a country we often do not recognize that folks do have technological disparities, as well. So I think as a community, that is something to, kind of, keep in mind and address. And like you said, Khair, I think the biggest -- you know, concern for us, is in doing all of those, that we maintain trial

integrity, and that -- you know, assessments are validated, and there is quality between assessments that are potentially being done locally versus at one site or multiple sites, as well.

DR. ELZARRAD: Thank you. Thank you. All that is some really important issues. And I, kind of, think of, sometimes, cell phones, as -- you know, unifying factors, as everybody has a cell phone. But I was correctly, very simply, that even the signal is not available to everybody in an equal way. So thank you for that.

DR. MUELLER: Yeah.

DR. ELZARRAD: Nick, you kind of touched a little bit of that in your presentation. But can you expand for us, a little bit on this, too?

DR. JOHNSON: Yeah. I mean, I think -- you know, moving forward and being able to accelerate progress, I think the kind of pre-competitive collaboration we were able to, kind of, use the opportunity and the need, really, to drive progress forward, I think -- to continue to accelerate.

You know, touching on what -- something

that Christine says -- one of the real challenges is to maintain study integrity. We made decisions out of necessity this -- during the pandemic, and I'm hopeful that they were correct decisions -- and we are going to end up with data that suggests that, that might be true or not true. But I am a little bit cautious in making sure we do not put the cart before the horse, in terms of some of the remote assessments, and making sure that we -- you know, continue to collect that in a reliable fashion moving forward.

So -- and then, also -- you know, again, one of the great things that we have done -- and Christine hit on it, as well -- is that the ability to use our central radars -- to hop on camera with a local site and be able to really watch reliability exactly at that moment, which is, I think, going to provide a better quality across the board. So lots of ability with technology.

But I suspect that we are not as fast as we think we are, in terms of getting if off the ground, unfortunately.

DR. AUSTIN: Yeah. And let me just add

one thing to that. I think, not only are -- what Nick said -- and this is preaching to a choir, 'cause this is an FDA meeting -- but there is this belief out there that a Fitbit readout is an FDA approvable endpoint. And it has got to be a validated readout, just like anything else. And I think we need -- you know, all of us tend to -- we over-rely on our technology, I suppose. So we tend to actually trust what it is telling us. And it -- but FDA should not take that as gospel, any more than it takes anything else. And so -- well, we need to make that point to researchers, 'cause I think I often find that academic researchers, at least, do not understand the difference between academic acceptability and regulatory acceptability. They are really quite different things.

The other thing I want to mention, which I think is really important on the technology accessibility issues, is something, actually, that Dr. Woodcock has talked about and written about in the context of COVID. And she and I have talked about this a lot, given that we have been in the trenches

together on COVID -- which is -- what we have learned through COVID is our -- the academic medical centers that we know and love and trained in -- including the Virginia Commonwealth University prominently among them -- is they are wonderful meccas of innovation, and medical care. But for clinical trials, they are -- let's just face it -- not ideal for patients to have to do these pilgrimages to them, at least, with the reportativity -- sorry -- the regularity we would like. And they are actually not that great at recruiting for clinical trials. That is what we have found, for a variety of reasons. And so what we have realized is that those academic centers -- and VCU is one among them -- that they virtually all do -- they all have satellite centers in the community. And that is where the patients want to go. And that is where they are seen. But we have not tended to do research there -- at least, research of the sort that we are talking about.

And so -- and that will have multiple benefits. You know, one, it will disseminate the joys of research -- and they really are the joys of

research -- to more people in the community. It will be different kinds of research, of course -- but to the community. Secondly, it will spread the resources of NIH to more communities, which is a good thing. Thirdly, it will allow the kinds of technologies that we are talking about, to not have to go to everybody's home. You know, if you can go to your community health center and use those resources and connect them with the academic health center, like where Nick is, who is actually running the trial, that could be a really potent model.

So I think what you are going to see after COVID is a lot of rethinking about what our nationwide clinical trial infrastructure looks like. And I think that is a very good thing.

DR. ELZARRAD: Yeah. Thank you for that. Rachel, do you want to add to that?

MS. SHER: Yeah. Just to, briefly, echo a lot of the things my fellow panelists have been saying. I mean, I think it is clear there is a lot of enthusiasm, particularly in the rare disease space, for this move to broader use of these remote

technologies in the context of clinical trials, without a doubt. But I think everyone has hit on a couple of things that I think we all have to think clearly about, and patients need to understand and be concerned about, which is the validation of all of these tools. And FDA, again, has done a fantastic job getting out these guidances, and working with patients and industry to get their best advice out there during these situations. But I think it is going to take a lot of time and resources that FDA needs to have to be able to continue this work. And really, think about what aspects that have worked during the pandemic should be carried forward, and which one should not.

So you know, from a patient perspective, we need to care as much about ensuring all of these tools are validated and acceptable and are going to lead to the same level of safe and effective treatments, ultimately, for the rare disease community. We cannot let ourselves get, sort of, overexcited about the use of these technologies during the pandemic, to the detriment of -- you know, ultimately these products.

The other thing I just want to really hit on that we heard a lot during our work last year, hearing directly from the community, is the disparities issue. There is -- it is not uniform across the country, in terms of access to these technologies. We had one meeting in Montana where they needed to go to the local school to get adequate broadband access to even be able to use the school's computers, when obviously the school was empty at the time in the peak of the pandemic. So I mean, that is something that we really need to keep in mind with this work going forward.

And the other thing that we heard very loud and clear is that we also do not want a system that tips in the opposite direction, so that patients are, sort of, pushed into remote technologies when they would much prefer to see their provider in-person. So that concept -- and this is reflected in our principals -- that concept of patient and provider choice, preserving that, is going to be really important. And I think that has a role in the conversation about the use of these technologies in a

clinical trial setting view.

DR. ELZARRAD: That is a great point. Thank you for that.

Actually, something you said and something Christine mentioned, too -- it reminded me of the multiple efforts that were ongoing around the clinic trials. I was in a meeting recently for the National Academies and we are in clinical trial 2013, how we envisioned clinical trials. I know CTTI, Clinical Trial Transformation Initiative, have another clinical trial -- so work streams -- and a lot of the work -- and when I was meeting, I sensed some kind of frustration, because we feel like we know where we should be heading in a lot of aspects, at least. And we know that two years ago, when we -- all of us feel a shift has to happen. And I was wondering, how do you guys see us in -- you know, 10 years from now -- in 2030, how do you see the clinical trial infrastructure -- you know, relevant to rare disease, but also beyond, moving forward? Where do we need to go? And what factors need to get us there? I know we can have a whole meeting around that. But I was

wondering if each one of you can maybe touch a little bit in how -- what is your vision of the future, and how can we get there? Starting with you, Chris?

DR. AUSTIN: Well, I will give you two views. I feel like Dickens in a Christmas Carol, here. The -- or -- and two alternative outcomes. The outcome that is possible, and the outcome that will happen unless we take proactive steps to make it a reality.

The one that could happen is the one that Rachel was just talking about. And I think the technologies are there, now. I think the realizations are there now about how to have a more democratized -- if you will -- and flexible system that does rely on technology -- appropriate technology -- validated technology, when it is appropriate. But we do not force that into situations that are not appropriate. But that results in a more rapid and inclusive recruitment and retention in clinical trials, because we reduce the burden on patients. Particularly rare disease patients who are already dealing with all kinds of issues. So I think that could be a really, really good outcome.

What I fear is that we will do as human species what we often do -- which is that our memories are short, and we will go back to what we are comfortable with and what our current infrastructure supports. And that would be a tragedy, I think. And so, I think we have to all realize that for these changes to happen, we have to go beyond Gandhi, for -- that is, to be the change you want to see in the world, you have to advocate for it with payers and congress, if you are able to -- I am not. And neither are you, can do, but others can. And I think something that I have talked to Dr. Woodcock, actually, about that comes to mind here, is that -- and I hope this does not sound pejorative, 'cause I do not mean it that way. That a lot of people in the current system are very comfortable. Things are okay for them. And for them, they do not want the system to change. You know, the system is optimized to perform in its current form. And so, those systems are very resistant to change because a lot of people benefit from the current system. A disrupted system is going to disrupt a lot of people, and they are not going to like that.

And so they will -- even if they know it is the right thing, they will not want to do it and they will fight it. And so we have to think -- I think, proactively, who is going to be negatively affected, and how can we bring them into the conversation and make them partners, and say, "Well, gosh, you know, we still need you. We just need you doing B, instead of A." I think that is really important. But it is not going to happen by itself.

DR. ELZARRAD: Thank you, for that. Rachel, I am wondering your perspective on that, too?

MS. SHER: Yeah. I mean, I think to the question of how do we envision this 10 years from now, ideally -- and I agree with Chris, that there is, sort of -- there is the ideal system, which hopefully we will get to. But then, there is -- you know, who knows what the other one looks like. But ideally, we would get to a point where all of these tools that we are talking about are validated, available, and used where appropriate. And then, there is also another route for -- you know, patients, for instance, who are participating in a clinical trial close to the site,

that they can go there. And we can have it be both ways. I mean, and that same concept applies, as I mentioned, on the access to routine care. There is not -- particularly, when it comes to rare diseases, there is not a one-size-fits-all approach. So in our mind, ideally, we would have a system that can accommodate both the use of these technologies, but also -- you know, routine and direct access to providers and clinical trial sites where that is appropriate.

DR. ELZARRAD: Yeah. The -- and technology. I see, Nick, you are shaking your head. Do you want to follow up to that?

DR. JOHNSON: Yeah. I mean, I think the best-case scenario is that we are using outcome measures that really capture what is really important to the patient -- you know, when it happens, and a, kind of on-demand -- I think there is a lot of opportunity for that. I think -- you know, we will have to work diligently, both in terms of validating that, and then, also providing the structure to make sure that with these disparities that we see, in terms

of our trial recruitment, that are already an issue in rare disease, do not get worse, because we are -- you know, doubling down on issues that systemically exist. So I think there is a lot of opportunity, but -- you know, it is going to take a united effort, and a lot of people working on this. So -- I am excited, though.

DR. ELZARRAD: Thanks for that. Christine, do you want to provide your perspective on this, too?

DR. MUELLER: Yeah. I mean, I agree with everyone. I think -- you know, from the FDA perspective we want to develop safe and effective treatments for rare disease patients, and -- you know, make sure that is done in -- you know, fine-tuned ways, in terms of the validation of outcomes, and assessments, and -- you know, also being flexible in terms of what patients want, in terms of where they go to be assessed, of course. I guess, as a clinical geneticist and someone who grew up in a rural area, as an aside, I would just, sort of, caveat all of that with, like -- you know, that maybe we need some more infrastructure in those areas in doing this, as well.

You know, not just that we are relying on the infrastructure that we have right now. But you know, some of that needs to be built for patients in some areas of the county so that they have the expertise and -- you know, the adequate lab assessments in their areas, compared to academic centers.

DR. ELZARRAD: Thank you. I know, we are out of time. I appreciate you highlighting quite a bit of actually how we can shape the future, hopefully, and take these lessons we learned through this nasty year, now, into the future with us. And hopefully, we can see that materializing in the next 10 years, and all of us can, hopefully, be part of the solution, too.

So, again, thank you, so much. I appreciate your time. I have learned a lot. I hope our audience learned a lot, as well. And I am going to turn it back to Lewis at this point. Thank you, so much, all.

DR. AUSTIN: Thank you for having us.

DR. FERMAGLICH: Great. Thank you, all. We will now take a 10-minute break. Please rejoin us

at 2:10 for our next panel.

(Off the record)

DR. FERMAGLICH: For our final panel of the day, we will get to hear directly from the FDA Center directors about the challenges and opportunities they see for rare disease product development.

This panel will be moderated by Dr. Erika Torjusen, the director of Pediatric Device Consortia and Rare Pediatric Disease and Humanitarian Use Device Designation Programs. During her training in general pediatrics, and sub-specialty training in allergy/immunology, she not only learned how to clinically care for patients with rare disease, such as cystic fibrosis, and severe combined immune deficiency, or SCID, but also gained an appreciation for the many challenges that patients and families face throughout their rare disease journey. Impressed by their strength and bravery, she is grateful for the opportunity to work in the Office of Orphan Products Development to create a public health impact for the patients who inspired her career.

Dr. Torjusen?

DR. TORJUSEN: Thank you, Dr. Fermaglich. Good afternoon. I want to thank you all for joining us today for FDA's Rare Disease Day. As you know, my name is Erika Torjusen, and it is an honor for me to work in the Office of Orphan Products Development supporting the development of products for rare diseases and small populations, such as pediatrics. As the final population --

As the final panel for the day, we are closing the discussion with Center perspectives on new challenges and opportunities for rare disease product development. I have the pleasure to introduce our esteemed panel of Center directors. At this time, I would like to make sure all the Center directors have their videos turned on for brief introductions. So I have the pleasure to introduce the panel members.

First, we will start with Dr. Shuren, the director of CDRH.

DR. SHUREN: Hello, everyone. Pleasure to be here.

DR. TORJUSEN: Okay. And next we will

go to Dr. Marks, the director of CBER.

DR. MARKS: Hi. It is Peter Marks.

DR. TORJUSEN: And next, Dr. Cavazzoni, the acting director of CDER.

DR. CAVAZZONI: Hi. It is Patriza Cavazzoni.

DR. TORJUSEN: So to start us off, each panelist will provide a summary of the main points that they would like to convey addressing recent accomplishments, or initiatives related to rare diseases that they would like to highlight from their Center, and what we have learned from our experience with COVID-19, in terms of strategies that may be useful in rare disease product development.

First, we will start with Dr. Shuren in CDRH.

DR. SHUREN: Oh. Thank you, Erika. And again, pleasure to be here, talking with everyone today.

In spite of the pandemic and the massive workload that it entailed, we have continued to take actions to help advance the availability of

important medical technologies for individuals with rare diseases. So let me talk through some of those activities. So for example, over the past year, we have authorized the Plasma Delipidation System, which is for individuals who have homozygous familial hypercholesterolemia. We also authorized Sonelete, which is an MR-guided high intensity frequency ultrasound that is used in individual who have an osteoma. Just a non-invasive way of treating them, particularly individuals who have developed intractable pain that is unmitigated with medications.

We have also taken steps to further advance the availability of medical technologies for children with rare disease. And you think about thirty million Americans today have a rare disease, and about half of them are children. But a lot of challenges in being able to assess technologies. And for that reason, we see very little innovation in the med-tech space when we are dealing with our children.

One other thing we have been involved in, is helping to co-found a public/private partnership called the Systems of Hospitals for

Innovation and Pediatric Medical Devices, or SHIP-MD, which you heard a bit about this morning. And that is a network of institutions, primarily pediatric academic medical centers who, rather than your individually going to places trying to find pediatric patients to recruit, they come together as a network to, kind of, pool their resources and expertise, to then recruit patients to clinical trials, conduct those clinical trials, then vet the technology, too, to see if there is actually a good potential for assessing. And now, they are working on a single signature contract to really streamline the ability to set up and conduct a clinical study. And one of the next steps is trying to bring in the door of the state Medicaid directors, because 40 percent of children in the U.S. receive their healthcare through Medicaid. And hopefully, this way we find greater guarantees around reimbursement. And this combination of activities, we hope will be a shot in the arm for greater investment in medical technologies for our children -- particularly, children with rare diseases.

And then, we have been taking steps to

also advance the role of patients and their care. One of those efforts is to better understand their preferences. So for example, the study underway with UC San Francisco Stanford Center on understanding the preferences of children with heart failure, to then inform the development of new technologies and patient reported outcomes. We have established a network of patient organizations called the Patient Caregiver Connection. And that provides us, really, with patient experts to serve as advisors to the FDA and steps we should take and help inform some of our decisions. And that network has 16 members -- we are almost at our 17th -- and includes some of the organizations representing individuals with rare diseases, like the National Organizations of Rare Disorders and the Muscular Dystrophy Association.

And one of our big strategic priorities for the Center is a creation of something called collaborative communities. Now, we engage in collaboration all the time. But often, it is government in the driver's seat in one-off activities. A collaborative community is where the key

stakeholder groups in that community come together to solve shared problems and achieve shared outcomes in an ongoing fashion through a continuing forum, and where government -- FDA -- has a seat at the table as a member of the table. We do not drive it. We do not run it. But we act as a member. And if the community comes up with a solution, and that is where they want to go, and it is in the best interest of patients, and it is not contrary to our statutory mandates, we are likely to adopt it as our solution. So really putting the community in the driver seat. Already, we have signed up for 10 of these communities. We have many more in the hopper. And now, some of them are starting to engage in work that can impact rare disease, such as the one that has been established for thalamic imaging.

Lastly, let me close with some of the lessons learned out of COVID. Because I do think it would be a terrible tragedy from this pandemic if we did not learn from our experiences. And two, in particular, come to mind that I think are relevant in the rare disease space.

First off is regulatory flexibility. You know, when the pandemic hit, we were able to take advantage of our emergency use authorization authorities. And it allowed us that flexibility -- allowed us to truly tailor our approach to the technologies -- to those balances -- we got safe and effective devices out there, but also very timely patient access. And we think applied in the rare disease space -- critically important.

And secondly, is engagement. Taking our approach in the breakthrough devices program, with a lot of early and often engagement -- but putting it on steroids where developers literally were engaging with us in real- or near real-time basis, submitting data on a rolling view. We had a 1-800 24/7 hotline setup, and e-mail boxes, and a variety of other actions. That engagement with developers, I think, helped lead to -- along with regulatory flexibility -- the development in technologies like tests, within -- you know, weeks, and validation and authorization in literally weeks, rather than what would take months to a year or longer. And again, that kind of approach advanced in

the rare disease space, we think can be a game-changer.

With that, I will turn it back over to you, Erika.

DR. TORJUSEN: Thank you, Dr. Shuren. That was a great summary. And it sounds like your Center has been extremely busy. I really liked the points you made regarding collaborative communities. I think those are really promising. Certainly, your points regarding regulatory flexibility are certainly well-taken. I think we are all learning that lesson moving forward. And the real-time interaction sounds really exciting. And I am sure that, that would be something that a lot of innovators would love to take advantage of moving forward. So thank you, Dr. Shuren.

So with that, now we will have the same question to Dr. Marks in CBER.

DR. MARKS: Right. So thanks, very much. So now, our Center handles cell, tissue, and gene therapies. And among the excitement over the past two years has been the gene therapy approach is to treat -- or potentially even cure rare diseases, are

becoming a reality. In some cases, the results of these treatments have been almost spectacular and demonstrate particular promise in inherited genetic disorders. And since these disorders, though, are both numerous -- with over 7,000 been identified or defined -- and are -- currently many of them poorly treatable, we have a long way to go. And increasing the number of potential treatments have to be -- increasing the number of treatments have to be a very important priority for us. And what we realize is that, currently, there really isn't an optimized path forward for the development and access to these therapies, particularly, when the disease population is extremely small, or in the situation of individualized treatments, or treatments where there really isn’t a strong commercial interest.

Some of the roadblocks to broaden efficient application of gene therapy approaches to the thousands of disease populations that could potentially benefit, are really the fact that the manufacturing, currently, is just a challenge. And the approaches we have do not allow us to have easy

scalability, reproductive validity, or regulatory generalizability as we go from one gene therapy to another.

Additionally, a lot of what has happened is we have had very siloed propriety processes. So there has not been, kind of, the sharing of information that allowed all boats to float higher in moving ahead the production of gene therapies. And this is all even aside from some of the challenges that the clinical development has in these rare diseases, where you have very small populations where randomized trials just are not practical, and one really has to look at changes from some baseline natural history.

So because of that, we have taken the tact of trying to develop a program in individualized gene therapies, gene therapies for populations that are relatively small -- that is probably less than 100 treatments in the United States. Sometimes, perhaps, it might only be five or 10 treatments in the United States. This is a category which we are calling the Bespoke Gene Therapy category, because it is really

specifically tailored for individuals -- just a few individuals.

And we have been working, now, with leadership at the NIH, in the pharmaceutical industry, and with folks at FDA, since 2019, to try to put together a group to help assess these challenges and try to address them in a pre-competitive public/private partnership. And the Foundation for National Institutes of Health has now adopted this as a project. And we are currently working with industry and academic representatives to try to put together a pilot program, in which we will try to take through several gene therapies for rare disorders through a process in which we actually leverage manufacturing information, leverage information about -- that we know about the vectors that will be used to carry those gene therapies into people's cells so that we could potentially increase throughput of products through by not having to re-invent the wheel each time a new product comes along. Essentially, it is a -- what we would consider almost like -- not quite -- it does -- not quite something that falls in Dr. Shuren's

bailiwick of razor blades, but it is analogous to this idea, that the gene therapy vector, that is what helps carry the gene of interest into cells. But that does not really change. And the properties of that does not change. But it is just the insert that has to be characterized each time, anew.

And we think that if we can understand and get some experience with this, we would be able to speed up the development of gene therapies for rare disorders, so that we would be able to address multiple ones more quickly. Ultimately, the goal would not just to be have a pilot, but would be to develop a playbook, so that this could be used in academic laboratories -- but even more importantly, in the commercial setting, so that there is commercial viability. And this would, then, take on a life of its own, with manufacturers making gene therapies for small populations of individuals.

So we are hoping that by moving in this direction, we will find a way to get important treatments to the rare disease community, particularly, those that really have very small

numbers of treatment necessary, per year, in the United States.

And I will stop there.

DR. TORJUSEN: Thank you, Dr. Marks for that excellent summary of the unique considerations related to these types of products. Your point, certainly, tie in nicely with Dr. Abernethy's point made earlier today, where we need to develop a playbook. And I think you actually used the same word, exactly. So I think that, that is a great strategy moving forward. And I think the rare disease community is excited to see how further outcomes from this type of approach. So thank you, very much, for that summary.

So next, we will hear from Dr. Cavazzoni, with the same questions, from CDER.

DR. CAVAZZONI: Good afternoon, everyone. It is a real pleasure to be here. Similar to the other Centers, we have had to, obviously, focus on the pandemic response, while continuing to advance all our other work. And obviously, work in rare diseases is very important. And despite everything else that

has been going on over the past year, I think we can count some really notable accomplishments at CDER.

For instance, we have approved the first treatment for molybdenum cofactor deficiency type A. We also approved the first treatment for weight management for people with certain rare genetic conditions, over the past year. In addition, we approved the first treatment for Hutchinson-Gilford Progeria Syndrome and some Progeria laminopathies. And lastly -- recently, we have approved a targeted treatment for rare Duchenne muscular dystrophy mutation.

So lots of activity. We are also continuing to focus on how we can streamline and facilitate and shorten the development of therapies for rare diseases by working with sponsors to develop clinical trials and development plans that are going to give us quality data, while at the same time, not following the -- you know, the traditional paradigm of two or more randomized controlled studies, and so on, because we realize that, that paradigm is very challenging in the rare disease space.

When it come to the -- you know, the experiences over the past year, and -- you know, what we have learned from COVID, and what we might be able to actually take forward once we get to the new normal, when it comes to rare disease clinical trials -- you know, we have certainly learned a lot when it comes to the application of the centralized clinical trials. This used to be more the exception than the norm, before COVID, and certainly over this past year, it has been necessary to really deploy the centralized approaches to continue to advance clinical trials, including clinical trials in rare diseases. And we are thinking of how we can continue -- you know, to promote the adoption of the centralized clinical trials after the pandemic.

Similarly, we have seen an expansion of the utilization of digital health technologies for data collection. Obviously, that goes hand in hand with the centralized clinical trials. It is an important tool to collect data that is amenable to collection through digital health technologies from the patient’s home without having the patients or the

caregivers having to travel to an investigative site.

And obviously, all of this speaks to -- you know, facilitating the recruitment and the -- of clinical trials, and retaining patients in clinical trials, and make it easier for their caregivers to have them participate in trials.

The other area that is of ongoing focus for us is really looking at how we can facilitate and promote adaptive platform trials. And certainly, we have seen this really take off in the -- during the COVID pandemic in the development of therapeutics. And obviously, this is an area that we think has a very strong applicability for rare diseases. Obviously, we have some very notable examples, such as the HEALY trial -- platform trial for ALS. But we really see this platform trial as being an important tool in streamlining development, decreasing the exposure to placebo when it is necessary, and so on.

Similar to what you have heard from Jeff Shuren, and Peter Marks, what is also very -- you know, a very -- that really continues to attract a lot of focus is the concept of, really, data sharing, and

working in a collaborative way in pre-competitive space. And as many of you know, we have established the Rare Disease Cure Accelerator, which is really meant to facilitate a cooperative approach, and a common standardized platform to better characterize rare diseases, including incorporating patient perspectives in clinical outcome assessments, and building a clinical trial readiness in the pre-competitive space by sharing information and making it as accessible as possible.

We have also -- you know, taken some different approaches when it comes to how we do the work within CDER and within the Office of New Drugs. And to that effect, we have established a new OND rare diseases hub in the Division of Rare Diseases and Medical Genetics, which is comprised of two collaborative groups that are focusing 100 percent on rare diseases, and, sort of, working in a metrics fashion. And we think that this focus is really very important.

We also, really would like to continue to emphasize for stakeholders the -- not only,

obviously, being, sort of, aware and engaging with us as part of -- as early as possible in the development cycle, and obviously, referring to our many guidances in this space, but really this concept of pre-competitive collaboration is something that I cannot, sort of, emphasize enough. And I think it is really a fundamental element of advancing rare disease treatment development.

So I am going to stop here, so that we have sufficient time for Q and A.

DR. TORJUSEN: Thank you, very much, Dr. Cavazzoni. Certainly, sounds, again, like you have a lot of great initiatives for rare diseases. I was really interested to hear how you are trying to consider -- especially for rare diseases -- these patients, it might be difficult for them to travel to different clinical study sites. So it is great that you are trying to capitalize on what we have learned from COVID-19 to be able to help these patients continue to participate in clinical studies. As well as platform trials. That is a great opportunity to, maybe, work together to, kind of, create something

great, instead of, maybe, having a whole bunch of people working independently, and maybe not answering the full question. So I think that is great. And certainly, the Rare Disease Accelerator -- I think we are all looking forward to seeing what we learn from that experience, as well. And I can tell you, our office is looking forward to working with the rare disease hub in CDER, as well. So thank you, for all of those updates.

So now, I am going to go give another question to Dr. Shuren. So I was wondering if there are any unique considerations that apply to developing devices for small populations, such as pediatrics, in the rare disease space? And how is your center working to address these unique needs? I know you started that in your introduction. I am hoping you can expand on it further.

DR. SHUREN: And thank you for the question. Let me build on it. You know, I talked about some of the challenges in -- because of the small populations -- in recruiting subjects for clinical studies and conducting those studies. And to give you

a flavor, I mentioned the sono device, where we authorized it based on nine subjects in an open label study. And the plasma delipidation system, that was six subjects. And that is really what we -- you know, had to deal with. And still challenging to do that.

And so -- you know, the SHIP-MD approach is one way of trying to tackle, we talked about. We are also leveraging our Pediatric Device Consortia -- kind of, a network of institutions who are -- innovators in this space. And one of the opportunities is a meeting between the innovator, the consortium, and our Chief Medical Officer of pediatrics and -- populations, and all coordinated by the Office of Orphan Product Development --

And but one of the other big challenges in on the regulatory side. You know, in the device space, you cannot get the economic incentive, like you do in drugs, because -- you know, even the opportunities on waiver for -- you know, for another product, does not really help here, because you can re-engineer around the technology. And so what congress came up with is a very different regulatory

pathway for these small patient populations for -- device exemption. But is limited to 8,000 patients or less. It has got lots of bells and whistles. Adult populations, in most cases, cannot collect a profit, you got to get IRB approval. Very challenging.

And Congress has tried to change this and fix it three times since 2007. And guess what? Over the past decade, only six HDE technologies to the marketplace. We just have to say, this pathway, it just does not work. We need to actually take advantage of the lessons learned from COVID. Regulatory flexibility.

So imagine instead of the HDE today -- took away that standard of probable benefits outweighed probable risks, and we took away the bells and whistles -- so we do limit to just 8,000 -- we did not have the IRB. We made it more flexible. But we address another problem we had -- who even if we authorized and HDE product may not want to pay for it because of the lower standard to market. Instead say, you know what -- we can bring you to market under the HDE standard, much more flexibility, maybe a larger

patient population -- of course, the larger you get the more confidence you want to have in benefit/risk, 'cause you can get more subjects. But after a period of time, you have got to meet the full standard of reasonable assurance of safety and effectiveness. And you combine that with works like SHIP-MD, with a guaranteed network for gathering evidence, our greater opportunities for leveraging real-world evidence to support decision making, we can have a new flexible, regulatory paradigm that is fit for purpose, particularly, for small populations. And I think this combined level of effort can make a huge impact in the rare disease space.

DR. TORJUSEN: Thank you, Dr. Shuren, for that -- another excellent summary. I had the pleasure of working with CDERH on a bunch of these things. So I had the pleasure of working on the SHIP-MD. I was in one of the workstreams. And so, certainly, it is an exciting time, I think, for pediatric medical device developments. SHIP-MD definitely seems to have a multi-faceted approach to the unique challenges in the pediatric device

ecosystem. So we look forward to that. Certainly, hearing that you are looking at your programs and how you can better refine them and maybe create new pathways that might address some of the needs, I think that is really important. Certainly, we cannot do the same thing over and over again. We have to evaluate what we have, and what we need to do to improve the situation that we are dealing with.

So it sounds like CDRH is doing that on all fronts. So thank you, very much, Dr. Shuren.

So this next question, I was actually going to ask to Dr. Marks. And I think some of this was also addressed in your opening comments. And I was going to try to roll this into a -- I was going to try to roll this into one of the questions that I saw in the chat. I am trying to scroll up on it. Sorry.

But, basically, Dr. Marks, we had seen questions that were related to some of the gene therapies. And so the question that I had for you, that you already, kind of, opened up with initially -- but I was wondering if you could expand further, from a regulatory perspective -- we have seen increased

interest in the therapies for ultra-rare and small populations, such as individualized therapies. And how is your Center working to address regulatory considerations in this space as it related to gene therapy? And I wanted to let you know that someone has asked a question that was asking, how are we going to, also, coordinate some of the standards across the different Centers? Like, for instance, if there is a therapy that comes into CDER, CBER, if all of these -- how are these Centers going to coordinate to make sure that we are addressing these unique considerations?

DR. MARKS: That is a great question. So -- I think, first of all, let's start on the upfront part. Which is that, I think, increasingly we will -- you will see, kind of, cross-collaboration across the centers, because we cannot have a different endpoint, necessarily. We -- if -- the endpoints, we are going to have to agree on between Centers, right? I mean, gene therapy -- whether it be a small molecule, a protein replacement, or gene therapy, we need to agree on the endpoints. And we probably should not have different bars in different Centers,

right? I mean, so I think we need to, at least, agree upon what we are working on. So there, I think -- there is a good opportunity to have crosstalk, here, in the rare disease space.

Then, in terms of what we do to facilitate, here -- and I think, in some ways this is why there is this playbook necessary. Because, right now, I think, the concept is -- people do not realize, that even before you have your gene therapy, if you do your natural history study before you have your gene therapy in your Phase one, you might actually be able to get there much faster than if you do not do that preparatory work. Because if one knows what a baseline is -- or what some decline is in function, and then one intervenes with a gene therapy, one does not need to worry about Phase one, two, three. If one prevents that decline very clearly, it does not take that many patients if it is a big effect. And sometimes gene therapies do provide a very big effect.

You know, there, one can see getting to a regulatory -- a place where you could have a regulatory approval much more quickly than if you do

not know what decline is, and you go through Phase one, and you say, "Okay. Well, we observed this." But you do not know whether what you have observed is making a difference on the natural history of the disease. Because that is the only way we can tell. I mean, that is the way -- this is a way of doing this.

Obviously, if you have a large enough population that you can randomize -- or if the decline happens so quickly that you can randomize, that people do not mind being randomized for three or six months, or a year. But I think, for some of these populations -- it is -- the populations are so small that to try to randomize where you have 10 or 20 patients, it is just very challenging. And I think we have to think about other ways to get there.

So that is, kind of, the way we have been thinking through this. And we know we can -- we think we can get there, because, at least, when you have things that really work, you do not need a ton of patients, right? If you look at the data behind -- on a SMA gene, or -- the therapy for a type one spinal muscular atrophy -- you know, with 15 patients, we did

not need a statistician to know that you are making a tremendous difference in outcomes.

So, hopefully, we will see more of those. Not every gene therapy will be like that. But we would like to have some homeruns like that.

DR. TORJUSEN: Thank you. Thank you, very much, Dr. Marks.

And Dr. Cavazzoni, do you have anything that you wanted to add to that? Or would you like me to give you another question for the audience?

DR. CAVAZZONI: Yeah. I actually, it is up to you. I certainly, echo Dr. Marks comments about -- you know, the importance of achieving a greater understanding of the natural history of disease. We have -- you know, we know that there are some very rare diseases out there, that despite being very rare, are also quite heterogeneous. And so, really understanding the course of disease is very important. And you know, as taking from the -- you know, the tremendous advances that we have seen in gene therapy, obviously, that speaks for the importance of also investing in studying the biology

of disease, and understanding the molecular targets that would, then, allow for the development of -- you know, very fit for purpose and targeted therapies for rare diseases.

Happy to take more questions.

DR. TORJUSEN: Excellent. Thank you. So we do have about five minutes left. So in our last five minutes, I was hoping -- there is a question in the chat that is asking that -- you know, we often recommend engaging with the Agency early. And I think this is a question that applies to all of the Centers. So I was wondering if, maybe, you each could just, kind of, give a plug on how you suggest that these innovators, and developers engage with the FDA and start their interactions early to get on the right track.

So we will start with Dr. Shuren.

DR. SHUREN: That is probably our top advice. Engage -- lots of mechanism to do it. Like, throughout -- you know, Q-sub/pre-subs. And of course, if you qualify in rare disease space, likely will, through our Breakthrough Device Program, we

offer that out of the gates. And some additional opportunities, too, like, regulatory sprints. Identify a problem we need to solve, and we commit to solving it, working collaboratively -- and solve within 45 days.

DR. TORJUSEN: Excellent. Thank you. Dr. Marks?

DR. MARKS: Thanks. So -- again, I am going to echo what Dr. Shuren said. We think that is really important to come in very early. And we have programs -- one called the Interact Program, which allows people to come in before they actually are in the pre-IND stage, just to discuss the development plan for a specific product. And we would encourage people to come in early, have those -- have that dialog. Because it can potentially save wasted effort, which, ultimately comes at a cost to patients getting a therapy sooner.

DR. TORJUSEN: Excellent. Thank you, very much, Dr. Marks. And Dr. Cavazzoni?

DR. CAVAZZONI: Well, similarly, it is a -- I agree with Dr. Shuren. This is our top advice.

Engage with us early, talk to us, dialog with us. You know, do not go off and -- you know, take a different path without dialoging with us, because in the end -- you know, if we have made some recommendations or provided guidance, and then that is not followed, and then -- you know, two years later, we are presented with the results of a clinical trial -- you know, it certainly does not -- it is a situation that does not -- you know, accelerate things. And sometimes it actually get us -- creates a bit of a bottleneck.

We also have a lot of information out there. And I am in no way suggesting -- you know, the guidance supersede coming to talk to us. But you know, there is a lot of information out there. So for CDER we have -- you know, we have issued a guidance on demonstrating substantial evidence of effectiveness that really specifically also talks about the substantial evidence requirements in situations, such as rare diseases. We have guidance on development of rare diseases, on natural history studies, and so on. And so that can be, sort of, a foundational, sort of, resource, that then may actually allow sponsors or

patients who -- to come to us, sort of, understanding -- already understanding our general thinking.

DR. TORJUSEN: Mm-hmm. Thank you, very much, Dr. Cavazzoni. And I certainly think that, that is a point that is echoed across the Agency. We see it time and time again, that innovators and developers -- drug developers does -- for some reason, do not want to engage the Agency, and then, they have put in a lot of work, and it is a big, wasted effort when they are told to start over again. This happens with devices. And so, certainly, it is one of those things that we recommend early interaction with the Agency. So that is great message.

So I think we only have one minute left. And so in that last minute, I am just going to say thank you to our great panel. I really appreciate all of our Center directors for taking time out of their day to speak with us. We really appreciate participation in Rare Disease Day. Thank you to all of the audience members who provided questions. We really appreciate it. And our time for this session has

ended.

And so, now, I would like to introduce Catherine Park. She is the program management officer in the Office of Orphan Products Development. And she will be taking over for the open public comments portion of our meeting. Thank you, very much, Catherine. I will turn it over to you. Thank you, all.

MS. PARK: Thank you, Erika. Hello. My name is Catherine Park. And I will be moderating the open public comment portion of the meeting. Today, we have 12 speakers registered. We have a mix of live and pre-recorded comments. Each speaker will either have two minutes to speak or have provided a two-minute recording. If a speaker finishes early, we intend to move on to the next speaker. We will call each speaker by their name. When it is your turn, if you are providing your comments live, please turn on your camera, and unmute your microphone to provide your comments. For transparency purposes, we ask you, please, disclose if you are affiliated with an organization, or if you have significant financial interest in a rare disease medical product

development. As a reminder, you will also have the option to submit comments to the docket, which will remain open until Friday, April 2, 2021.

I will now call on the first speaker in the open public comment period. We have Dale Sanders. Thank you.

MR. SANDERS: Hi, friends. I am Dale Sanders. My career spans 37 years serving as an Air Force officer at the National Security Agency Intel Corporation, and more recently, healthcare. I am now a hospital and clinical research executive at Intermountain Health Care, Northwestern University, and internationally. I am currently an advisor to and investor in several companies that specialize in healthcare and life sciences technology, several of which are focused on rare disease.

I am here today in two capacities. First, to represent close family and friends and the thousands of patients I have seen who have been affected by rare diseases, such as ALS, Williams Syndrome, multiple myeloma, Dravet Syndrome, and more. Second, I am here as a data strategist. That is a

person who specializes in the use of the data to make better decisions in multiple domains. In those two capacities, I can confidently say we are looking at rare diseases from a wrong and poorly informed perspective. Contrary to popular belief, the total societal impact, the emotional and financial of rare diseases is far larger than chronic diseases. The ripple of these battles affects an extensive social network of family, friends, and colleagues in very material ways, financially and emotionally, much greater than what I have observed with common chronic diseases. We must look at rare disease through the broadened lens of total societal impact, not through the narrow lens of how many patients are affected.

As a data strategist, data is fundamental to treating and curing rare diseases. We need a coordinated national data strategy for all rare diseases, and each rare disease deserves its own unique data strategy. The data from electronic health records is grossly insufficient. Like a GPS map that is only accurate to within 10 miles. We need more and better data. Every rare disease must be supported by a

standardized national registry, and it must be a single registry, not the competing multiple registries that we have now.

Thank you for letting me share my thoughts today. God bless all the patients and the families affected by rare diseases. Thank you.

MS. PARK: Thank you, Dale. Next, we will have Jennifer Ostrom.

MS. OSTROM: Thanks, everyone, for having me. My name is Jenny Ostrom. I am a wife, mother of six children, and a patient with multiple myeloma. I started the HealthTree Foundation because I am an impatient patient. And I cannot wait for a cure. So even with remarkable progress that has been made in myeloma, it remains incurable and terminal.

Now, in our effort to finding a cure for my disease, my husband and I observed that the various data silos caused by regulation is the single biggest barrier to a cure. We believe that patients are the key to connecting the dots. We knew that connecting the patient community and their data with researchers, clinicians, pharma companies, and their

stakeholders would help develop new hypotheses, which it has. The challenge is that this requires patient trust.

So we spent a lot of time understanding the patient problems at a very deep level. And we developed a tool called the Health Tree Cure Hub, where over 8,700 patients contribute deep data sets, their labs, prior treatments, genetics, patient reported outcomes, in order to obtain benefits back during a lifetime with their disease.

We validate the medical records to make sure they are accurate. And then, patients can see personally relevant treatment options, or clinical trials they are eligible to join. They can find their disease twin, get a telehealth visit for a second opinion, or use it for clinical trial follow up, and the provider can see all of their aggregated medical records. They can find crowd-sourced solutions to common side effects and watch a comprehensive myeloma university taught by over 100 specialists.

That deep technical experience led us to develop eight unified software platforms to enable

rare disease communities to help their patients across their lifetime with the disease. So as we give patients these tools to navigate their disease, they contribute their patient experience, because there are real practical benefits in doing so. We partner with academic investigators to facilitate their surveys and studies. And it is making clinical trial recruitment significantly easier.

And now, we are expanding myeloma with this cut and paste set of tools to build community that supports patients and drives research simultaneously.

Now, market disruption, that was talked about earlier, requires that you serve the needs of an unloved and underserved community. And in this case, it was the patient. I wanted to let you that it is possible, if you put the patient first, and you preserve trust.

MS. PARK: Thank you. Next, will have Eric Hartman.

MR. HARTMAN: Hello. My name is Eric Hartman. I am the director of advocacy for the

Choroideremia Research Foundation. I am one of the founding members, and a patient. Choroideremia is an inherited retinal degenerative disease that starts with a loss of peripheral vision and night vision, and shrinks into the middle, to where there is no vision at all. Males are predominantly affected. But females, also are. And we are indebted to the NEI for their work in putting together a new natural history study for this negative -- disease as a natural history study.

We want to thank the FDA. Especially the members of CBER for their work in our current trials. We have several trials underway, both for AAV2 vector, and directed evolution vector. We want to thank them for allowing us to give our input before the committee to let them better understand he patient perspective of choroideremia.

We also think it is incredibly important that will all of these potential therapies that are out there -- including stem cells and gene editing -- that it is imperative for the inherited retinal diseases of the eyes, that you get genetic

testing.

In our foundation, the vast majority of our patients were originally diagnosed with another eye disease, retinitis pigmentosa. And we think that the standard of care should now be for all existing patients to get genetic testing. There are large groups of patients out there that have not received a genetic confirmation. And believe that in the long run, for our patient population, and for all of them, that they will be empowered through the knowledge of having a confirmation of their disease and being able to seek both a treatment and the support they need.

We also want to thank the FDA in their work in helping us try and get our data out of these silos through the RDCA DAP grant that they had issues. We think it is incredibly important that we, as rare patients who travel from near and far to be in these natural history studies, do not want that data locked away for all times.

Thank you.

MS. PARK: Thank you, Eric. Next, we

will have Jason Colquitt.

MR.COLQUITT: My name is Jason Colquitt. I am CEO of Across Healthcare. I am blessed to have a 22-year career in the health care IT arena. I personally have a rare mitochondrial disease, have friends with rare disease, have friends with kids with rare disease, and too many friends that have lost loved ones to rare disease. This fuels my passion to disrupt the way we care for and cure rare diseases.

I have four challenges for today. The good thing is most of them have been heard today. So that is awesome.

Patient reported data and registries. I would like to see more encouragement of collecting and using patient reported data. Rare disease patients and caregivers are typically willing and -- to diligently collect their -- data. The patient voice through their data needs to be heard and leveraged more.

The second challenge is remote and de-centralized approaches. We have heard this today, as well. The pandemic has taught us trials and studies cannot be centralized and have patients traveling to a

single site. Technologies have been used for throughout the pandemic. We need to figure out how we can adopt and utilize these remote technologies to keep patients at home, or, at least, local. This pushes beyond our all-too-common Zoom experiences, and move toward remote sensors, remote sites, remote tools, and other exciting de-centralized trial aspects.

The third challenge is around electronic health records. And you have heard this from the speaker earlier. But my 15-years career was building EHR's. I then, moved for seven years to aggregate, consume, and curate EHR. EHR's are a wonderful source of historical data in rare disease studies. But is all too common that it is expensive, timely, and these siloed environments are hard to get to the data. It is just messy. I would encourage the FDA to collaborate with other HHS agencies and offices to influence -- that have influence over the EHR to keep research as an end goal.

My last, and fourth, is collaboration. Encourage collaboration. It is easy for us all to put

blinders on and care for our own disease or research area. I would like to see more encouragement and incentives for collaboration across agencies. Given how many and how fragmentated rare diseases are, uniting together is a way for us to increase our impact.

Thank you for this opportunity. And I pray that we all are able to listen, learn, and act on what we have heard today to make a difference in the lives of all rare disease patients. Thank you.

MS. PARK: Thank you, Jason. Next, we will have Dean Suhr provide comments.

MR. SUHR: Thank you. And good afternoon. I am a rare disease dad, president and co-founder of MLD Foundation. We serve the metachromatic leukodystrophy community, which is a terminal genetic para-metabolic disease. Pre-symptomatic therapy today is transplant. But we do have a gene therapy that has been approved in --

MS. PARK: Did you push your mute button? We cannot hear you, right now. Dean?

MR. SUHR: MLD has a natural history

registry -- grant program, as well. So thank you for that. I wanted to venture, just briefly, today, a policy, as an important issue for those of us that are advocates this rare disease week. Many of us have been advocating on Capitol Hill. And for the audience, I want to make sure you are supporting the work of the FDA by engaging in policy.

We have many issues this year that we have been putting forward -- one of them is access to the Rare Indications Act, which requires payers to honor the entire FDA approved label. We also have the STAT Act, establishing a rare disease center of excellence, and the HEART Act, to continue and improve the rare disease patient and FDA engagement. And of course, we are always asking for appropriations. Your organization continues to need funding and continues to need good staffing support.

Also, as I mentioned, we have a gene therapy coming. But I want to make a general comment about that. There is a tsunami of gene therapies for numbers of diseases that are coming. And we want to encourage the FDA to consider that many of these are

platform therapies, and that, that may need to influence how reviews are done in the future. Do not sacrifice quality or any of the standards. But separate the difference between the base platform and the disease specific information, so that we can be more efficient.

And then, finally, on COVID, I did miss panel three due to a conflict. But Dr. Abernethy started us off this morning talking about templates and roadmaps. And I really want to encourage you to apply the lessons that -- and all of us, to apply the lessons we have learned the rapid COVID vaccine development to rare disease. Our clinical trials are going to take longer than just a couple of months, like the COVID ones did, but we can learn a lot, to take the gaps out and to be more efficient about how we work our way through the regulatory approval process.

Thank you very much, for your time and your hard work.

MS. PARK: Hi. Dean, before you step out. Do you mind repeating what you talked about,

about your organization and what it does? Your audio, kind of, cut out, back there.

MS. SUHR: Oh. I apologize. Right at the very beginning? Yes. My name is Dean Surh. I am a rare disease dad, president and co-founder of the MLD Foundation for metachromatic leukodystrophy. It is a terminal genetic para-metabolic disease. Pre-symptomatic therapy, historically, has been transplant. And there is a gene therapy that has been approved in the EU, late 2020. And we are currently working -- I say, we -- the sponsor is, currently working its way through the FDA. Two of my three kids were affected with MLD. Thank you.

MS. PARK: Great. Thank you, so much, Dean. Next. We will hear comments from Brian Smith.

MR. SMITH: Good afternoon. My name is Brian Smith, and I am a law student at the University of Illinois College of Law. I am speaking in my individual capacity, today.

I independently research rare diseases as a public health crisis. And I have numerous family members who have a hyper-rare disease, that is found

only in my family.

As I am sure you all know, rare diseases are not actually rare. In fact, the best evidence estimates that over 30 million Americans have a rare disease. Despite this shockingly high number, therapies for rare disease patients are limited. Even though the Orphan Drug Act has spurred innovation for many rare disease therapies, 95 percent of rare diseases still have no FDA-approved treatment.

So clearly, current law and economic incentives are not adequate for millions of Americans suffering from rare diseases. The FDA appears to have some tools to help promote the creation of rare disease therapies for even the rarest of the conditions.

First, the FDA can consider prioritizing review of products that are approved by the European Medicines Agency, but not yet by the FDA. This would not be a short cut, rather it would be a supplement to current FDA review.

In addition, the FDA should create new standards for how drugs for hyper-rare conditions are

examined for safety and efficacy, as gold standard trials are difficult for these conditions.

Lastly, I implore the Office of Orphan Drug Development to communicate with its account managers in the Office of Congressional Appropriations at the FDA. That office is uniquely situated to provide input to Congress on how FDA processes can be streamlined to better serve rare disease Populations. In addition, they can relay to Congress information on what additional support the Office of Orphan Product Development needs to promote would be rare disease therapies.

Thank you for allowing me to speak with you all, today, and for the dedication you showed to the rare disease community.

MS. PARK: Thank you, Brian. Next. We will hear from Sophia Zilber.

MS. ZILBER: Thank you. My name is Sophia Zilber. And my outline today is about patient registries for a disease. As a disclosure, I work at Pfizer, but I am here on my own behalf.

My daughter died from mitochondrial

disease. Due to my professional experience in data analysis, I was able to contribute to mitochondrial disease patient registry efforts. These are some challenges that I have encountered.

There is a lack of awareness regarding things that are critical for success of a patient registry. For example, understanding what is involved in collecting useful and meaningful data, importance of data standards, user appropriate technical resources, having governance and oversight, selecting registry platform most appropriate for the goals of the registry. As a result, a lot of data collected is not useful for research. At the same time, enormous amounts of time, money, and hope is spent on creating multiple patient registries for the same disease. Patients in the patient registry that I have analyzed have commented on how upsetting it is to participate in various registries and having nothing come out of it, over and over. Education, awareness, and a dialog is needed.

In an effort to address this, I have written a very concise and easy to read paper about

patient registry design for Rare Disease Foundation with Jason Colquitt, who also spoke here. I have also created a Google group to unite mitochondrial disease advocates and encourage discussion and collaboration. It is also important to empower patients, to ask better questions which will result in greater accountability. I would love to continue this conversation with FDA, or other stakeholders. You can contact me at sophiazilber@gmail.com, or you can find me at my LinkedIn page. Thank you very much.

MS. PARK: Thank you, Sophia. Next, we will have Parvathy Krishnan share her comments.

MS. KRISHNAN: Good afternoon, everyone. My name is Parvathy Krishnan, and I am here today to talk about an ultra-rare condition my children have: constitutional mismatch repair deficiency syndrome, or CMMRD. There are less than 250 patients worldwide diagnosed with this condition. Only about 50 of them are still alive. As of today, our son is the only child identified in the world with a homozygous F CAM deletion.

While this is a genetic ultra-rare disease, it manifests itself as progressive pediatric cancers. Less than five percent of total NIH funding is provided to pediatric cancers. All pediatric cancers are rare diseases. As a category of only 400 of the 7,000 rare diseases currently have a therapy. Our daughter had multiple rare diseases and passed away two weeks after her fourth birthday.

Much like the world came together to accelerate treatment of COVID vaccine research and clinical trials, we ask that the FDA support collective finding of a cure for rare diseases this year, more than ever before. We know how to fast track, now. And the same process for COVID crisis vaccines and treatments may be applied on a broader scale to rare diseases.

Everyone represented here can help us fast track this by working together and collaborating on research studies with patients and patient advocates. Inclusion in the concept stage, before a clinical trial begins, as well as integration throughout the process would bring patients and

therapy providers together for accelerated learning.

In addition, we hope you will expand the PRV program for pediatric specific treatments and drugs. If PRV's were expanded and more researchers were compensated for therapies and rare diseases, perhaps another family would be spared our grief and our loss. This is my dream, and my passion.

And thank you for giving us a voice today to share our story. And I hope you will all continue to involve us directly in the work you do every step of the way.

MS. PARK: Thank you. Next. We will play a recorded comment by Mary McGowen.

MS. MCGOWEN: Good afternoon. I am Mary McGowen, CEO of the Foundation for Sarcoidosis Research. Thank you to the FDA for this opportunity to share comments on pressing issues for the sarcoidosis community.

Sarcoidosis is marked by the formation of granulomas in one or more organs throughout the body. For those with advanced sarcoidosis it is not uncommon to have significant multi-organ involvement.

Drug development in sarcoidosis is excessively slow.

In Sarcoidosis there are very limited medications approved for use. Most treatments are prescribed off-label, creating significant delays and barrier to access, and heavy financial burdens on the patient. Many of these medications demonstrate clinical significance.

It is true that industry may seek new indications for an already approved medication. But this only happens very rarely, with less incentive for seeking such indication in rare disease. The FDA has an important role to play in changing this landscape. We do not wish to stifle the innovation associated with off-label use, as it is a literal lifeline for our patients. However, we believe it is time for the FDA to develop better scaffolding around clinical use data for off-label drugs for drugs approved in other areas.

Additionally, we urge the FDA to consider ways to broaden the incentive for manufacturers to seek new indications. Especially, for rare diseases. To accelerate research in sarcoidosis

it is critically important to partner with researchers and the pharmaceutical companies to identify and expand the opportunity for use of surrogate and intermediate clinical endpoints.

While the Foundation for Sarcoidosis Research and clinical investigators in the field continue to work to identify strong biomarkers such as, imaging testing, pulmonary function tests, and genetic markers, progression toward treatments and cures must not stagnate.

Thank you to the FDA for this opportunity to share our concerns, and we look forward to working closely with you in advancing the care for those living with sarcoidosis and other rare diseases.

MS. PARK: Thank you. Next, we will have another recorded comment provided by Christina Brundage.

MS. BRUNDAGE: Hello. My name is Christina Brundage. I live in Irmo, South Carolina. I am 26, and I have idiopathic hypersomnia.

IH is a chronic neurological disorder that results in having excessive daytime sleepiness, even

after a full night's sleep. Because of this, people with hypersomnia have a hard time holding down jobs, staying in school, and maintaining marriages and friendships. Currently, for hypersomnia, there are no FDA-approved medications. This means people like myself have to fight insurance to get treatment, or pay out-of-pocket, which as you can imagine, gets very expensive very quickly.

So far, I have participated in three clinical research trials to help get a mediation to the market. The only bad thing I have experienced with trials, is that if you have found an amazing medication that works for you, you still have to potentially wait for years in order for it to be available. One of the medications I tried for a trial was my miracle treatment. It completely took away my symptoms, and I felt more awake than I ever have before. But it was a stage one trial. So I have to go along, knowing that there is something out there for me, I just cannot access it yet.

There are treatments out there that could tremendously change the lives of people living

with rare diseases. We just need to work together to get them approved. I think it is very important for the FDA and patients to keep engaged with one another, because without us, you will not know the stories, and the huge need for approval. And without you, we will not get safe medications for our diseases.

Thank you, so much, for the opportunity to speak, and for holding this Rare Disease Day. I really appreciate it. And I look forward to the rest of the day. Thank you.

MS. PARK: Thank you. Next, we will hear another recorded comment provided by Qais Abu Ali

DR. ALI: Hello. My names is Qais Abu Ali. I am a medical geneticist, and the chief medical officer for IMR Therapeutics [ph]. I would like to thank the FDA for giving me the opportunity to talk to you today.

Having spent the majority of the past two decades diagnosis and treating patients and families with rare diseases, both in the clinic and the lab, then, working on developing therapeutics, I have, as many of us, witnessed the tremendous advances

in knowledge, that left us with many new answers for which we are still trying to articulate the correct questions.

What patients and families of rare disease have taught us all along, is that their unwavering effort becomes their daily life, often times leading to a notable relief, but also, a significant void once a diagnosis is made. In partnership with their healthcare providers and diagnosticians, such patients and families will then try to embark on their next journey, trying to find a treatment.

Unfortunately, such an odyssey might not be successful for all patients and families equally, as an expert working with therapeutic developers may not even exist for their specific disease. Various types of consortia for rare diseases have been established over the years. Some more prominent than others. But what is obvious, is that as a broader community, we need to have a concerted effort towards a national framework that provides a link to all clinicians, diagnosticians, and rare

disease therapeutics developers.

Such representation or task force will need a private/public partnership, with FDA being central to these efforts. Especially, as more new rare diseases get identified, further therapeutics will get developed. I am hoping that the next decade in the rare disease community will be the one where having even one single patient diagnosis with an ultra-rare disease is enough justification for us to advance developing its therapeutics.

Thank you for your attention.

MS. PARKS: Thank you. Next, we will play our final recorded comment, from Mary Faxas.

MS. FAXAS: Hello. My name is Mary Faxas. And I am here as a desmoid tumor patient, to provide insight in ways to increase the medical communities understanding of desmoid tumors.

Like with all rare diseases, I have a lot of questions about how to bridge the current gaps in the regulatory landscape and clinical research. Currently, desmoid tumors do not have a standard of care, or an agreed upon treatment plan. The lack of

comparative studies, and incredibly low patient population make it difficult to establish a standard of care and definitive sequence of existing treatment options.

My diagnosis was initially unclear and has taken over eight years to access a doctor who knows enough about desmoids to help. The drugs that work best for me are being used in an off-label manner and are indicated for other cancers. There are no validated response criteria established to measure drugs' effectiveness with desmoids. Desmoid tumors are not being recognized as the cancer that it is, thus making diagnosis and treatment nearly impossible. Because I had to wait so long for treatment, I have three different desmoids in my leg, and I am disabled because of it.

Clinical research remains difficult for desmoid patients, as many studies are terminated early due to side effects and lack of definitive evidence. Recently, Dr. Mrinal Gounder utilized the FDA grants to conduct a study on the use of sorafenib in desmoid tumors. This research is promising and provides hope

that more clarify surrounding desmoid tumors will arise.

Additionally, we would like to encourage companies to seek orphan drug designation for tyrosine kinase inhibitor drugs. These cancer products are the most promising treatment for desmoids. And by obtaining orphan drug designation, the FDA can assist with clinical research to expand the drug's indication and provide more information to the medical community and desmoid tumor patients.

Lastly, desmoid patients would like the FDA to continue to develop the Rare Disease Global Trial Network.

Thank you for all your time and hard work, and for taking my comment, and experiences into consideration.

MS. PARK: This concludes the open public comment period. We really appreciate everyone participating today. I will now transition to Janet Maynard to provide closing remarks. Thank you.

DR. MAYNARD: Thank you, so much, Catherine. And thank you to the participants in the

open public comment period. We will now transition to closing remarks.

On behalf of the FDA, I would like to thank all of the panel participants, speakers, and everyone on the webcast for participating in today's meeting. We have greatly appreciated your attention, and your interest in these topics.

I would also like to think the Cross Agency Planning Committee, who helped organize today's meeting. And offer a special thank you to Catherine Park and CDRH Studios.

This has been a very important meeting to all the participants, including FDA, patients, researchers, and industry representatives. We greatly appreciate the perspectives and experiences that were shared with us today. We heard about the strategies to facilitate rare disease products development. There is significant unmet need for patients and families living with rare diseases, and it is important to share these strategies to support the development of rare disease treatments.

In the morning, we discussed rare

disease partnerships, collaborations, scientific advancements and patient engagement. Key points included the importance of patient engagement throughout rare disease product development, and the importance of including patients in all aspects of product development.

In the afternoon we discussed strategies to support rare disease product development during COVID-19 and updates on the development of drugs, biologics and devices for rare diseases.

While the vast majority of rare disease do not have approved treatments, it is an exciting time in the development of treatments for rare diseases. We are seeing new opportunities to catalyze the development of treatments for many rare diseases. As Dr. McCormack said today, "Research is a source of hope."

Facilitating the development of rare disease treatment is critical, as rare diseases have significant impacts on patients and families. Looking forward, we will continue to enhance collaborations, and innovation, to support optimal development of safe

and effective products for people with rare diseases.

After this meeting, if you have any questions, or you would like to follow up with the FDA, the Office of Patient Affairs can help. You can send them an e-mail at patientaffairs@fda.gov. They can help you stay connected with other activities at FDA, and also help address any future questions. You can also connect with the Office of Orphan Products Development at orphan@fda.gov.

In addition, if you would like to share additional feedback or perspectives after today's meeting, please submit comments to the docket, which will remain open until May 2, 2021.

Following this meeting you will receive an e-mail survey, which we request that you complete so that we can continue to improve our public meetings. We greatly appreciate your input on today's meeting.

And on that note, I am closing this public meeting. Thank you and stay safe.

(Whereupon, the meeting concluded at 4:00 p.m.)

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I, CARL HELLANDSJO, the officer before whom the foregoing proceedings were taken, do hereby certify that any witness(es) in the foregoing proceedings, prior to testifying, were duly sworn; that the proceedings were recorded by me and thereafter reduced to typewriting by a qualified transcriptionist; that said digital audio recording of said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

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