FOOD AND DRUG ADMINISTRATION (FDA)

FDA Rare Disease Day 2020:

Supporting the Future of Rare Disease

February 24, 2020

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DR. JANET MAYNARD: Good morning and welcome to this public meeting, FDA Rare Disease Day 2020, Supporting the Future of Rare Disease Product Development. My name is Janet Maynard. I am the director of the Office of Orphan Products Development at FDA, and I am excited to have this opportunity to engage directly with you to help support the future of rare disease product development.

We would like to welcome the various rare disease stakeholders who are here today, including patients, family members, patient advocacy organizations, healthcare professionals, and individuals from academia, industry, and government, including many from FDA. Many individuals are here in the Great Room at FDA for this very important meeting. We know it can be challenging to travel to FDA, and we thank you for being here today.

In addition, thank you to those joining by webcast. We understand that not everyone can be here in person, and we appreciate you taking the time to participate and contribute online.

Developing a treatment for a rare

disease can present unique challenges. The goal of this meeting is to obtain stakeholders' perspectives on challenges and solutions in rare disease product development and identify commonalities that can support product development across a variety of rare diseases. To accomplish this goal, we have a full agenda today. We will review this agenda after we review a few logistic and housekeeping points.

First, please silence any cell phones or mobile devices, as they may interfere with the audio in the room today. If you haven't already, we ask that all attendees sign in at the registration tables outside of the meeting room. Restrooms are located in the lobby, past the coffee area, to the right and down the hallway. At any point if you need to get up for any reason, please feel free to do so. There are smaller rooms available around the Great Room if you need space either during the meeting or at lunch.

If you have any questions, please ask the volunteers at the registration desk. If you would like to pre-order your lunch, please go to the food

kiosk outside of the conference room. The pre-ordered lunches need to be purchased by 9:30. Thus, if you have not pre-ordered your lunch but would like to, we recommend you pre-order now.

If you decide not to pre-order, you may purchase snacks, sandwiches, and food items a la carte. The kiosk outside the conference room will be open from 8:00 until 5:00 to obtain food and drinks.

For media inquiries, our press officer, Monique Richards, is here today. If members of the media are here today, please sign in. And if you have any questions or are interested in speaking with FDA about this meeting, please connect with Monique Richards.

This meeting is intended to give FDA the opportunity to listen and interact with rare disease stakeholders, so the FDA participants and other FDA employees will not be available to make statements to the media.

Please note that if you are asked to participate in an on-camera or off-camera interview, you may accept or decline that invitation at your own

discretion.

For the wi-fi in the great room, the network and passcode are displayed on the screen. A public docket is open until March 29th to submit comments. We highly encourage you to do so.

This meeting is being transcribed and a live webcast is being recorded. There will also be filming in the Great Room today. If you have any questions, please contact Monique, and she is happy to address these questions. For urgent issues, please speak to the registration desk staff or any FDA staff you see in the room wearing name tags.

In case of an emergency, please exit the Great Room and follow the exit signs to leave the building.

Also, please let us know how the meeting went today. For individuals in the room, evaluation forms will be placed on your seats at lunch. If you do not receive one, please stop by the registration table. For individuals on the web, evaluation forms will be emailed to you.

We will now review today's agenda. The

goal of this meeting is to obtain stakeholders' perspectives on challenges and solutions in rare disease product development and to identify commonalities that can support product development across a variety of rare diseases. To accomplish this goal, we will have a variety of remarks and panel discussions from various rare disease stakeholders.

The morning session will focus on registry and natural history data collection to support rare disease product development. The afternoon session will focus on new opportunities and challenges in rare disease product development.

In terms of the morning agenda, after the conclusion of my welcome, Dr. Abernethy will provide opening remarks. We will then have a panel discussion with FDA senior staff, followed by a 15-minute break, and then a panel regarding natural history and registry data in rare diseases. We will then break for lunch at 1:30.

In terms of the afternoon agenda, the FDA Commissioner, Dr. Hahn, will provide opening remarks for the afternoon, and then we will have a

panel with the FDA Medical Product Center directors. We will then have a ten-minute break, followed by a panel on perspectives on individualized therapies, and then a panel on the ecosystem of rare disease product development.

During the panel throughout the day, there will be the opportunity for those in the room and on the web to ask questions and provide perspectives. For those in the room, please raise your hand if you would like to speak. We will bring a handheld microphone to you. Alternatively, you may go to one of the microphones that are located throughout the room. You may remain anonymous or state your name, and we encourage you to state the disease area you are representing if that is applicable.

For transparency purposes, when you are sharing a comment, we ask that you please disclose if you are affiliated with an organization, if your travel has been funded, or if you have any significant financial interest in rare disease medical product development.

For those on the webcast, please type

your comments in the chat feature. We will be periodically checking in to see what our remote attendees are sharing in the chat box.

After the last panel in the afternoon, we will have an open public comment period. The open public comment period will provide anyone in the audience the opportunity to make a comment. To participate in that, you would have needed to sign up prior to the meeting or sign up today at the registration table. Participation is first-come-first-served and can accommodate up to nine commenters.

We will close the sign-up for the open public comment period at the end of our afternoon break around 2:00 PM or when the sign-up is full. Speakers will each have three minutes to speak. If there is additional time at the end of the open public comment period, individuals in the room can share remarks on a first-come-first-served basis during the remaining time. After the open public comment period, I will provide closing remarks.

Now we will briefly cover a few rules

of engagement for our discussion today.

We encourage all individuals to contribute to the dialogue, either today in the meeting or through the public docket. We appreciate the opportunity to hear your perspectives. The views expressed today are personal opinions. Please be respectful of others and allow participants to finish sharing their experiences without interrupting. Participants in the room should use microphones so the webcast attendees can hear their remarks. And please complete an evaluation form to let us know how the meeting went today.

After the meeting ends today, there will be additional opportunities to interact with FDA. The Patient Affairs Staff and the Office of Orphan Products Development are here and want to stay in contact with you, whether it's helping you stay connected with other activities at FDA or addressing any future questions you might have.

This slide contains our contact information. Also, if you choose to tweet about today's meeting, please use #FDARare2020.

In closing, I want to thank everyone for participating today, and I look forward to a very productive meeting. Thank you.

So our introductory remarks will be given by Dr. Amy Abernethy, who should be arriving shortly, or is here. Great. Thank you, Dr. Abernethy. So Dr. Amy Abernethy, MD, PhD, 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 cross-cutting initiatives that impact the regulation of drugs, medical devices, foods, and tobacco.

As the Chief Information Officer, she oversees FDA's data and technical vision and its execution. She has held multiple executive roles at Flatiron Health and was a professor of medicine at Duke University School of Medicine, where she ran the Center for Learning Healthcare and the Duke Cancer Care Research Program.

Dr. Abernethy received her MD at Duke

University, where she did her internal medicine residency, served as chief resident, and completed her hematology-oncology fellowship.

She received her PhD from Flinders University, her BA from University of Pennsylvania, and is boarded in palliative medicine. Welcome to Dr. Abernethy. Thank you.

DR. AMY ABERNETHY: Thank you very much. I think somebody's calling us with beeps.

Thank you all for being here with us today. Your voice is so important to how we take this journey forward.

So as I reflect on where we are today, I reflect on the fact that the combination of government incentives -- maybe we should check. Anything you need from me? I sort of feel like E.T. The combination of government incentives, scientific advances, and the promise of commercial opportunity has fueled extraordinary investment in orphan drugs.

Since the passage of the Orphan Drug Act in 1983, the number of orphan indications approved in the U.S. has risen dramatically.

In addition, the proportion of novel drugs that are for orphan indications has tended to increase over time as well. In 2018, we saw a record number of drugs and biologics approved for rare diseases. In 2019, we continued to make strides in the treatment of these rare diseases. And specifically in 2019, the Agency approved 22 novel drugs and biologics with orphan disease designation and a total of 76 orphan indications.

These product approvals addressed many unmet medical needs. Some of the approvals included new and expanded uses of already FDA-approved drugs.

For example, FDA originally approved a drug in 2014 for the treatment of patients with idiopathic pulmonary fibrosis. This is a serious and sometimes fatal lung disease that results in lung scarring and that gets worse and makes it hard for people to breathe.

In 2019, it was approved by FDA to slow the rate of decline in pulmonary function in adults with another disease called interstitial lung disease that's associated with systemic sclerosis or

scleroderma. These are rare lung conditions.

This was the first FDA-approved treatment for the rare lung conditions and represents the shift of a drug approved in one setting to now an orphan indication.

Not only have we seen tremendous growth in the development of products for rare diseases, but the very landscape of rare disease product development is changing. There is an increase in the development of targeted therapies, more interest in the development of biologics, including gene therapies, and tremendous growth in the oncology space.

Moreover, orphan drug research and development has led to medical breakthroughs and further scientific understanding across a wide range of conditions beyond rare diseases. But despite the success, we remain cognizant that developing rare disease treatments remains enormously challenging. Working with stakeholders, especially patients and patient groups, it's critically important in addressing the challenges.

Given that rare diseases are rare by

definition, it's important to learn as much as we can from each patient with rare conditions.

Patients living with rare diseases and their families can provide invaluable insights that directly impact medical product development and improve day-to-day care in the clinic for people today and in the future. Our unique experiences as patients provide critical input into which then helps inform the design of clinical endpoints which help us understand what will be most meaningful in your day-to-day lives as medical products are developed.

People who are willing to participate in natural history studies help provide data points that can be tracked over time and allow us to better understand disease progression in the real world. Participation in clinical trials facilitates getting safe and effective therapeutic options to the market.

Understanding the natural history of rare disorders is critical to developing appropriate clinical trial endpoints for rare diseases, because otherwise these diseases are poorly understood. It also helps us understand how the disease course can be

variable across patients.

Detailed natural history case studies are also used to create historical controls that can be used to evaluate the efficacy and safety of new treatments and similar trials, this way decreasing the need to randomize patients when it is unethical or impossible to do so.

In this morning session, we will hear from rare disease stakeholders on opportunities and challenges in the use of registry and natural history data to support rare disease medical product development.

As we think about data to support rare disease product development, it's also important to consider real world data and real world evidence. Real world data and real world evidence are playing increasingly important roles in all facets of the healthcare ecosystem. What is it? These are data collected during the routine process of providing healthcare, like through the electronic health record or through a glucose meter. And clinical evidence generated from the analysis of these data help to

provide meaningful insights as to how patients fare t eh real world when exposed to medical products outside the rigid and uniform settings that we usually see in clinical trials.

The healthcare community is using these types of real world data to support coverage decisions and to develop guidelines and decision support tools for use in clinical practice.

Medical product developers are also using real world data and real world evidence to support clinical trial designs and observational studies to generate evidence to support approval of novel treatment approaches.

FDA uses real world data and real world evidence to monitor post-market study information, informing safety and our regulatory decisions.

In response to the 21st Century Cures Act, FDA developed a real world evidence program to evaluate the potential uses of real world data in generating evidence of product effectiveness to help support approval of new products for new indications, including in the rare disease space, or to help

support and satisfy post-approval study requirements.

Stakeholders can engage with us, particularly patient engagement. And this has been and will continue to be an important part of our real world evidence program.

With these exciting opportunities for the use of data, it's important that FDA modernize our technology platforms so that we can support the advances coming to make a difference in your lives and our lives.

In September, the FDA rolled out our Technology Modernization Action Plan. This is an ambitious strategy that includes modernizing our technical infrastructure in ways that allow us to receive, analyze, and use data in ways to support our regulatory mission.

One way we are working to meet this goal is by designing technical interfaces and tools to enable to streamline submission and review of data. Creating standard, digital safety reports is an important step towards more sophisticated data and technology solutions at the FDA and to support

efficient development of safe and effective medical products.

In support of rare disease product development, the FDA will strengthen the information technology processes and our orphan drug technology modernization efforts. This effort will streamline the orphan drug designation request process by moving from paper-based processes to a new cloud-based online submission portal. The new online portal will allow sponsors to submit orphan drug applications electronically. This effort is another example of FDA's commitment to broader efforts in overall technology modernization and orphan diseases.

Importantly, the foundation of these technical enhancements are supporting the development of safe and effective products for rare diseases for patients and families.

I am grateful to be part of an agency so committed to integrating the patient perspective in everything that we do. Patients and the care of the American people is the heart of a regulatory mission, and this is our core focus.

It's essential that we work with you, all of us, those who are directly impacted by diseases. And this informs our efforts as we move forward. We are here to listen and work together with you.

Thank you for the opportunity, and we want to make sure you know we're listening. Thank you.

DR. JANET MAYNARD: Thank you so much to Dr. Abernethy. And now I am pleased to invite our first panel up on the stage. So as they come, everyone can take a little bit of a stretch. I know it's a long day, and we're so excited to have you here.

So our first panel will be a discussion with FDA Senior Staff. Thank you.

DR. ERIKA TORJUSEN: So first, I just wanted to say thank you for being here today. Any time that we can get together and discuss rare diseases is certainly a special day. So I wanted to thank you all again.

I just wanted to introduce myself. My

name is Erika Torjusen, and I am the Director for the Rare Pediatric Disease Designation Program, as well as the Humanitarian Use Device Designation Program, as well as the Pediatric Device Consortia Grants Program.

So my purpose when I come to work every day is actually to promote and support the development of products to treat rare disease and special populations, small populations, such as pediatric patients. So this is a cause that's very near and dear to my heart.

So we have the great fortune of being the first panel for today. And so we are going to be laying the groundwork for the discussion regarding natural history and registry data, with a focus on the regulatory perspective. Our goal is to allow about 20 to 30 minutes for audience participation, both in the room as well as online. So that's going to occur in the second part of our panel today.

So first I'm going to introduce our panel by name, and then I'm going to give each of our panel participants an opportunity to provide a five-minute background on where they are in the agency,

what role they fulfill in the agency, and also provide you with a couple of key points regarding their perspectives on natural history and registry data.

So first I'm going to introduce Dr. Stein, who is immediately to my right. Next is Dr. Caños, and then next we have Dr. Bryan. So I'll have you start, Dr. Stein, first, providing your five-minute introduction.

DR. PETER STEIN: Great. Thank you very much. I want to thank everyone for being here today. This is such an important day and opportunity to hear from patient groups from other stakeholders about their perspectives on the work that we all do together to develop drugs for rare diseases.

I am the Director of the Office of New Drugs, which is the office that regulates drugs that are coming in from approval. It also regulates drugs that have been approved and participates with other offices in assuring their continued safety and the appropriate continued benefit-risk of those drugs.

And I say new drugs, but as Dr. Abernethy mentioned in her opening remarks, many of

the drugs that we are seeing are for rare diseases, orphan designated diseases. Indeed, as she mentioned, last year it was about 40 or 50 percent and the year before that, about 60 percent of the new drugs that we approved were for rare diseases.

So, much of the work that we do across my organizations is involved in supporting companies during their development phase, during the IND development phase for rare diseases, and then reviewing applications for rare diseases. And that's a large part of what we do in many different parts of our organization. We have an Inborn Errors Team that works on particular rare diseases that involve enzyme deficiencies and related conditions. But across all of the different divisions -- neuroscience and endocrine and many other divisions -- we see applications both for the development and then for approval of drugs for rare diseases. So we are extensively involved in helping to find ways to treat these important diseases.

I'll just say a few words about natural history studies, because I think we're going to spend

a fair amount more time both on this panel and in the next panel talking about these really important means of gathering information about these disorders.

Natural history studies really refer to studies that are collecting information or obtaining information about the clinical course, presentation, and progression of diseases. It can be both retrospective -- so chart reviews, using medical records, using other sources of information, it can be cross-sectional within the cross-data that's existing -- or, very importantly, it can be prospective collection of data. Really collection of pre-specified data, data that is specific to the objectives of that study that informs. And we often will refer to that as a registry. It's really a platform for collecting prospective information.

And what I'll say is at a high level these are incredibly important projects, incredibly important activities, because it informs much of what we do and how we think about rare diseases, defines the course of the rare disease, its presentation, its diversity and heterogeneity, its complications, the

burdens of its treatment. All of that can inform everything from how we design clinical studies, it can serve as control groups, external control groups for clinical trials, they can help us to develop instruments like clinical outcome assessment tools and biomarkers, and so many other purposes. So these are critical sources of information that help us develop drugs and help us approve drugs for rare diseases. And I guess we'll dig into some of the specifics of that broad overview.

DR. ERIKA TORJUSEN: Thank you. Dr. Caños?

DR. DANIEL CAÑOS: Thank you. I am the Acting Director of the Office of Clinical Evidence and Analysis, and I work in the Office of Product Evaluation and Quality within the Center for Devices and Radiological Health. And so really our office is geared to address some of the challenges and the needs to incorporate evidence from a clinical experience into regulatory decision-making.

Really, you know, we just finished our reorganization last year to this opaque structure.

And my office supports the Office of Health Technologies. Individual device technologies are within these offices, cardiovascular, ortho, et cetera. And our office supports the development of evidence from clinical experience from the conduct of studies for even such as protections. Good clinical practice, laboratory practice.

Also on the epidemiology side to address the -- assess the relevance and reliability as well as to the quality and completeness of data sources, devise aspects for the analytic portion, and then also the outreach and collaboration with hospitals and providers. So really trying to provide kind of a soup to nuts support and assessment of clinical evidence and really kind of breaking down some of the artificial barriers between the standard clinical trials and really viewing it from a holistic approach as far as the evidence generation. And through supporting that, we are developing and assessing real world evidence sources, registries, as was mentioned, and really partnering with, you know, Office of the National Coordinator and with ARC, other

stakeholders, industry, professional societies, patients, and academia to assess the quality of data sources, developing registry infrastructure, and developing a maturity model to assess the ability of certain registries to address questions for the various stakeholder community.

And in doing so, establishing this infrastructure, we can assess clinical reported outcomes, observed reported outcomes, patient reported outcomes, develop the infrastructure to capture these items. And we are working towards a large infrastructure.

So registries -- I think we'll get a chance to talk about this -- there are some plusses and minuses to registries, some limitations in what can be captured. But we are approaching evidence generation from, as I mentioned, a larger holistic approach and really thinking about a collaborative stakeholder community for evidence generation. So not just the registry infrastructure, but also looking at electronic health records, medical billing claims information, and tying all this information together

for a national evaluation system for health technologies.

So we've actively supported the creation and use of real world evidence and have undertaken many activities to support this. One is through promoting implementation of unique device identifiers, also increasing the use of regulatory decision-making that utilizes and leverages clinical evidence. It's supported over 50 regulatory decisions within CRDH. And then, as I mentioned, we're partnering to build a National Evaluation System for Health Technologies that can capture this information and address with real world evidence the regulatory questions at hand.

So with this system, the National Evaluation System for Health Technologies Coordinating Center has stood up. And it's more than 12 network collaborators, which represent 195 hospitals, 3,942 outpatient clinics, and over 494 million patient records. And this is just the start of the system. In the coming months they're going to establish and release a quality framework document as well as a

methodology document which partners well with the guidance document that was released with CDRH and CBER with respect to real world evidence uses for regulatory decision-making that kind of map out the needs for relevance, reliability, quality, and completeness that we assess when looking to leverage this data for regulatory decisions.

DR. ERIKA TORJUSEN: Thank you. Excellent. And now Dr. Bryan.

DR. WILSON BRYAN: I'm Wilson Bryan. I am a neurologist with a background in neuromuscular disorders. I now serve as Director of the Office of Tissues and Advanced Therapies in the Center for Biologics.

Advanced therapy is a somewhat pretentious term that we borrowed from the Europeans. It generally refers to cell therapies and gene therapies. And the Office of Tissues and Advanced Therapies, which I refer to as OTAT, one of the best things I like about working in OTAT is that over 90 percent of our applications are for serious and life-threatening diseases. Approximately 50 percent are

for rare diseases. And several of the gene therapies, there aren't -- we don't have many products approved yet. But the science over the last couple of decades has really moved forward quickly. And so we have very exciting products in development that will be coming out over the years ahead.

One product that I will mention, a gene therapy that we approved last year, is Zelgensma, a treatment for spinal muscular atrophy.

Now, spinal muscular atrophy, if you're not familiar with it, it's a bad disease. It's a neuromuscular disorder. The form of SMA, spinal muscular atrophy, that was studied was an infantile form. So these infants start becoming weak by the age of six months, and most are dead by the age of two from respiratory failure.

There are now two products approved for SMA. This is a huge change for patients and for their families. For decades there was nothing. And key to development of this gene therapy for SMA was the natural history data, the natural history study. It wasn't a big natural history study. The natural

history control that we used only had 23 patients. Twenty-three. That's almost nothing. But it can be enough if the course is reliable.

Where we get into trouble is when natural history data don't give -- don't seem reliable, don't give reliable endpoints. Highly variable pools. But when the course is predicable and we can get reliable endpoints, then natural history data can be used in some cases as the control for Phase III studies as was done with infantile SMA. I expect that you'll hear more about that in the next session from Dr. Kaufmann, who has been more closely related with this development than I have.

With the sequencing of the human genome, there are now thousands of genetically-defined diseases. Many of them very rare, many of them very bad diseases. And we know that we will get at some point the technology to address these with gene therapy. We haven't yet figured out how we're going to get that therapy for every patient who has those rare disease. And we at CBER are very committed to working with other stakeholders like the NIH to figure

out how every patient with a rare genetic disease is going to get a treatment that works. And that's years ahead, but that's where we're going.

DR. ERIKA TORJUSEN: Thank you all for those introductory comments and remarks. So, actually, I see we've used already a good amount of our time. So I think what I'm going to do is I'm just going to have one question for you all, and we'll see where we're at. And then we might actually be able to open it up to the audience for audience participation where they can ask some questions of our panel members. So first we're going to ask one question to you all.

So given your knowledge and experience with natural history and registry data, do you have any examples of lessons learned that you would like to share with the audience today? We'll start with you again, Dr. Stein.

DR. PETER STEIN: Well, just to pick up on some of the things that I think you've already heard. Natural history studies can be used in a whole range of ways. And I think we're going to speak a

little bit more about their use as external controls so that we can take information from a single-arm trial and have a comparison group that allows us to draw conclusions and potentially to use that as the basis to approve a drug or to approve a biologic, a gene therapy.

But to be able to do that requires that the natural history information be very rigorous, that it be collected in a way that provides detailed information that's comparable to the information that we're getting in the clinical trial. And that's really the challenge. Because very often the natural history information we get is not necessarily on comparable patients, doesn't necessarily have a comprehensive data collection or similar data collection, data quality issues may occur.

So I just want to step back and think a little bit about how we can utilize this information. Now, again, very often we do have to look towards randomized clinical trials, because they provide a very rigorous way of being able to compare the treatment to a control group. And sometimes those

really are the only ways that we can go when there is, for example, a small effect size or a heterogeneous population where we don't have the natural history well-defined.

But where there is a larger expected effect size and where we have data that provides us clear information with a predicable clinical course and detailed information down to the patient level, it does support our ability to use natural history comparison groups, whether from a registry or from retrospective chart reviews.

But I think it's important just to think about, again, what's needed to make that work. It does mean that we've defined the patient population in that comparison group very clearly. Are we sure that those patients are actually similar to the patients in the stage and the stage of progression and the type of disease that they have? Diagnostic criteria, for example, change over time. If we look at diagnostic criteria from 10 or 15 years ago, we may be looking at different patients than the current study that we're trying to compare those patients to.

Or the outcome assessments; were they assessed in a similar way? Very often we found that the types of methods and outcome measures and the way the disease was assessed over time changes from when it was looked at 10 or 20 years ago to how it's being collected in the context of the clinical trial.

Are the treatments that the patients are getting concurrently similar or quite different? And what is the data quality? Was it really collected for this purpose, or is it collected for clinical care where some of the information that we need is there, and some of the information we need might not be there.

So that all provides substantial challenges when we get a comparison group submitted compared to a single arm trial, can we really compare it. And I really would push to say that what's really critical as we go forward and are working collaboratively together with patient groups and with other stakeholder groups as we think about the development of registries' prospective collection of information, the design of those, the infrastructure

of those, the data quality issues become absolutely essential as we move forward. As there is marked advances in our ability to identify new drugs and new biologic therapies, our opportunities to treat rare diseases are going to continue to expand. But if we're going to be able to use natural history or registries for that, we have to make sure that the quality of that data improves over time dramatically so that that data really provides us with a comparison group that's robust and from which we can draw conclusions.

And we've had some examples of natural history studies where they're quite limited information. And what our groups here do is do everything they can to ask more and more from the sponsor to go back to the medical records to pull all kinds of information that help us to do the best comparison we can. And sometimes it requires us to just continue to collect data over time so that we can see whether the course of the disease really differs from the course that we're seeing with the treatment group.

So what I would say is there is lots of examples over the past about 15 years. We've approved something like 20 drugs using external control data. So quite a few drugs approved that way, outside of oncology. Oncology is even more than that. But in each one of them, I would say that we've seen substantial challenges in trying to get matched groups. It requires a lot of work to be able to draw a robust conclusions. So we certainly want to make sure that the drugs we're approving are effective and are safe.

And so I think one of the things we have to underline is the importance of the quality of the data and of the completeness of the information so we can actually increasingly use these kinds of studies to make decisions as early as we possibly can.

DR. ERIKA TORJUSEN: Thank you. And Dr. Caños, do you have anything you'd like to add from the CDRH perspective?

DR. DANIEL CAÑOS: Yeah. I think you really hit the nail on the head as far as the quality and the representativeness of the evidence that's out

there, as well as the definitions, you know, consistent definitions and how those outcomes are ascertained really are challenges that we are seeing with evidence from clinical experience.

And I'd like to speak to some of the work items that we have at CDRH and are working to actively address those concerns. We have funding through a Patient-Centered Outcomes Research Trust Fund through that through a grant we are working with stakeholder community. Patient representatives are in these meetings or on the calls as well as industry stakeholders, professional societies, and academia. And working within selected registries, 12 coordinated registry networks that we are targeting and developing.

We are trying to arrive at a core data set, definitions and variables to be routinely collected within each of these registry sets and critically assessing the capabilities of these registries to address regulatory questions. And within that same effort, we are also working on increasing the quality from these registries so that

there can be a fair appraisal of these evidence systems.

And in my introductory comments, I mentioned this National Evaluation System for Health Technologies Coordinating Center, housed within the Medical Device Innovation Consortium, the MDIC. This NEST will kind of point to certain nodes within the healthcare system. Network collaborators that I mentioned before, registries. And, you know, the work of this trust fund effort is to provide that evidence and our -- kind of the assessment from the stakeholder community of the quality of the evidence from those individual registries. So that takes out some of the guesswork up front as folks, you know, look to the registries that they know where the stakeholder community is as far as the quality and completeness and representativeness and the definitions that are utilized so that folks know where to go to, where the system can point to where those nodes could be and areas that we can, frankly, improve.

In addition to that, you know, we have on the structure side, and we are working to build the

infrastructure and collaborating with the stakeholder community.

On the methods side, from the epi and the biostatistical side, we are working to leverage external evidence as best we can. As you mentioned, it can be utilized at times when appropriate for control arms within studies. We are working from the evidence standpoint and biostatistical standpoint to develop methodologies where we can borrow certain parts of data if it were to be found to be representative. And so it could lend some support or lesser support if the populations aren't representative of the population, the indication for which the sponsor is seeking.

In addition to supplementing the control arm, it could supplement some portions of the treatment arm. And these are methodologies that we are publishing off of and also jointly developing through research work as well as collaborations through the MDIC.

So, you know, we're trying to approach it from a few different aspects; the methodological,

the analytics side, the partnership side for developing the infrastructure, as well as the methodologies to really maximize the use of evidence from the clinical experience for regulatory decision-making.

DR. ERIKA TORJUSEN: Excellent. Thank you. And Dr. Bryan, do you have anything you'd like to add from the CBER perspective? I know you touched on some of this in your introductory comments.

DR. WILSON BRYAN: Just a couple of things. First, when advocacy groups or drug companies or the NIH, whoever starts a natural history study, I think they usually have in the back of their minds that these data will hopefully be used as a control in clinical trials. But natural history data do so much more than that. They are very important for designing the development program, for deciding what endpoints to use, what populations to study, and how long is the trial going to need to be to see a change in that endpoint in that population.

Too often we have scientists, investigators come to us with a new, exciting product

that they've been working on in the lab. And these are often gene therapies. And they're ready to give it to humans. And they ask us at the FDA to tell them what the clinical trial should look like. And it's a rare disease, there haven't been clinical trials done in this genetically-defined disease before. We don't know the answers. Those of you who have met with us many times know we often don't know the answers.

And so it's very important that the scientists who are working on these rare genetic diseases, as soon as they start working in the animal models, that's the time that they need to be starting to talk to the clinicians about the human disease so that those natural history studies are being started well before it's time to actually do the clinical trials.

So people just need to talk to each other in this business. And too often the scientists have been too isolated. And we need to get the natural history study started much earlier.

DR. PETER STEIN: If I could just underline that, because I think that's such an

important point. Very often when scientists dive into trying to identify the genetic background and understand the biology of the disease and begin to work on targeting it, there is very little known. There is often case reports and case series that are highly selective and don't necessarily collect all of the background information on the heterogeneity of the disease or its course, or really what are the more common complications or its rate of progression.

So, very often they jump in looking at five or ten case reports or case series, thinking that defines the natural history and that should be sufficient. But when it comes to us and we really want to understand, well, how long, how large, what endpoints, what patients should be included, what's the range of the disease, that is not known without having done a properly-performed natural history study, whether it's looking retrospectively, or even better, prospectively collecting that information. That's a gap, and I think that's the disconnect. Scientists may not realize when they're in the lab that that information doesn't really exist in a robust

way that can be used to inform clinical program development. So I just want to underline the importance of that early collaboration between patient groups, other stakeholder groups, academics, the scientists, FDA where we can help out with this, to try to really work together to get these studies moving so that there is -- so that when they are ready to bring something to the clinic, we understand the disease well enough to actually design an informative program. I think it's really important to underline that.

DR. ERIKA TORJUSEN: Excellent. Thank you. And so I just want to finish with one very, very brief question just to finish this topic, because I think this is an important one.

DR. PETER STEIN: You mean you want us to be brief.

DR. ERIKA TORJUSEN: Maybe. I do want to have time for the audience participation. So I just wanted to know, do you have any recommendations on when sponsors or advocacy groups should reach out to the agency regarding whether they're going to be

using a natural history study, designing a natural history study or registry? Do you have any advice or recommendations in that regard?

DR. PETER STEIN: Well, I think the answer is early. And we are very much open to have these kinds of discussions with stakeholder groups to provide direction, to engage with them. And we are working on a rare disease accelerator, which is intended to be a new infrastructure for registries so that we can support and work with patient groups to develop these. This is a collaboration with NORD and with the C-Path Institute to try to provide this for patient groups as a resource.

But I would say early. You know, come to the division early. If there's a program going on, if there's development in this area, talk to us about what we think might be needed. We are here to try to be collaborative and to be part of the solution.

DR. ERIKA TORJUSEN: Excellent. Thank you. And do you both agree with that recommendation?

DR. WILSON BRYAN: Yeah. It's a challenge, because we know that there are thousands of

rare diseases. And we would like to see natural history studies in all these thousands of rare diseases. Now, does the Agency have the capacity to work on the trial designs for thousands of natural history studies? I'm not sure that we do. But we want to do what we can.

But I think more of us need to develop expertise in how to do these natural history studies so that they meet regulatory requirements, you know, formative for a drug development.

DR. ERIKA TORJUSEN: Excellent. Thank you. So I think I would like to open it up to audience questions at this time. So if anyone does have a question, please step forward to one of the microphones in the room. And also, we expect that we will receive some questions online as well. So we're going to bounce our about 20 minutes left for the audience questions then.

So I'll start with the gentleman all the way down in the corner there in the white shirt.

DR. DEAN SURH: Great. Good morning. Thank you for hosting us here today. I am Dean Surh

with the [redacted] Foundation. Just a couple of comments more than a question. You know, engaging -- and I don't know our audience, but I presume it's pretty diverse in terms of experience and so on. So just two comments more directed perhaps at them.

Engaging early with the FDA is really important. They're always willing to converse. And the same thing with any pharma or academic research partners.

But I've got to tell you, I don't think my crystal ball is any better than the FDA's, or in some cases the scientist's when we're putting programs together. And oftentimes particularly advocacy groups are years if not decades in front of the science or the regulatory reviews of therapies that are yet to even be thought of, much less emerge.

And so I just want to emphasize that a very structured natural history study/registry is typically targeted to validate a particular point. And if you don't know what that point is, which might be a clinical trial endpoint, if you don't know what that is, that doesn't mean you shouldn't start with

your natural history and your registry. And for patient organizations, gathering data, we know the disease from a certain perspective, typically not so much a scientific perspective. But to gather that data early, gather it broad. Maybe it starts with demographics and some of those basics so that you can go back to those families when you get closer to a clinical trial and dig in deeper.

I just really want to encourage you to think about that process needs to start very, very early. And it's extremely valuable. Some will say it's not scientific. You know what? Knowing where the patients are, that's where the science starts. And so we need to start our work early.

DR. ERIKA TORJUSEN: Thank you for that comment.

DR. ANNETTE BAKKER: Annette Bakker, President of the Children's Tumor Foundation. First of all, I think this is fascinating as a panel. Thank you so much.

I have a question with regards to would it make sense to start thinking -- because I heard a

lot about longitudinal natural history data, and the quality, and therefore the use of that data. Is there an opportunity here maybe to collaborate across the sector to develop some kind of framework, let's say some umbrella framework for this is what quality looks like, especially for these very rare diseases where people collect data and then it ends up not to be the right data? Is there any guidance that you guys are developing to say, okay, this is a framework, infrastructure as the minimum data set to start collecting data that people at least collect in the beginning the right data?

DR. ERIKA TORJUSEN: That's a great question. Who would like to tackle that first?

DR. PETER STEIN: Just as a -- I mean, I couldn't agree more that being really thoughtful about what you're going to collect is critical. And I would say, you know, a couple of things as resources.

We have a guidance that was recently released on natural history studies that does talk about a number of the elements that might be collected. A lot of what's collected really has to be

based upon what the purpose and the objectives and the particular leads in that disease are for further information.

But I also think it's very important to partner with experts, epidemiologists or others who have a better understanding of sort of the structure and the architecture of the data and can work with the patient groups and can work with academic groups or other stakeholder groups to really define what's the gaps, what do we need to know, what are we trying to do with this study so that it's designed properly. Because data quality, completeness, and consistency is absolutely critical.

It's wonderful to put a lot of different kind of data into a database, but if it's not rigorously defined and appropriately collected with appropriate attention to detail and quality and lack of missingness, then the utility of it will just -- it will be still useful, but its utility will certainly be much less.

So prospective definition, working with experts. There is a lot of literature out there about

registries, what can be collected, and different frameworks that can be used as resources. And we are a resource as well.

DR. WILSON BRYAN: And we have a guidance out that talks about --

DR. ANNETTE BAKKER: I saw that. But I think the question of connecting them, maybe allow especially those ultra-rare diseases to maybe come together as a bigger group. Right? If we tart collecting it across diseases maybe in a similar way. I don't know, I'm just...

DR. WILSON BRYAN: And you're talking I think about the specific data elements as well.

DR. ANNETTE BAKKER: Or like those that will be used, as you said, for clinical trial design and for really to understand the course of a disease. I think there is some rigorousness maybe in...

DR. WILSON BRYAN: Well, certainly I think we all believe in gathering rigorous data to try to move this ahead. Doing these natural history studies is not easy.

DR. ANNETTE BAKKER: Exactly.

DR. WILSON BRYAN: It's a lot of work. And many natural history studies that have been done in the past -- I'm going to say probably most -- were done by academic clinician investigators trying to understand a particular disease. I remember back in the early 2000s going to a conference on spinal muscular atrophy. And they had just completed a large natural history studying SMS. And I asked, well, okay, these different endpoints that you looked at, how much of a change in these endpoints makes a difference to patients? How much is clinically meaningful? And the answer I got was, well, we couldn't figure out how to assess that, so we didn't look. And I'm thinking you just did a four or five year natural history study, and you didn't look to see how much of a change matters to patients?

It's important, as Dr. Stein mentioned, to talk to other people who do this and look at other trials and figure out how to get the information that's going to be useful for drug development. Because I can tell you here at the FDA, we want to know how much of a change matters to patients. And we

have to get the -- that's the kind of information that's key to a regulator that to an academician just might not occur to them when they designed the trial.

DR. DANIEL CAÑOS: So I just wanted to add that I completely agree with your comment. And the NEST Coordinating Center, as I mentioned, being a multi-stakeholder community, is a collaborative community, meaning that that community comes together and serves the purposes of the entire community.

So in Dr. Abernethy's opening comments, remarks, she mentioned not only the FDA's regulatory body, but also the payor perspective. And you've heard mention of the patient perspective; what is of value to the patient? And clinically, you know, what is a clinically meaningful difference. And within this multi-stakeholder community and this collaborative community, those discussions are ongoing. And that's part of that methods framework document I mentioned that's going to come out from NEST Coordinating Center, as well as the quality framework to really speak to as to this collaborative community what is meaningful for methodologies within

the framework for medical devices.

DR. WILSON BRYAN: I'd like to add something to the comment from the gentleman who spoke first about having broad data collection in these natural history studies.

It's also important that, particularly for these rare diseases, that you enroll every patient that has the disease and try not to be selective in just enrolling a small group. Now, we realize that means more effort, more resources. But not going in with preconceived notions about which patient are going to be informative and which patients are going to respond to the intervention. I think enrolling all the patients with a rare disease when you're starting a natural history study is important if feasible.

DR. ERIKA TORJUSEN: Thank you.

DR. PETER STEIN: And just as a quick sort of follow-up as well. I did like the comment that he made about getting started. Because, you know, while we're talking about the rigor and the importance of complete data and data quality, sometimes just getting started, identifying the

patients, pulling them together, creating a network, that has real value. And it may be over time there is a need to evolve it towards other objectives such as providing a really robust data set as a comparison for an external control arm for clinical trial. But early on just creating that network of engaged stakeholders, of engaged patients and parents and families and physicians and identifying the patients can be hugely important. And it may be over time that more rigor and more consistency of what's collected comes into it.

We certainly don't want to discourage you getting started, because getting started is critical. Downstream we can think about additional ways that natural history study or registry can evolve.

DR. ERIKA TORJUSEN: So I would also now like to just make sure that we acknowledge we have a very large online presence today for this meeting. I believe we have well over a thousand individuals registered today. So I would like to use this time just to check in [illegible] e and wee if we have any questions

from the online community.

DR. ERIKA TORJUSEN: The first comment. Yes.

DR. JANET MAYNARD: Hi. Can you hear me?

DR. ERIKA TORJUSEN: Yeah.

DR. JANET MAYNARD: We do have a lot of questions. So to start, what is your perspective about using the placebo group from approved drug clinical studies as the comparator group for a new medicine for rare disease.

DR. ERIKA TORJUSEN: Excellent. So we have about ten minutes left.

DR. PETER STEIN: Just to say I think that in those examples where that's been done, I think that can be a very rigorously-collected set of information if it's collected -- again, it's the same set of considerations; what was collected, over what time it was collected, what were the patients who were in that placebo group. All of those will be relevant to whether it can serve as a comparison group. But if it was rigorously collected data, that can certainly

and has been used as a comparator group for subsequent trials.

DR. ERIKA TORJUSEN: And do you have anything else to add?

DR. DANIEL CAÑOS: Not on the drug placebo side, no.

DR. WILSON BRYAN: I would agree. I think we are very fortunate when we're in that situation and have such data. And in most cases in rare diseases, we don't have such data.

DR. ERIKA TORJUSEN: Excellent. And maybe we'll come over -- I'm sorry, we'll come over here.

DR. JANA OBERMAN: Hi. I'm Jana Oberman from Ovid Therapeutics. Just quickly going back to the dialogue around timing. I think we all agree in theory that engaging early and often with regulators is critical, and well before you're in the clinic so that we can design these natural history studies optimally. But in practice, I think we all know that we are only granted typically one pre-IND meeting. And so our hands are often tied in trying to

figure out how to engage well in advance, but not using that opportunity too far in advance when things can often change a few years before you do enter the clinic. So do you have any specific recommendations on how we can go about interacting with you more effectively?

DR. WILSON BRYAN: I'll be honest. I have limited experience in this. I did get a call about two or three years ago from a scientist who was working on several different genetic disorders, very rare disorders, and said that he was going to develop a gene therapy for these variety of disorders and wanted to do five different natural history studies. And I said I can't review five natural history studies. Send me two. Send me two protocols for natural history studies. And I enlisted some statisticians to help me look at them, but they were never submitted. They never came in.

And I think that reflects the challenge, that it's not easy to get these things done. And the scientists who are working in the lab, they've got a lot of other things on their minds. And

they often just don't get around to working with someone to get the natural history studies done. But I expected most of us here at the FDA would love to see a protocol for natural history study. And they'll probably do what I did, which is dig around to try to find somebody to take a look at it. Now, hopefully we'll get better than that.

DR. PETER STEIN: And just as a quick comment. First of all, while we typically have one pre-IAB meeting, try to be flexible about it. So that there's not -- that's not a statutory regulatory limitation, just practical. We also have the CPIM meetings, which are forum for stakeholder groups to come in a sort of non-binding way, but can have a very informative, particularly earlier, discussion with us.

We also often attend patient stakeholder meetings for patient-focused drug development meetings and talk about registries and, you know, have an interactive discussion. We're on panels and in a lot of different patient stakeholder meetings under the rare disease group and the inborn error group. And many other of our division staff go

to these meetings and interact with stakeholders. Academic meetings. There's lots of forums in which we are there or where you can come and speak with us.

But again, I think if there's a program ongoing and we can be helpful in directing that, that's what we're going to try to do.

DR. ERIKA TORJUSEN: And Dr. Caños, do you have anything to add from the device perspective?

DR. DANIEL CAÑOS: So I think Dr. Stein's comment with respect to our external engagement is really where we find a lot of value, right? So some of the questions that come in with those pre-submissions are questions that the community may have at large. And so those meetings in the pre-competitive space where we can discuss and provide our thoughts or feedback is many times far more effective and can address the wider stakeholder community questions. And so when those pre-subs come in, they're more targeted questions that we can, you know, kind of dig into and help out with. So I think the external stakeholder and our engagement has been very crucial.

DR. PETER STEIN: Just as another opportunity, is we have a biomarker qualification program both for CO8 patient-reported outcomes as well as biomarkers, which is many patient groups that are looking to find endpoints and measures that they can develop so that will facilitate drug development interact with us in that way as well. That's another opportunity.

DR. ERIKA TORJUSEN: So we have a little more than five minutes. So I just wanted to just check one more time about if there's another question online.

DR. AMY ABERNETHY: Okay. Can you hear me okay?

DR. ERIKA TORJUSEN: Yes.

DR. AMY ABERNETHY: So from a patient perspective, how does an individual caregiver or rare disease patient make sure their data is being collected properly, their clinicians are aware of the value of collecting specific information with respect to their disease progression, and their data is being shared to every relevant disease and/or investigator

that can make use of their information?

DR. ERIKA TORJUSEN: Would you like to start, Dr. Bryan?

DR. WILSON BRYAN: I actually think that patients and patient advocacy groups do have a lot of influence in this arena. And they need to use that influence more aggressively I think in ensuring that their data is available not just to the one scientist or one pharmaceutical company that they're working with, but generally available to everyone working in the field.

And I think that advocacy groups and patients do have the ability to have those negotiations and ensure that open access to their data, but it needs to be done up front when the natural history studies are just beginning. And so I think it can be done, and it's very important.

DR. PETER STEIN: So patient voices is crucial. And I mentioned the reorganization that we just finalized last year, part of which was the establishment of a patient science engagement aspect. And we've had public workshops last year and are

working to put together a few others as well this year, which are fantastic venues for engaging in that exact conversation. Right?

Dr. Abernethy had mentioned, you know, that information and clinical evidence that's generated from the medical devices that patients actually carry on them. And, you know, we talked about patient-reported outcomes and patient voice. And so I think it's very important for patients to talk about what is meaningful for them, how can they be engaged in the research, and also get information out of that research and make sure that there is that kind of the bang for the buck that the question was kind of alluding to.

So, you know, we'll look forward to hearing more from patients engaged in that conversation and in the workshops that we will be establishing within the early spring and kind of late spring and early summer.

DR. ERIKA TORJUSEN: Dr. Stein, do you have anything else you'd like to add?

DR. PETER STEIN: Just to underline

that when you're -- if you're interested in participating in a registry, which is a wonderful way of accumulating information that's defined and for a particular purpose, it's important to understand how that information is to be shared. Is it open access, or is it more restricted? And I think it's very important to assure up front that that information is appropriately curated, that there's appropriate respect for privacy, and that there are appropriate controls, but also that there is access for researchers for use of the data so that it can really be used to provide the various purposes that this important data can be used for. So there's access. It's not just for one company or one academic organization, but that it can be broadly accessed. And you can assure that by asking questions when your data is being entered, what are the access rules for this, what kind of researchers can utilize this information?

DR. ERIKA TORJUSEN: That's a great point. Thank you. And I think we have two minutes left, so I just wanted to get one more question in.

WOMAN: And very quickly. Gooey morning, everyone. As a patient suffering from myositis, interstitial lung disease, and pulmonary arterial hypertension, one of the things when you're talking about looking at the patient in your studies, natural or otherwise, the gentleman said at the first statement about -- I can't remember exactly, but it had to do with looking at the patient in its entirety.

One of the reasons why my treatment has taken so long is because I was exposed to secondhand smoke. And I would like to ask if at any point in any of your research -- I know I'm looking at the National Institute of Health -- environmental factors are taken into consideration. But I haven't seen anything that's dealing with the patient and indoor air quality. So that's either a question or a comment about how you're approaching that from your perspective. So I'd like to know if any of your research that you're doing addresses that factor.

DR. PETER STEIN: You know, I can't -- I don't have the answer to that question. I'll try to find out, but I don't have the answer. But I do want

to just point out -- I mean, what you've raised is exactly I think the importance of talking to patients. Because your asking that question might prompt someone designing a registry to say let's collect that information, let's make sure that that's something that we're going to pre-specify and assure that we are collecting information on second hand smoke, or other risk factors, or other environmental factors.

So your experience of the disease, what you see is impacting you is incredibly important in helping us inform how that information should be collected so we can answer the question that you are raising.

WOMAN: Yes. Thank you.

DR. ERIKA TORJUSEN: And I don't know if any of you have a quick point to add to that.

So I think at this point I just want to say thank you to our panel members for the insightful discussion, as well as our audience for their participation, as well as online. It's greatly appreciated. And also our panel members have kindly offered to stick around in the conference room for you

to be able to ask questions during the break, which immediately follows this panel. So if any of you didn't get to ask the panel a question, they will be available for the next few minutes during the break. Thank you all very much. Thank you.

(Break)

DR. TERESA MULLIN: Please take a seat, and we're going to get going with the second panel now. And, again, I wish you a very nice morning, and thank you and welcome to everyone in the room and on the webcast.

This is panel two on Natural History and Registry Data in Rare Diseases. So I think we're going to get into a little bit more perhaps technical depth. The first panel did a very nice job laying out the issues for us. And we're going to discuss them even more, because there's a lot to discuss.

I'm Theresa Mullin. I'm the Associate Director for Strategic Initiatives in the Center for Drugs and at FDA.

So I'm going to -- with me we have a fantastic panel today, so we're going to get a lot of

depth, rich depth and insight from these folks.

So first we have Katie Donohue. She is the Clinical Team Leader in the Division of Gastroenterology and Inborn Error Products in the Office of New Drugs and FDA Center for Drugs.

Jen Farmer, the Chief Executive Officer of Friedreich's Ataxia Research Alliance. Petra Kaufmann, Vice President of R&D and Translational Medicine at AveXis, It's a Novartis company. Anne Pariser, the Director of the Office of Rare Disease Research in the National Center for Advancing Translational Science at NIH. And Klaus Romero, Executive Director of Clinical Pharmacology and Quantitative Medicine at the Critical Path Institute.

Welcome to you all. I'd like to ask you now to please give a little bit more of a description of your background, each of you. And starting with Katie, what are some of your key takeaway messages to just sort of set the stage here regarding the value and sustainability and other aspects of registry data and natural history studies that you'd like to talk about in this panel?

DR. KATHLEEN DONOHUE: Sure. Good morning and welcome. I'm excited to be with you today. I work on developing treatments for patients with rare diseases, inborn errors of metabolism. And so this is sort of the front lines. And I'm really appreciative for the questions we've had from patients so far. I think they kind of ask the $64,000 questions. You know, what data do we need to collect, when should we start. And you're hearing the right answers. Start now.

And I think the key pieces of information that we need are -- do you want comments or just intros?

DR. THERESA MULLIN: I think you can start with your overarching messages or things that you want to come back and talk more about.

DR. KATHLEEN DONOHUE: Okay. So I think the first step is we believe so strongly in the importance of natural history data that the FDA has launched a Cures Accelerator Initiative that Theresa Mullin is actually leading and Klaus Romero is also working on. And it's a common platform. Right? So

we don't think that patients and their caregivers should have to be data scientists in order to help move the field forward. And so that platform is there to serve as a common infrastructure. And so we don't need to be an expert in how to manage the database, we've got some help. So I really just want to put that plug out there. And then in terms of what data we need to collect, we can circle back to that later.

DR. THERESA MULLIN: Okay, very good. Thank you.

JEN FARMER: Hi, I'm Jen Farmer I'm the CEO of the Friedreich's Ataxia Research Alliance. And my experience with FARA has largely been in the development of both our patient registry and our natural history study.

And so in 2005, I was initially hired to start a patient registry. And that was a patient-entered registry. So anybody was entering their own information from their home onto a web portal. And that registry was so valuable for us in really identifying where patients are, establishing better prevalence of the disease. And we were able to use

that registry for the next 15 years to help enroll research studies and clinical trials.

At the same time, several of our clinician researchers also started studies and clinical outcome measures. And FARA worked closely with those clinicians to parlay that into a natural history study. And so we've had a prospective natural history study with clinician-entered data going for almost 18 years now. Yeah.

And so, you know, as much as I can share with everyone what our experience has been with both a patient registry -- from my perspective that's patient-entered information -- as well as natural history prospective studies and sort of the role of the advocacy group in facilitating that, I'd like to be able to share those experiences with everyone today. And thank you for having me.

DR. THERESA MULLIN: Thank you.

DR. PETRA KAUFMANN: Good morning. My name is Petra Kaufmann. I am a neurologist. And for most of my career, I've been taking care of patients with rare neuromuscular diseases. So having taken

care of patients with rare neuromuscular diseases for most of my career, I decided a couple of years ago to leave the NIH where I actually was directing the Office of Rare Disease Research, which now Anne is heading so capably. But I decided to move to industry and work on gene therapy because I saw these transformative effects and thought finally as a neurologist I can do more than make a diagnosis and help my patients. So I'm excited to be here.

And I'd like to in particular share an experience that I had from going back to my time at Columbia University where I had the opportunity to work with colleagues from the Boston and Philadelphia Children's Hospital on a natural study.

At the time, there was really no effective treatment for patients. So we would see the patients with spinal muscular atrophy, and when we first saw them, they would be at their strongest and then just, you know, get worse. And asking the families at the time to participate in a natural history study was asking a lot. Because, you know, we were saying this is to develop better treatments, but

it wasn't so clear really when it would happen. Right? And they were the heroes, because they did this and came repeatedly with sick children to the centers. But it was then so gratifying to see how the data set, and then another one that we launched when I was at the NIH with NeuroNex, another second independent data set that actually helped to get the gene therapy to patients.

And looking back, I would like to share with you what are some of the things that I think were important and made this happen that also in now in my new capacity where I try to work with other communities on natural history data sets and studies, what are some of the things that could have been even better, to make this even more fit for purpose.

And I think, you know, the challenges are often funding. So in some of the diseases I have been working on, you know, natural history studies don't get easily funded by the NIH. Sorry to look at you, but -- and I get the challenge. When I was at the NIH, there was like thousands of rare diseases. And how do you pick one without getting, you know,

into this difficulty of justifying that choice over another. So I think that emphasizes the point of, (A), we have to look at this as a platform and make it efficient so that we can get to all the many, many diseases and the many, many patients and leave no one behind. And the second point there is that, you know, were lucky we got funded by the SMA Foundation. That made it possible.

And then the second point is to really make sure that the data are fit for purpose. So, for example, a study where patients come every two years and miss half of the visits.

Well, for practical purposes for drug development and for trial planning, that's not really going to give you what you need. So better to invest and focus on more frequent visit, on avoiding missing data and making it easy for patients to come (inaudible), you know, once (inaudible) where we actually, you know, got funding for patients to -- we helped them travel or we went to them even. So you have to think outside of the box to get high-quality, complete data. Frequent visits, especially in the

beginning, and as fit for purpose as possible. That can be done by talking early to people who have experience in drug development or, when available, even having regulatory -- like having interactions with regulators. I think that's some of the things that make the data sets useful, but also that, you know, could have been even improved upon. And I look forward to hearing more from the other panelists and share more detail. Thank you.

DR. ANNE PARISER: Good morning. I'm Anne Pariser. I'm with the Office of Rare Diseases Research at NCATS, NIH. So thank you for inviting me.

I've been with NIH for the past three years. But prior to that, I spent more than 15 years here at the FDA. First, actually, with the Inborn Errors Metabolism Team, and then started the Rare Diseases Program, started in 2010.

So I've been on the receiving end of natural history studies, been promoting natural studies, and now we are trying very hard to help people develop natural history studies.

So we do this through some of our

research networks that we have at NIH, but also I heard questions to this effect; where can patients go for some information on how to do this. So I'm just going to throw a shameless plug here for a program that we have. It's called RaDaR, which stands for Rare Diseases Registry. I've left some flyers at the desk here. But if you don't get a flyer, just Google NIH Rare Disease Registries, and you will find it. So I just have to throw that out.

DR. KLAUS ROMERO: Thank you. Klaus Romero, the lead for the Clin. Pharm and Quantitative Medicine program at the Critical Path Institute.

We are the ones leading, together with NORD, the Rare Disease Cures Accelerator. That was the effort mentioned by Dr. Stein in the previous panel. And essentially what that platform is intended to do is provide a home for the standardization and the integration of patient-level data across rare diseases. And this stems from the experience that we've gathered at the Critical Path Institute with the support of the FDA and being able to integrate data from registries, observational studies, and clinical

trials from industry.

And I want to make sure that this sinks in. Because there's always this perception that industry protects their data. I understand that, and I don't dispute that fact. But being able to integrate patient-level data from industry trials, not only the control arms but also the active arms, from the contributions that we've gotten from our industry members across our different consortia. We've been doing that for the past 15 years.

And we have a few examples in rare diseases where, for example, we have the largest integrated patient-level database from clinical trials in Duchenne muscular dystrophy. And in fact next Thursday we're going to have a meeting with the agency who are writing one of our submissions for the quantitative drug development tool intended to optimize clinical trials for that condition.

We want to be able to replicate that across rare diseases, and we want to provide a platform for those data to be integrated. So the data from the NIH, the data from industry, the data from

registries that the patients entered, but also the registries that are formally set up at the centers that actually see those patients in clinical care. That's the vision.

And so we are in the process of integrating, like I said, the data we already have from our consortia that deal with rare diseases, Duchenne muscular dystrophy, polycystic kidney disease where we have three of the largest registries already integrated, Huntington's disease, and then Friedreich's Ataxia, where we have a large integrated database of different data sources. So that's the vision. That's the intention.

And of course a lot of things were said in the previous panel and in the comments right now that really set up the value proposition for what we intend to do. Because it's not just -- you're absolutely right, having frequency of observation at a frequency that actually makes sense for clinical trials is important. But also having the long-term follow-up to understand the linkage between those frequently-measured things that matter in a clinical

trial versus what happens later in the lives of those patients. And not a single source can provide all those pieces of information. And that's why you need to be able to integrate all those components together. So that's me, that's the group I represent. And I'll stop at that.

DR. THERESA MULLIN: All right. So my next question is sometimes people talking about registries use that term almost interchangeably with natural history studies. So I'd like to ask this panel, since you've obviously deeply experienced, you know, how do you think and define those? Are they almost synonymous, or are they really rather distinct? And so how might you define them if they are a bit distinct, and what roles do you think each of those could or should play in supporting drug development?

DR. KATHLEEN DONOHUE: I tend to think of natural history as sort of a spectrum. And so sometimes it's our clinical understanding of a disease based on seeing patients and patients' direct experience of the disease. It can be sort of qualitative. Whereas a registry implies to me a

certain level of scientific rigor. You know, you're planning to collect certain kinds of information at certain timepoints. And so the level of scientific rigor with which the data is collected has a lot to do with how far it can take us.

JEN FARMER: And I think some of the comments from the first panel are also important to discuss, which is natural history studies specifically can be retrospective or prospective. And so I think it's important to think about what type of natural history study it is, what the scope of the study is going to be.

When we started our natural history study, it was focused primarily on the neurological aspects of the disease over time realize you know, the cardiac aspects of this disease and the endocrine aspects of this disease are also important. And so we were able -- that natural history prospective study, we were able to add additional outcome measures and expand the focus of the natural history to be beyond one system into multiple systems.

And so sort of going to your point

about fit for purpose, one nice thing about some of these studies is you can start with one purpose in mind, and then grow and expand from there. Which is I think why sometimes the terminology gets confused. Right?

DR. PETRA KAUFMANN: I agree. I think that some of the nomenclature is really historical. We have to think about step back and say what do we really want. You know, we all want to make sure that these innovations that are now upon us, and we are opening almost like a new era of medicine with really targeted treatments, that these innovations can benefit as many patients as possible as quickly as possible.

So if it takes us like ten years for each rare disease to do a natural history study and enormous resources, then we will not get to everybody. So I think registries, whatever you call it, or natural history studies, the words come from the different groups that maybe started them. Sometimes registries are started patient groups, and they are a very grassroots, maybe low-resource endeavor. Natural

history studies sometimes are started by academic investigators who play another role in the ecosystem or they are started by industry. What matters is that the data are shared and that they are all collected with the same purpose in mind and that they think about that purpose. So I don't really know that that distinction in the long run will hold. I think the goals are important, and they are shared. And like you said, there is different levels perhaps at the beginning versus when you get closer to developing the treatment. But it should all be as integrated as possible, and patients should demand that the data are being used for direct development or treatment development.

DR. ANNE PARISER: So how we have been defining these is -- registry is a very broad term. It's really any organized collection of data, usually observational data. So there can be many different types of registries.

A natural history study, the intention of the natural history study is to really define the disease, define the entire scope and spectrum of the

disease.

So I think someone was mention this in the last session, but a registry could be for example a communication registry. This could be the first effort to try to organize the community, and you could be collecting some very simple data, people's emails and maybe how old they are and do they want to be contacted or not if there's research. And you can go to the total opposite end of the spectrum and be collecting very detailed clinical data that could have MRIs and biopsies and genetics. And then there's everything in between. And as mentioned, this can evolve over time. You may start one place and then start to go in a different direction or broaden out from where you were.

And I just want to emphasize these are all useful, and it can really depend on where you are in your research program. And the first step in a research program is often a very simple communication registry that someone can operate off their home computer off a spreadsheet for really no cost at all. And many times we've seen that serve to really unite

the community and really get a program together.

So all efforts are good. It's about being very organized in the way that you do it, defining your terminology, be transparent, and share.

DR. KLAUS ROMERO: Yeah. I think Anne hit the nail on the head. In the world that I operate, I don't like to have terminology get in the way of progress. So because the intention of the work that we do is so we integrate all data sources that are relevant, it really doesn't matter really to me if you call it, oh, this is a patient-entered registry versus a formalized registry in a center of excellence versus an observational study and clinical trials from industry. Sure, I understand the distinction between those if you want to categorize them for funding and for publications, all those things. And of course the clinical trials from industry that are intended for driving regulatory discussions.

But in the world that we operate, we want to integrate all those pieces of information. Because it's all those pieces of information that give you the different angles from which to approach

starting to generating the answers as to, okay, what are the sources of variability, what are the measures that actually matter to the patients and objectively to drive drug development decisions and capture drug effects, determine baseline severity so that we can set up the inter criteria for a clinical trial, which again, relates to the source of variability of disease progression and drug effects. The placebo effect, especially in certain neurological conditions, that is absolutely critical. You need to understand the onset and magnitude, duration, variability. And that's going to become critical when you want to optimize clinical trial design.

So I just want to echo some something that was mentioned in the previous panel. Sure, using and optimizing control arms using quantitation and looking at disease progression is awesome, but that's not just the only thing that comes out of integrating and quantifying the diseases themselves, the many diseases themselves, because that's what gives you understanding of all the aspects that really matter when you want to design a clinical trial. Because

what's the name of the game here? If we want to accelerate drug development for rare disease, we need to provide industry with the tools so that they can design optimal trials. Because if the value proposition for industry is going to be I have too much uncertainty, that gets up the chain of command in their dealing with other therapeutic areas where they may say, well, mine certainly is not that great.

So the name of the game is really understanding and quantifying uncertainty so that you can deal with that uncertainty and you can provide a value proposition with optimized clinical trial.

DR. THERESA MULLIN: Thank you, Klaus. So I've been hearing some people talk about having your registry data be fit for purpose. Okay? So I'd like you now to talk about best practices that you've seen and what you've encountered in registries that you've had to deal with or look at, or maybe have developed.

And then also for those of you who've looked across areas, just what are weaknesses that you've seen that have made a registry less than what

you'd ideally like to see for fit for purpose?

DR. KATHLEEN DONOHUE: So I think I want to start with the question that one of our patients asked, which is how can I make sure that my data is going to be used by the people who need it. And the answer to that is something called a data use agreement. Klaus Romero's group is really good at this. They have a lot of experience with negotiating these. And getting this right from the beginning can save you a ton of time on the back end. So wherever you are in developing a registry, taking some time out to think about what am I going to ask patients to sign in terms of how we're going to store their data, who we're going to share it with, and how that's going to work. So getting that right really helps. It's sort of like the cornerstone of your registry. So that's the first step.

And then the second step in terms of what data to collect. I can touch on some broad categories, but this is where having an epidemiologist who is an expert in how to do these kinds of observational studies can really help to future-proof

your registry. So, you know, you may be starting out with just patient contact info, but if your vision is to grow it eventually into something that could help inform the design of clinical trials or even serve as an external control, well, you're going to need to anticipate some of those needs.

And so it's things like how are patients coming to attention. Right? That's changing over time. So it used to be you had to present with, you know, the canonical symptoms of a disease in order to get a diagnosis. The diagnosis may have been clinical for a lot of patients. But now we have patients who get diagnosed because of genetic testing once an older sibling is diagnosed. And so the natural history of those two patients is going to be so different. We have to be able to understand that.

So how are patients coming to medical attention? What were the results of those genetic tests? Do we have other biomarker tests that are getting done, and can we capture the results of that? Units. It's so boring. But if units are different, this creates such a headache. Like, thinking about

that really matters. And epidemiologists can help us do that.

And then I think the next area where there's a lot of opportunity for academic clinicians who care about patients to sort of move this forward is writing guidelines.

So if there's a guideline that says we need functional testing every year, whether it's lung function or a six-minute walk test, whatever that functional testing is. But we need some sort of disease monitoring at regular intervals that's standardized and can be done all around the world in the same way. And we're going to use the results of that testing in order to drive some of the supportive care, whether that's swallowing tests to inform when we're going to put in feeding tubes, or walking tests that might be able to inform when we're going to need to add in assistive devices like walkers or wheelchairs or things like that. So all patients are getting care of some kind. And standardizing the predictors for when patients are going to need that and how they're going to get that is really helpful

because that standardization is powerful scientifically. And then it creates a shared infrastructure around the country and across the world for how often those things are getting monitored.

So it's one of the reasons why the oncologist basis had so much luck with -- and it's not luck, it's really hard work -- with natural history controls, is that they've got guidelines saying you've got to image these patients at pre-specified intervals to look for progression, and that's happening in the same way all across the country and globally. And that's really powerful information.

And then lastly, tying that functional testing, whether it's imaging or walk tests or lung function, tying that to the clinical outcomes that really matter to patients. Right? You know, I've never had a patient come and talk to me and complain, doc, my FEV1 is low, but they tell me I can't walk up the stairs. Right? So tying it to how a patient feels is another really powerful thing that registries can do. And then we don't have to run the clinical trial all the way to a clinical endpoint, which is

hard in rare diseases, we can use that functional data. Because we already know from the registry that it predicts the clinical outcomes that really matter for patients.

JEN FARMER: Well, just to underscore your point of getting proper consent and data sharing up front, when we started our clinical outcome measure study in 2004, our consent was not broad enough for the data sharing that we eventually needed. And by the time we realized that, we were more than 500 patients in and needed to go back and re-consent everyone. Fortunately, people were coming back annually for visits, and so we were able to eventually accomplish that. But yeah, lived that one.

So, you know, we set out on our clinical outcome measures study so that we could help support clinical trials down the road. And we were fortunate to get some good advice as well, which was that the data needed to be collected in a rigorous way, that we needed standard operating procedures, case report forms. We needed a robust database that would handle queries to make sure that the data was

being captured correctly and in a very standardized way. So I'm fortunate for that, because we made that transition to an electronic data capture system with data oversight only two or three years into that clinical outcome measures study. So that was -- you know, I did not appreciate all of those things when we got started, but I'm very grateful for them because we were able to then use those standard operating procedures and case report forms in future clinical trials.

And we only have around eight centers in the United States that are collecting this data, but those sites are now kind of clinical trial-ready sites for FA clinical trials. And that was also one of our goals and objectives.

But one of the challenges with only eight sites is the burden is on the patient to participate and be in the study and contribute data. And so we couldn't collect data as often as you might like in a clinical trial. We couldn't ask people to come back, you know, once a month or every few weeks. And so we settled with annual visits and being very

systematic and collecting the same data every single year. And that really has helped over time figure out which of those measures are going to be the most sensitive to change in a particular subgroup of our population. And we're now at a point where all of that has come together to help us with clinical trial design.

But what we don't have is really what that placebo response looks like. And we learned that the hard way as well in doing some of our initial clinical trials. Those first few trials we did, we observed the placebo response. Could have not anticipated it from our natural history data or our clinical outcome measure data. And, you know, realized that, okay, this is the next gap we really need to address if we're going to use this to help us design better clinical trials.

And we've been able to take our outcome measure study and natural history study and combine that with the placebo data from four clinical trials that have been completed. And that's the basis for this FA-integrated collaborative database that's now

at C-Path to help us understand that placebo response and hope they design better trials in the future with that data in hand.

And so I guess the point I'm making is you have to be flexible over time. you have to realize that, you know, you're going to make some progress in certain areas, and then you're going to learn there are some gaps that you still need to address. And being able to kind of maneuver is important.

And I was humbled early on. Sharon Hesterlee, a colleague, told me about ten years ago -- I was so excited. You know, we had our clinical outcome measures study that was now becoming a natural history study. We were using good data collection process. We had all this in hand. And I'm like, this is great. We're done. And she was like, no, no. Sorry. You're not going to be done with this. You're never done with this. And I was really deflated. But I understand a lot of what she was saying, and I'm really glad she told me that then so that we started thinking about this, about how we're going to continue

to meet the needs.

And, you know, now I'm thinking about when there are approved therapies, how this registry helps us understand the evolution of the natural history in light of therapies in the disease.

So it really is a process. And I think understanding that and knowing you're not going to tackle everything at once is really important. But trying to set something up that is flexible and adaptive over time is critical.

DR. PETRA KAUFMANN: Lots of great points made already. So I would just add maybe one thing. So we are fortunate because of all the work of FARA and being able to access the data through the Critical Path Institute to build on that strength, which makes a big difference when you try to bring gene therapy to a real disease. So now there is, you know, thousands of rare diseases, millions of patients waiting for these kinds of treatments. So how can we make sure that -- I think that would be an important aspect, that not every endeavor is reinventing the wheel, but that we can have almost like a platform

approach, that we can use lessons learned from diseases where there is already more drug development. And also think about perhaps outcome measures. Maybe some functional measures don't need to be redesigned for each subtitle of a disease or some patient-reported outcomes or quality of life measures could be used or borrowed sort of from other indications. Because I think if you're having sharing and having some platform approach to this will help us all get there faster.

And I think I did a great job teeing this up for you, Anne.

DR. ANNE PARISER: I mean, there's been a lot of great points made, so I'll just maybe hit on two.

At the end of the day, we really need to end up with something that's interpretable. So any reasonable, regular investigator or patient group could take this data and really know what it is that you're talking about. And so you need to spend a lot of time on the really tedious, boring parts of really defining that data and make sure the metadata is very

understandable and is transparent. There's nothing worse than seeing a year's-long collection and at the end of the day not being really able to figure out what they meant.

I'll give you one example we had for a GI disease many years ago. We were using the medical term dysphasia. And to some people that meant pain with swallowing, to some people that meant I couldn't swallow, some people meant choking, some people meant food impact. And so we had all this dysphasia, and nobody really know what that meant. And that's really terrible to be looking at at the end of the day and not being able to really understand what was intended.

And then the second one, it's really important to get all the critical stakeholders there from the beginning, and especially the patient groups, but the investigators as well. It's important to investigators. Is it necessary or is it important to patient? But you want the spectrum represented there.

And for the patients especially we think -- I heard this from Jen. Again, these go on for years. And to really burden the patients with

some of these just really can burn out your community. So just make sure that when the protocol is together, you spend a lot of time deciding what exactly you want to collect. You can't collect everything. So some tough decisions have to be made. But we want people to be able to stick with this over time so that we can really understand the disease.

DR. KLAUS ROMERO: Yeah. I agree with everything that has been said. The one thing that I would add to sum up what is truly needed if you want to succeed in setting up a registry or an observational study is to essentially think about the following things. The consent, and set up the consent in a way that doesn't inhibit and stifle innovation and that ensures that the data will have its maximum impact beyond the primary analysis that is intended. And that's something that is critically important to patients. They don't want to see their data die with the primary analysis. That's a message that we have heard loud and clear, not just in rare diseases.

Think about how to set up the structure of how you are going to collect and what you're going

to collect. And that's a question about standards of data. And this doesn't mean that all of the sudden we're going to start telling people what to do. That's not the case. But what we're saying is that whatever you do, this is the kind of information that you need to collect so that it becomes ensured that whatever you collected becomes reproducible.

And there's a big lesson from industry to learn here, because as my colleagues from industry well know, as of December of 2017, CDER mandates that every single data point from all the studies that industry submits to the Agency have to come in this forum called CDISC, the Clinical Trial Data Interchange Standards Consortium standards. That set of standards were designed for that kind of purpose.

But if you think about those standards, that's like a coin with two sides. One side is the control terminology. And that's where the NIH is absolutely critical for that so that you call sex the same way. And that's like the simplistic sample of a very intuitive, binary variable. Well, my FDA colleagues know that when we started doing this in

Alzheimer's disease, we started with nine clinical trials from industry. Nine different ways, I kid you not, of collecting sex. As I told people, that's the best example of misuse of creative time, but that's the reality of things. And that gets even more complicated when we start dealing with biomarkers and with outcome measure scales and patient-reported outcome instruments and all that stuff. So that's critical, the control terminology side of that coin.

But then there's another side of that coin, and that's the data structure. And that's where people get really confused and they don't care, and it's boring, and nobody pays attention. That's equally important, because that's what sets up the data platform and organized in such a way that it becomes interpretable.

So even though CDISC is not a mandate of observational studies or for registries, just the control terminology piece, if people were to adopt that just from the bat, that would solve a lot of the headaches that we have to go through whenever we get our hands on data and we have to standardize every

single piece of data. So that's another important point.

And we're here to help. If you want to talk to us on how to annotate your case report forms and think about how to set up a structure of a database, we would be more than happy to have that conversation.

DR. THERESA MULLIN: Thank you. And could I just ask Anne, is this something that the information on radar, does it also speak to the data standards? So if people wanted to understand what they might want to do today, could they get some information about that at the website that you've mentioned?

DR. ANNE PARISER: Yes. We do have that on the RaDaR website. So RaDaR is actually -- it's set up -- and book isn't the right term, but it's set up deliberately in a very walk-you-through-this manner. How to get started, we have downloadable checklists, we have spreadsheets, we have referrals to things like fair data practices and some more of these data management terms.

So I would really urge you to go take a look. We built this with the patient community in mind. We wanted people to come to this new, not being database managers or architects, and be able to set this up on their own. And you can also come ask us for help. We would be glad to.

DR. THERESA MULLIN: Thank you. One more kind of question I would like to just ask our panel, and then I want to turn it to the audience and the people on the webcast.

In earlier discussions we talked about sustainability as an issue. So if you have any more to say about either sustainability and/or the international aspect, because rare diseases are ones where in particular you want to try to take a global approach, if you can, to try to capture more of the community with that disease. So if you have anything you want to add about those or another point to make before we turn to questions, that would be great.

DR. KATHLEEN DONOHUE: I want to hear your questions.

JEN FARMER: So sustainability is a

very big issue, and it's something that our organization made a commitment to early on in making sure that, you know, at least a certain portion of our resources were being put towards the sustainability of these resources as they were being built. But it does limit what we can do as well, because our resources are not unlimited, and usually in the rare disease space, our advocacy organizations have very limited resources. And so that does dictate what you're really able to do. And especially on an international level the resources that are required to have a registry that is compatible with every language that you're going to need is very difficult. That's a really high bar. And also having clinician-entered data as well that's going to be collected internationally is challenging just in terms of all of the different rules around privacy and data handling across different countries becomes really challenging.

And so, you know, again, similar to the advice that came out earlier, based on what you can invest in, you know, scope it for where you are. But I think it's important to remember that this is a

long-term investment for organizations, especially if it's an advocacy organization that's taking on the development of these tools and resources. It's not a one-year project, it's not a two-year project; it's a long-term project. And plan for it that way. And that's I think a very important point.

DR. THERESA MULLIN: Okay. Thank you, Jen.

DR. PETRA KAUFMANN: So these kinds of data sets are really for the benefit of patients. And the patients are in there for the long term, and therefore I think they are probably the best and most sustainable sort of guardians of these, with the support of other partners who need them. And having the patient groups guardians in my experience is also easier in terms of international collaboration, because there are different privacy laws and regulations in different regions of course, as we all know. And different institutions who may become guardians of data for reasons that -- you know, if it was started by an investigator there -- have greater difficulty kind of getting through these regulations

and rules. And therefore I think when patient groups are involved, that's an advantage. And also the data don't necessarily have to move across jurisdictions, but there can be, you know, sharing of data sets potentially that could make that easier.

DR. ANNE PARISER: Very, very quickly. Try not to go it alone. There are many groups out there now and the rare disease umbrella groups who have set up platforms, a platform being a durable infrastructure that can support multiple studies. So there are several out there, and I would just urge you to look around and reach out.

DR. KLAUS ROMERO: And just to understand the cultural aspects. Because we know that there are clusters of rare diseases in different geographical locations. And understanding the cultural aspects when you want to get in and run an observational study and start a registry, that is critical.

DR. THERESA MULLIN: Thank you very much. I see we have a number of people. And I wasn't looking, so I don't know who was up first. So I will

start with -- just if you don't mind, and go one by one. Yes?

MARIA PICONE: Hi. Thank you. Maria Picone. I'm the CEO of TREND Community, and I also have a daughter who has Prader-Willi syndrome.

And I just wanted to expand upon Dr. Pariser's point about the importance of educating the community as our understanding of our diseases evolve. My daughter last year was also diagnosed with narcolepsy. And I know that questions have been added to the registry about narcolepsy and also cataplexy. But I wonder, you know, do the people who are completing the surveys understand what is cataplexy?

And I know, Jen, when we worked together and pain emerged as a very sort of maybe not underrecognized symptom, but something that people weren't associating with, you know, as related to the FA. You know, how do we educate our community members so that not only are we collecting the right data, but that people know how to answer those questions early on.

DR. THERESA MULLIN: Who would like to

take that question? This goes a little bit to I guess the sort of point that Anne Pariser was making about the terminology that might make sense to a clinician after years of training.

JEN FARMER: Yeah. So, I mean, one is to have a data manual, publish it, and put it up on the web and just be extremely transparent. But we've also seen people put video clips and things on their website. I think most of information sharing now is via the internet. And there are many tools that are very accessible to patients.

DR. KLAUS ROMERO: And understand from the industry perspective what appetite there is and what interest there is in tackling that specific aspect of the disease. Because that's going to help you understand what information you want to prioritize collecting over others. So the bottom line message is not approaching that as a truly intellectual exercise, but have a clear end in mind with practical applications. And that's where connecting with industry -- and patient groups have that unique ability to have that bride with industry.

DR. THERESA MULLIN: Thank you. Yes?

MEGAN O'BOYLE: Thank you. My name is Megan O'Boyle. I ma the PI for the Phelan-McDermid International Registry. But first and foremost, I'm Shannon's mother. And Shannon has Phelan-McDermid syndrome.

I did what most groups do when you start a registry; I started from scratch, I asked questions. We asked stakeholders for help, researchers. Even Dr. Pariser was at FDA when we started our registry. And we tried to do everything right, and we did a lot of things wrong. I have whole presentations on what we did wrong. And I'm watching other brand-new genetically-found diseases do the same thing over and over again.

So I just want to put in a plug for RaDaR and also NCATS has the toolkit for drug development, which takes you from the registries to post-market. Had we had RaDaR, I would not have a presentation on all the mistakes we made. The overburdening, the too many questions. We had the knowledge to have IRB and things like that that other

groups did not.

I just want to make a plea. You all don't have to answer this. But for anybody who has not started a registry, there are platforms that exist. And some charge you money. And you all use the word investment. I understand that. It's taken a huge investment, half a million dollars for our organization over the years, for very little return in many ways. And I really believe that rare diseases in particular should not have to spend all their research money on collecting data that is going to be used by other stakeholders.

And the other thing is there are also free options. And that means you're giving up your ownership or stewardship of the data.

I have a huge problem with rare diseases collecting data from the families they trust and having a platform sell it to biotech and make millions and millions of dollars off of selling my data. I don't mind if somebody makes millions of dollars, but one, be transparent with me, and two, share the rewards.

So I think everybody needs to step back and think about this sense of patient ownership. Again, the rare disease community more than anywhere, this is a sacrifice. Our families, to answer a survey, they're giving up a meal or a shower. You know, special time while their kid is in school. And I really think that there should be some respect to the patient community for that. Thank you.

DR. THERESA MULLIN: Thank you.

ERIC HARTMAN: Hi, I'm Eric Hartman. I'm the director of advocacy for the Choroideremia Research Foundation. And we are fortunate enough to have two gene therapy trials underway, and a third about to begin. One of the challenges that we have found in our disease is one in 50,000, supposedly 6,000 in the United States, is we believe 70 percent of our patient population hasn't been genotyped to actually know they have that disease. So our challenge right now is our known patient population, we may only have 30 percent. But on a global basis, we are trying to find our patient population. We started our own patient registry, but it's just a

contact registry. And we are receiving huge pushback from -- you spoke earlier about the international invocations, the cultural problems, because we are based in the United States, of this huge prejudice that seems to be out there about our data being stored here and whether or not it's GDPR-compliant, which it is. But are there -- we're struggling. And we've got patients all over the world that we're trying to find because we have these potential treatments. One is already in Phase III and all the patients have been treated. So we're trying to locate those patients and we're trying to find some means of fighting against the perception of non-GDPR as opposed to needing to set up registries globally in a more regional basis. And I don't know if you guys have any suggestions on how to fight that.

DR. THERESA MULLIN: Anne?

DR. ANNE PARISER: Well, one suggestion is to try to find a local champion within country. You don't have to keep the data all in one place just so long as you're interoperable and you're able to share. That's one thing that you can try.

DR. KLAUS ROMERO: And be very clear about the fact that if you are indeed GDPR complaint, get that message out there. Don't be shy about tooting that more.

JEN FARMER: Yeah. We encountered very similar challenges when reaching out to the International community and trying to help them understand why being in the registry was important. There were just very different understandings around what the patient's role is in research even. And we have been spending more and more time building relationships locally with individual patients, patient families who can be spokespeople, who can speak the same language and really share the experience and what the goal and the objectives are of these registries, and that it's not just a U.S. thing or a FARA thing; that this really is an international effort.

We rebranded our registry. We changed the name so that it's not FARA at all. And we brought our international partners onto the governance and oversight of the registry as well. And so it's been a

lot of bridge building with the international community so that they feel confident in the registry and they also understand their level of ownership and involvement in that resource for the international community. But it's a challenge.

DR. THERESA MULLIN: I think we might have time for one more question. And I'm going to ask maybe if we take a webcast question. Because those in the room can follow up with the panel I think would be a way to go. Are there any questions on the webcast?

DR. AMY ABERNETHY: Yeah, sure. How does the Accelerator help the sustainability, international aspect, and data standards?

DR. KLAUS ROMERO: Works for me. Yes. Great question. So in terms of the data standardization, what we do every single time whenever we set up a data platform of any kind, and this one in particular, is we do an extensive remapping and standardization and curation of the data. That's for existing data that are contributed into the platform.

Now, the more important thing is that we want to establish this learn and confirm

(inaudible). So as we start integrating the data, we will find gaps with the standardization and quality of the data, the reliability of the information. We always communicate that back to the contributor in a positive way. We're not pointing fingers. It's just the reality of the beast. But that's a very powerful tool that the contributor can then use to then prioritize their funding to make sure that they collect information that is relevant in a probably different way, et cetera. So that's about standardization.

And the other part of the question was about sustainability. Well, we don't monetize the data. We don't -- we're not charging for data accessibility, we're not going to make millions out of sending the data. That's not the intention. The impact of what we do is that in generating the solutions for drug development, quantitative models that will help you optimize clinical trials aside, all those tools will also be publicly available once they get endorsed by the regulatory agencies.

So the sustainability is essentially

tied to the fact that the acceleration of drug development is going to be realized and the patients will have access. And through having the access, then they can have discussions about further funding, research in that particular area.

And there's another part that I forgot, but I think we're out of time.

DR. THERESA MULLIN: All right. I want to thank our panel very much, and thank you all. And so with this we'll close for lunch I guess.

(Break)

DR. NINA HUNTER: I am Nina Hunter. I am Director in the Office of Clinical Policy and Programs. And I am delighted to introduce Dr. Stephen M. Hahn, who was sworn in as the 24th Commissioner of Food and Drugs on December 17th, 2019.

Dr. Hahn is a dedicated clinician, having trained in both medical oncology and radiation oncology. In his previous leadership roles, he has always carefully balanced executive management with clinical time to continue to serve oncology patients, his true passion.

Prior to joining the FDA, Dr. Hahn served as Chief Medical Executive at the University of Texas and the Anderson Cancer Center, a facility that cares for more than 140,000 patients a year.

Before joining MD Anderson, he served as chair of the Radiation Oncology Department at the University of Pennsylvania School of Medicine from 2005 to 2014.

Dr. Hahn earned the rank of Commander in the U.S. Public Health Service Commissioned Corps while at the National Institute of Health's National Cancer Institute, where he also completed a fellowship in medical oncology and a residency in radiation oncology. He also completed a residency in internal medicine at University of California San Francisco. Please join me in welcoming Dr. Hahn.

DR. STEPHEN HAHN: Thank you, Nina, very much for that introduction. And it's really terrific to be here today. This is very meaningful. Of all the things that Nina said, one thing she didn't is that my wife and I are parents of four children. And nothing is more important in life. We just had

our first grandchild. And I know that what we're going to talk about today is very much close to families and of great importance to the American people. So me it touches home in many ways, but perhaps most importantly, personally.

So thank you very much for joining us today. I hear we have a great turnout, both in this room and online. So thank you very much. And of course this coincides with the commemoration of Rare Diseases Day. It is really terrific to see such a broad group of stakeholders and innovators, drugs and product developers, clinicians, researchers, and most importantly, patients and their families.

Together, by engaging in conversations like these, by sharing information, and frankly, by listening to each other -- and that's FDA's number-one job here, is to listen to you, the stakeholders in this room -- we can more effectively collaborate in support of our shared goal, which is the development of new and better treatments for rare diseases.

I spent a good portion of my career, as Nina mentioned, researching and treating cancer, and

in particular treating patients with sarcoma. This challenge of rare disease is something that's been central to my work as a clinician and very important and has personal meaning to me. And that's because many cancers, and nearly all of the pediatric cancers, are themselves rare diseases. And this has given me an opportunity to witness and in some cases be part of the extraordinary developments that we're seeing in the medical product sphere to treat patients with rare diseases.

But just as important is the impact that our work together with patients has helped us to formulate and reinforce some of the most important priorities for the FDA in the upcoming year. We have defined three priorities, and I think these priorities are very, very important for this particular group, and I'll try to explain why.

The first is to promote choice and competition through innovation. Everything we can do to increase the innovation, particularly for patients and families with rare diseases, would be very, very welcome and important to us.

The second is empowering the American consumer. That includes patients as well as consumers of over-the-counter and other medical products. And finally, using data, empowering data, unleashing data so that we can better get to the answers that we need to get to. And I think that's one area that's particularly important in the rare diseases. Because, as you know, these diseases are rare. We don't have the liberty of performing large-scale clinical trials to get to the right answer. And so how we use data in very fruitful ways will be important to advancing the field. And I am encouraged by the impressive advances we've seen and the innovation around the country and the world for rare diseases.

Consider that also since the passage of the Orphan Drug Act in 1983, FDA has approved more than 800 drugs and biologics for rare disease indications. Last year alone the Agency approved 22 novel drugs and biologics with orphan drug designation.

I'm going to list off some statistics which may or may not be interesting to you. But the

point of this isn't to brag about the Agency, but just to highlight that these innovations are coming fast and furious and that we need to do more and we need to be cognizant and that there are a lot of unmet medical needs out there. And hopefully what's happened in the past couple of years can accelerate even more.

To break down the numbers even further, CDER, the Center for Drug Evaluation and Research, 21 of 48 novel drug approvals last year, or 44 percent, were for orphan products. And in the Centers for Biological Evaluation and Research, CBER, 20 percent, or one in five of the biologic approvals were orphan product.

Now, this is an area that I want you to pay very close attention to in the next couple of years, because we will see dramatic increases in the number of biologics that will come across the playing field for all of us. And these are where I think we'll see some major advances in rare diseases.

And some specific examples. We approved the first triple combination therapy to treat patients with cystic fibrosis, the first treatment for

neuromyelitis optica spectrum disorder, a new treatment for tenosynovial giant cell tumor, a tumor that I had seen in practice myself, and a gene therapy to treat pediatric patients with spinal muscular atrophy. And of course we've all seen how that has affected children with this. And it's just a remarkable event, something that I hope we'll see more of in the near future.

Last year we approved also 76 rare disease indications, which means the drug label that we have is expanded for many new uses to treat patients with rare diseases.

We've also seen advances in medical devices, not to forget that important part of the medical product sphere. And since 1990, FDA has approved 77 medical devices, including the last three for orphan indications. Last year three for orphan indications over the Humanitarian Device Exemption Program.

So what do these numbers really mean? That we live in a time of unsurpassed innovation, of rapidly advancing science, that is really I think

unprecedented around the world. And it isn't just wishful thinking to say that we will find treatments and potentially cures for many rare diseases that have significant unmet needs, it's because we are spending a lot more time and energy across the country and the world with researchers and innovators in developing these products. But it also means, as I said, that we have much work to do, and we cannot step back from these efforts.

At FDA we are working hard to support the innovation that we are seeing across the world and to speed the development and regulatory process. We also welcome your input into how we are doing and how we can further support this innovation. And I've spoken to a few stakeholder groups, and I know that there are concerns about this, the ways that we approach things, maybe some of the processes we have. And we do want to hear from you, and we do want to adapt to this changing world that we see.

The Agency has already done quite a bit to lower regulatory burdens for innovators. And I think this is important because we need to increase

competition and choice for patients and providers, and we need to provide the necessary support and information about our regulatory requirements; that is clarity about the regulatory schema. We need to continue further along this path.

It is also important to emphasize that we are always going to balance speed and efficiency and the real need across this country to get therapies as quickly as possible to people with our gold standard of protecting safety and efficacy. I do not think that one precludes the other; I think that we can do both. I think the arguments that as we move forward with efficiency and speed that we give up on our gold standard are untrue. And I look forward to working on ways that we can process improve so that we can get to the absolute best place in approval of these products. We will always continue to look for ways to improve. And again, your input will be really important for that.

The other big part of this that I wanted to mention is the essential role of you, advocates, as well as families and patients with rare

disorders. Another one of our priorities, as I said, is particularly relevant here, and that is empowering the American people. That's giving information to people about the products that we regulate, but also hearing back from people about what they need in terms of medical products, both for themselves and for their family.

To effectively support the development of treatments and to inform our understanding of any given rare disease, patients must be involved in the process. And I look forward to working with you to see that happen more and more. Because what matters to patients and families should matter to us as regulators of these medical products.

The FDA has increasingly incorporated a patient-focused approach to its work, adding a number of effective ways to include the patient's voice in evaluating and developing treatments for disease, such as the patient-focused development initiative, our Rare Disease Patient Listening Sessions, and through public meetings like this one.

But what I can promise you is that in

addition to listening, we will do the absolute best job we can and we will uphold our faithfulness to the gold standard of assessing the efficacy and safety of the products that we look at.

I only want to end by talking about the power of data. This is the third priority that we've established for the Agency for the upcoming year. And one particular benefit that can come from the involvement of patients' concerns and patients' voice is an extraordinary powerful resource for finding answers; and that is using rigorous data.

Ensuring the availability and high quality of data enables us to maximize the extraordinary potential of science, better support the development of new medical treatments and cures, and increase the knowledge of patients and consumers that have to make informed decisions about FDA-regulated products.

We must, for example, make much more effective use and integration of patient-level data such as patient-reported outcomes, electronic health records, the data from clinical trials, medical

studies, and patient registries. And we have to have a better and more robust way of integrating all of these data sources into our regulatory decision making process.

Terrific work is being done at this Agency to modernize our approach to data. Much more needs to be done. And we welcome your input into helping us do that.

So we will continue to do everything we can to attain more and better data for the work that we're doing, to be more proactive in gathering these data, and to be more creative and thorough in our analysis of it.

I want to emphasize one other point. And that is that we will use the data that exists to make the absolute best decisions for the American people. I promise you that as FDA Commissioner, that we will always adhere to the science that we have. Sometimes that means we will make a decision that we later need to revisit because additional data are available. This is the sign of a learning organization. This is the sign of a health

organization. This is what we want FDA to do. And so I want all Americans to understand that we will be a learning organization, that we will look back at the decisions that we make, and we will use all the time and the most up-to-date data that we have, and science, to address those decisions and make the changes that are necessary, again, in the best interest of the American people.

So I end my remarks this afternoon by citing the extraordinary advances in research. I come from a research background, and it's so terrific to see that. I want FDA to continue to be the enabler of that research and innovation. It is an exciting time for rare disease product development. And with your help, I know what we can do even more.

The challenges we face -- scientific, economic, and medical -- are significant. We are all resource-constrained. But there are ways around these resource constraints if we work together and we use data appropriately. Some of this relates to the essence of rare diseases; the small size of the populations which can pose a significant challenge to

clinical research. This is the tragic irony. Because as you've heard time and again, the underlying challenge of rare diseases is that while they are rare individually, collectively they are not. There were 7,000 of them listed by us as rare diseases. Our priority at FDA is to help find and support the development of new treatments and cures -- yes, cures -- for rare diseases, and to do everything we can to advance this agenda through approvals, new and creative trials, funding of new research programs, and in other ways. And with your help, I believe we'll get there.

Most importantly, we look forward to listening to you. We will incorporate your input into our decision-making. We want to work with you and all of you who are here today to support rare disease product development. Together, we can and will find the answer and overcome these challenges.

I want to thank you for your participation today. It is so meaningful for the agency. And anything we can do to help you and your groups, your patients and your families, we are here

to do that. Thank you very much.

DR. NINA HUNTER: Thank you. That was a wonderful way to kick off the afternoon. And now we will transition to a panel with our FDA Medical Products Center Directors. If they could come up to the stage, that would be great. I know we're running a few minutes ahead of schedule, so they might not all be here yet. So while they are gathering, I just wanted to take a moment to thank all of you who are here today and also thank everyone who was involved in planning today's meeting. Thank you.

DR. JANET MAYNARD: So I am Janet Maynard. I may not have a microphone that's on. No, it sounds like it's on. Great.

So I am the Director of the Office of Orphan Products Development. And I am so excited to be up here to have a discussion with the Medical Product Center directors.

So the Office of Orphan Products development is located actually outside of the Medical Products Center. And I will say one of my favorite part of my jobs is working with the center directors.

And as I mentioned, the planning for this was -- a lot of folks were involved, and we had cross-agency representation from each of the medical product centers. And I think that's just one example of the type of dedication we have at FDA to supporting rare disease product development.

And with that, I will let each of them introduce themselves. I have Dr. Marks right next to me, and then Dr. Woodcock and Dr. Shuren.

DR. PETER MARKS: So I am Peter Marks. I direct the Center for Biologics Evaluation and Research. We handle the biologics that include blood products, vaccines, and cell and gene therapies. And that probably gets us into the rare disease space most, as well as certain products for hemophilia and other bleeding disorders that are derived from blood products. So that's all I have to say.

DR. JANET WOODCOCK: I'm Janet Woodcock. I'm Director of the Center for Drugs. And we handle small molecule drugs and therapeutic proteins of different sorts.

DR. JEFFREY SHUREN: Hello, I am Jeff

Shuren, Director of the Center for Devices and Radiological Health. And we oversee gizmos.

DR. JANET MAYNARD: I like that, gizmos.

So the theme of today's meeting is supporting the future of rare disease product development. What are some of the opportunities and challenges you are each seeing in your centers in terms of those considerations?

DR. JANET WOODCOCK: Well, I think the greatest challenge, as we all know in this room, for rare diseases is we just don't know enough about them. And there aren't very many patients to study when we do get some intervention we want to test. And so of course we're doing various things to try and address that.

But just this morning I had something come across my desk. And they were saying this is a very rare and very serious disease of children, it causes neurodegeneration. But some people don't seem to get neurodegeneration, and some do. And some progress fast, and some progress slow. And, you know,

how in the heck are we going to tell if something is working? So that's one of the challenges.

And I think the opportunities is with the genomic revolution and many other advances, we're getting much more precise in our understanding of what's going on with a lot of these diseases. And we can actually devise interventions, you know, against them. But the testing still remains a challenge, and that's what we're going to talk about I think a bit is developing registries and natural history studies and so forth so that we can just have some better understanding of disease and its variability is really going to help in developing treatments.

DR. PETER MARKS: I agree with everything that Janet said. Just the other piece is that we're able to develop therapies conceptually or in the laboratory space. But part of this is can we manufacture them in a way that is efficient that can meet the needs of the rare disease space. Because these products, these cell and gene therapy products, one wants them to be manufactured with the same high level of quality, whether it's for treatment of one

patient or a million patients. Right? And making sure that you have a level of quality.

Now, obviously there might be some differences there. I don't mean to exaggerate. But we do want to make sure that these are high-quality products. And figuring out a way to make sure that we accomplish that is one of the challenges.

DR. JANET WOODCOCK: And that they remain affordable or become affordable, which is another challenge.

DR. PETER MARKS: That's right.

DR. JEFFREY SHUREN: So I echo a lot of the points that were made. And the challenge on validation for small patient populations is even more acute in the device setting because of return on the investment. You have a number of the former products can get high payments for their use, but that doesn't exist on the device side.

And the second is when Congress was approaching this in the pharma space, they could provide an economic incentive for market exclusivity. That doesn't exist for the devices, because your

competition can reengineer around your IP, and so that market exclusivity is essentially meaningless. So Congress instead came up with a regulatory incentive in which they changed the standard to come to market if you're for a very small patient population. That's Humanitarian Device Exemption. And that used to be what we think of as an instance of about 4,000 patients a year. Now it's 8,000. A lot of bells and whistles. Many cases you can't collect a profit, reporting requirements, and you had to have an IRB approve the use in a patient. Now you can use a local committee.

So between that and the fact that low otherwise payment, we've not seen a lot of development under that HDE pathway. We've got ideas on how to fix it, but if something does not change and we're not willing to think out of the box and do some new things, then we will continue to not provide proper service and care to the patients in this country.

DR. JANET MAYNARD: That was very helpful. Are there certain things within your center that you're doing to support these opportunities and

challenges that you're seeing?

DR. JANET WOODCOCK: Well, I think you may have just heard about the rare disease accelerator. There was some discussion. So that's one of the things we're doing. You know, there's a whole range of ways in which patient advocacy groups and other groups can work with the Agency and with industry to develop better tools to get these drugs on the market faster and get them studied correctly. And that's everything from, as I said, having a good patient registry, or even a patient -- I mean, a registry -- what (inaudible) has done. Okay? I am rare and you can identify the patients and you have information what's happening to them and so forth. Accelerator would take that to a different level and have really quantifiable data elements so we could perhaps construct what they call, you know, external controls. Because you certainly hear from people with rare diseases, they don't like to be on placebos for a really long time, all the way through to supporting trial networks. And there's this whole area of biomarkers, patient-reported outcomes, clinical

outcome assessments. What are all these?

Well, these are ways that you can measure change and tell whether change occurred. And for rare diseases, often none of that has been developed. So working on any of those or on the biomarkers are critically important because a drugs that has a biomarker they can use as a what we call pharmacodynamic marker can be developed much, much faster and is much more successful usually than drugs where they're just flying blind and relying on maybe the symptoms get better in a couple years or something.

If you use something you can measure in the blood or in the lungs or whatever and you know you're making a change much earlier, then that really helps spur development and you can figure out the dose and so forth.

So we have initiatives along that whole spectrum, all the way from, you know, we put in some money for IAMRARE, you know, back when that was started, all the way through to biomarkers and so forth and so on. But of course we can't do this

alone; we have to do it with community. And I really feel that drug development science part, the part that goes on after drug discovery, that science really needs a lot of work and it needs a lot of attention and probably funding by various sources to develop all these tools so we can develop rare disease treatments better.

And I see Chris Austin is here. I think he probably agrees with me. Yeah. You know, over at NIH or NCATS, there's a portion, a very small portion, that's trying to work on this. But in general, much of the basic science enterprise doesn't do this. They aren't interested or it isn't their area of expertise. And it's critically important that we have the basic science to bring forth new insights that we can then use to develop treatments. But we also have to have the tools to develop the treatments, and they're kind of scarce right now.

DR. JEFFREY SHUREN: And all those are along the lines of how do we sort of de-risk the whole process and make more efficient that generation of evidence to assess these medical products. And we

have very complementary efforts around these developments of -- we'll call them medical device development tools, these either non-clinical or these biomarkers or patient-reported outcomes and have in place a whole very streamlined system for qualifying those markers, and we engage with the developers, academic centers on developing. And we had a few come out just this past year. Patient-reported outcomes, terribly important. We are now seeing over 60 percent of the clinical trials for high-risk devices now include patient-reported outcomes. And we're trying to push that more and more.

One of the other exciting things is in the area of pediatrics. Because that's one area in which we're seeing very little innovation occur in the device space, unfortunately. Over the past decade, only about ten percent of the high risk of these HDE devices have been for an indication just for pediatrics and for less than 18 years. Only about four percent for infants and toddlers.

So we've been working with some of the major pediatric hospitals in the U.S. on setting up

what we call Ship, a System of Hospitals for Innovation in Pediatrics. Because the challenge here is you have sort of wide -- you have these very tiny pediatric populations spread out across the country. We need to link them together so we can get the patients, we get the top expertise, and we get the kind of good monitoring on them to get that evidence on the clinical side, on the non-clinical side. It is critical. And if we can combine that with very important regulatory reform -- and hopefully we can talk about this, some call it progressive approval -- we can have a very refined engine to drive the development of new technologies for patients with rare diseases, and in particular for our children.

DR. PETER MARKS: And I think from our perspective in terms of gene therapies, it's increasingly clear that there are going to be any number of individualized gene therapies that are going to come along. And we have to put together essentially a pathway that those can follow in this area. And even -- there's rare diseases and there are diseases that are -- diseases that are very rare,

diseases that are not so rare. Even in the not so rare diseases, they become rare once you break them up into all the different genetic mutations. And so having pathways to deal with how one can think about the individual genetic mutations that might be addressed even within one of the more common rare diseases is really necessary.

So we're really thinking about how we can address that by leveraging what information we have. So the idea is that as we put together things moving forward, we're not thinking we need a lot of new regulatory authorities; we just need to leverage the ones we have to think about how people can leverage applications.

In other words, if a product has been made using one manufacturing technique and only a small modification has been made to that product so that it can address a different disease or a different subset of a given disease, can we allow the manufacturer to leverage the application of the original product as they have this modified product.

And so those types of things are things

we're having a vigorous dialogue about. Hopefully that will be articulated at some point in guidance. We also realize that we need to do all the things that go into product development on a very small scale, yet in a very efficient scale.

And so next Tuesday we'll be having right here in this room a workshop on individualized therapies, because we realize that at this point we have to start to think about how we can very efficiently do the non-clinical development, the clinical development, and the manufacturing of these products as well as how we can maintain the availability of them once they actually have been produced. Because one of my concerns is that we don't want to repeat mistakes that have been made in the past.

There was a gene therapy that was approved in Europe for a relatively rare disorder, and it was actually marketed for a time, but it's now off the market because it wasn't commercially viable. So this goes back to what Janet mentioned, which is that unless we can find ways towards commercial viability

or towards some sustainable method that these products can be provided, we're not going to be doing the job that we need to for patients in need.

DR. JANET MAYNARD: Thank you very much. And one thing you mentioned, Dr. Marks, was about leveraging and how can we do the best that we can possibly do for patients and families for rare diseases. And I know many patients and patient advocates frequently ask how can I get involved, what can I do to really help with product development. Do you have recommendations for patients and patient advocates who are interested in getting involved in rare disease product development?

DR. PETER MARKS: Well, I'm going to let Janet continue on. But I think one of the things that I would say is that one of the key things we need to understand for any of these products is the natural history of the disease to begin with. And to the extent that you might be waiting for somebody to develop that gene therapy, in the meantime while they're developing that gene therapy, getting baseline information on the course of disease, how fast people

decline, is really -- or how something changes over time, that's really important. Because then when you actually have the intervention, one can see if one is making a difference. And that's really important, to be able to have some clinical measure in addition to the ability to measure the product that's being replaced by a gene therapy.

DR. JANET WOODCOCK: Yeah, I agree. And practical ways to do that. Of course people with rare diseases should try to link together on social media or whatever and form a force, you know, so you're not just one individual struggling against the disease. And I know many, many groups have done that. Once you become a tight enough force or group, then it's possible to think about collecting these kind of data. And the NORD IAMRARE and the to-be accelerator would be two mechanics, but by no means not the only ones in which to do that.

Further down the pathway, like I said, working with or sponsoring preference studies, like has done by CDRH in certain areas, or developing PROs or working with the professional societies and medical

experts on biomarkers, raising money for that. All those things are really important, every single one of them. And they come at different stages. But unfortunately once somebody has a candidate product in hand, they wanted to have all that information a while ago. It's kind of too late. And that's one of the reasons it takes so long often, even after a discovery is made in the lab. People can't figure out why -- you know, I only heard of one patient that's ever had that disease. Like, how do I go from here? How am I going to test it, how am I going to evaluate it?

And so all these things need to be done in advance, and you can know if you're working on them that you're actually improving the probability that some treatment will occur in the future.

And in fact as Jeff said, you will be interesting developers in that disease, because they want to have a pathway that isn't so unbelievably risky to follow down.

DR. JEFFREY SHUREN: And to build off of that, if you think about it, pretty much everybody is or has been or will be a patient. So we kind of

think sometimes as patients as maybe passive recipients, or give us your thoughts. We have an army of patient scientist. And that's also what we need to come to bear to sort of help us, both in product development and evaluation. Today there are patient communities, they are do-it-yourself technology being put together. And now we're thinking about how can we in fact enable patients for developing technology that can help them in their own lives.

DR. JANET WOODCOCK: I have one more thing. I know an individual, and he's written a book. I think it was called My Chase for a Cure or something. I forget what it's called. But anyway, he was in college when he first developed a life-threatening illness. He almost died. And then he had relapses when he was in med school. Almost died. He found out -- here's what he found out. It was a rare disease. Nobody knew how to treat it. All people had different treatments. Okay? Every expert you went to had different hypotheses about what caused it and all this stuff. He had a variant that didn't respond to what people usually started with. People had no idea

what to do next. So they decided to treat him with chemotherapy. Okay? Which they did for a while. But then he continued to have relapses.

And now he had a leg-up because he was a med student. But still he wasn't like some advanced expert. And he went ahead and -- but he found the experts. They hadn't gotten together. And this -- Chris is, you know, something should be done about this, right? They hadn't gotten together and figured out the pathways, they hadn't shared information and data on the patients. There were little islands around the world where people had information about this disease. And they didn't have a consortium, they hadn't shared materials together.

And so he did some of those things, and he was able to find a treatment, an existing treatment that he tried and has kept him in remission. He sent me a picture of his baby and also a copy of his book.

So, you know, I agree about patient scientists. I really think patients have much more than they think as far as knowledge of their own disease and ability to contribute if we can only help

provide those pathways.

DR. JANET MAYNARD: And speaking about sort of forward-looking, we've seen additional interest in sort of the development for ultra-rare or small populations. And we have a panel this afternoon that's going to talk about perspectives on individualized therapies. But I was interested from your perspectives kind of what are you seeing in this space and how are you helping to address the regulatory considerations?

DR. PETER MARKS: So there's a tremendous amount of interest in this space, whether it's for antisense oligonucleotides, cell therapies that are specifically designed for one person's cancer or gene therapies that are developed for very small populations of patients, because they might be for one individual's mutation that might turn out to be either unique or only in a few patients. So we clearly have to find a way to get from where we are to being able to have treatments that get to patients.

So there are two pieces to that. There is the piece of how you go about getting the

regulatory perspective done, and the piece of how you go about getting the manufacturing done. We are collaborating with NCATS -- so you're going to hear from Dr. Austin later -- towards trying to find a way forward in some type of a public-private partnership that might happen in the future that can help with some of the -- serve as a model for how one could potentially get the manufacturing done.

And then from the regulatory perspective, I do think it's going to be a matter of thinking of how we can leverage as much as possible for these things. And it may not be that there's one size that fits all. It may be that some things will be -- that will treat a number of people will be things that could ultimately be a licensed product. There may be things that will never be a licensed product and will just be made available perpetually under an investigational new drug application, at least for right now. Because ultimately it's possible that 10, 15 years down the line many of the things that we're having difficulty doing in terms of making gene therapy vectors, those things will go away as we

have more advanced technologies. It's just the manufacturing is just not caught up to the rest of the science. In other words, this is one of these cases where science making the gene therapies and our science of being able to understand the genome has advanced far beyond where the technology to manufacture products in this space has.

DR. JANET WOODCOCK: On the smaller molecule side, we have had a number of applications for individualized treatment. In other words, molecules that were designed with a single patient in mind. Some of these have been made public. But we've had more than that, and we understand that we're going to see many more. So we're developing some policies on this. Because when you get down to a genetic level, actually, except maybe for some twins, most people are unique, completely unique. And therefore it's not surprising that when you talk about a rare disease and you start looking at the genetics that are causing that rare disease, there's going to be very unique genome across each person. And so how you address that if you're going to have a genetic

therapy, then that genetic therapy may be unique to each person or perhaps a small subset of people. And this is true even for relatively more common genetic-based disease.

So I regard this as a very interesting development. Like Peter said, we're wrestling with all the regulatory issues that we have to deal with and the issues of how these could be commercialized and so forth. But for people with ultra-rare diseases that have a genetic cause, I think this is something to, you know, have some hope, okay, that actually it's possible to develop an intervention that might help them. So we are on top of this I think is the best way to say.

DR. JEFFREY SHUREN: Yeah. And I would say that we understand I think the overall implications here. One of the issues in this very rare space is that we need to be thinking really globally. Because we don't want to reinvent the wheel over and over again in different countries. Right? If you have something that affects only five people in the United States, we don't want to have to have this

reinvented in Asia, in Africa, in Europe over and over again.

So I think we as a regulatory authority need to work with our global colleagues to find ways to really facilitate the development of these and break down barriers. Because sometimes we do have different regulatory structures and different regulatory frameworks that might inhibit the ability of these products to make their way from one regulatory jurisdiction to the other. And nobody wants to undermine another regulatory authority. I think if we don't come together and find ways to work together to find essentially common ground here, we'll do patients a disservice.

DR. PETER MARKS: So we get involved in these very small populations in a variety of ways. ON the one hand, it's the diagnostics, you know, to figure out sometimes who are these individuals. And we've been trying to foster in the genetic space databases and kind of that pooling of information on genetic variance. Because a lot of these, they are one-offs or few-offs, and you have to be able to

collect that information.

And I'll put a plug in, by the way. While not a tiny, tiny population, but it is rare disease. Friday we did approve the very first test for Fragile X syndrome and carriers.

The second place is on people's anatomy. Your anatomy is very unique. And we have already cleared devices we're 3D printing being made specific to your anatomy.

And then third is this issue I mentioned about that regulatory incentive, Humanitarian Device Exemption. It's really tiny populations. And Congress changed the standard. Instead of reasonable assurance of safety and effectiveness, it's really a reasonable assurance of safety and probable benefit.

And the challenge here is in spite of that, the incentives aren't strong for development. And once you get past 8,000, suppose it's 8,500 patients, guess what? You've got butkis. That's it. And then nothing that pushes you to get the rest of the data. So our idea on progressive approval is the

following. Let's not make the limit 8,000. You can keep HDE. But let's keep the standard of HDE in a small population. It could be 9,000, 10,000, 20,000. But then you have to get the rest of the data within a certain amount of time. So within three years you show reasonable assurance of safety and effectiveness. And if not, your approval sunsets. So you've got a hammer. And we tie it with two other things.

One, in order to do it, you have to have an existing data source where you can get that information. Right? So you're not doing a one-off clinical trial. There's a registry maybe available and that data is being collected anyway, so you know you're going to get the data.

And the second is in some cases, we might restrict distribution to those centers that actually have good oversight, good monitoring. And that bring us back to (inaudible)

So if on the pediatrics side we have progressive approval and (inaudible), we could have a very powerful engine for driving development technologies. But not only that, driving the evidence

to then better understand the use of technologies when out on the marketplace.

DR. JANET WOODCOCK: I just want to say, Jeff, my brother has two of those custom things in his body, and he's really happy.

DR. PETER MARKS: I would say that one of the wonderful things about genomic medicine is that we are lucky that in some cases if we do things right, if we have the right baseline data, if we have the right construct, we're lucky in that it doesn't take that many patients to actually see that something is working. Right? If somebody is not making any of something and they're dying because of that absence by a few years of age, and you make that something and they're not showing a decline and they're alive after a given timepoint, it doesn't take that many patients before you feel confident here. And so that is a great advantage here.

It's one of the reasons why we don't really have to -- it's perhaps a little bit different in biologics than it is in devices, because we can use our current framework to find efficacy, findings of

efficacy without having to stretch things too far out of our existing regulations, and I think it's very exciting.

And this goes to why doing the right pre-work, not settling for the wrong construct in terms of design of the therapy, being thoughtful, is so important in this area. Because these things, when they work, they can work really amazing.

I think the example that Commissioner Hahn noted about the therapy for spinal muscular atrophy, this is truly amazing. I mean, you're taking a disease that formerly was really uniformly fatal for Type I spinal muscular atrophy by two or three years of age, and now you have not just the children alive, but they're alive and they are for all intents and purposes normal. And that's truly remarkable. And that's just something that is incredibly gratifying for all of us who work here. I'm sure it's incredibly gratifying for their parents and their families. And I think it's wonderful to all share in this success. And we want to try to bring that to a greater number of diseases.

DR. JANET MAYNARD: So speaking of sharing, we would love the opportunity to hear your questions or perspectives from the audience. So if folks want to come up to the microphone, or please feel free to raise your hand and someone can bring a microphone to you.

WOMAN: Hi. I am a patient scientist, like someone said in the panel. I have Parry-Romberg syndrome, and I am a health outcomes researcher. So I analyze data on patients' reported outcomes, EHRs, claims, et cetera.

And they're mostly in a Facebook group. I connected on a Facebook group. After spending 20 years without having met anyone with the same disease, I connected with a Facebook group that has about 1,200 members that are spread across the globe, among which there are some identical twins, which is always interesting, like we mentioned, when we want to investigate genetic ideology.

So my question is for me as a health outcomes researcher, I see there the potential of a really amazing pool of data. But how can we leverage

this potential when people are spread across the globe? As you mentioned, we can't just ask them questions and make a study out of it. So how could we use these patients, how can we recruit these patients and really develop a study that has validity?

And the other question is not only recruiting for this, but how can we establish international collaborations between researchers that are doing research?

So I also participated in a research study that is trying to investigate the ideology of the disease. In months of work the investigator collected three samples. And all of these people in the Facebook group would be willing to participate. It's just that they cannot physically come here. So that's my question. Thank you.

DR. PETER MARKS: This is an interesting place where I think what you're saying is there are examples of collaborations which have been effective. And I guess this is where in the rare diseases space I think there might be an opportunity for sharing, because there are some where I think

people have very effectively brought together international collaborations with being able to do similar things of trying to get an investigator in each country of several of -- from several counties to be the lead investigator so that they can collect samples and share them under a protocol.

And so I would encourage you after this to network around a little bit. Because I'm pretty sure that I see people in the room who have helped facilitate some of that. It sounds like you're a little bit more on the early end of things. But still, getting those samples. And there's nothing that prevents, you know, multinational protocols from taking place, especially for sample collection where it doesn't even require global regulatory approvals. But even on the space where there have been interventional trials, clearly multinational trials in this space are quite possible.

DR. JANET WOODCOCK: Yeah. I think once the disease accelerator gets really set up, its intent is to be a good repository for the information once it's gathered. And it certainly is intended to

be international, not just in one country.

I think one thing is to find an investigator somewhere in the world who is really interested and motivated and thinking outside the box on how you do these things and how you might set up a consortium and a collaboration. So I think there are such folk around. It would have to be somebody who is working in the disease space who is willing to think beyond the individual investigator paradigm, and how do you set up a disease network so that you can really collect information, the specimens, and nothing is lost.

But that's great, you've gotten so far. It's a good step, because a lot of rare diseases aren't even there yet.

DR. JEFFREY SHUREN: And don't forget there may be opportunities on technology, too. Because if there are things you need to measure, sometimes those could be sensors or other information that doesn't require a blood sample, maybe some other kind of specimen. And that allows for gathering data from basically anywhere on the planet.

DR. JANET MAYNARD: Great point.

KHRYSTAL DAVIS: Hi, my name is Khrystal Davis. I am the founder of Texas Rare Alliance. And I am attending from a travel grant from Every Life Foundation. I am also an SMA mother to a Type 0.5 SMA patient.

Our son, Hunter, is now eight years old. He landed in the NICU at birth with respiratory failure. At eight weeks of age, we finally received a diagnosis. And eight weeks later, Hunter received his first (inaudible) ASO treatment in Cancun, Mexico. We continued those treatments for five years until he was able to cross over to the Spinraza EAP. And based on the trials, Hunter would not have qualified for treatment.

So I want to advocate for access for all patients across the spectrum of the disease for access in the clinical trials. And we're seeing it made increasingly clear that although the FDA is willing to grant a broad label on the basis of the data from the clinical trial, we're seeing the payors decline coverage because there are no data points on

those patients. And we know firsthand Hunter would not have qualified. But he is here today because he did receive those treatments. And what can we do collectively to change that, to make sure that we do bring all these patient into the trials?

DR. PETER MARKS: So I can start. And thank you for that. I think it is challenging. I think there are a variety of things we've encourage people to do, which is, (A), try not to have very restrictive registry criteria to the extent that one can. Unfortunately, sometimes the fastest way to get something approved is to take a more homogenous population.

That being said, we don't have any problems -- I mean, the problem is often not at the FDA level with expanded access and access outside of trials, it's that -- and this goes back to something I keep harping on manufacturing -- it's that they cost so much and are so complex to make that, for instance, in the gene therapy space, oftentimes manufacturers, particularly small ones, can't afford to make additional doses of their therapies.

I'm not defending that. Okay? The problem is that you may say how can this be? These are gene therapies. How can you make -- unfortunately, these gene therapies, the way we currently get gene therapy into people is we use viral vectors. Those viruses have to be made. The way they are made is they are made in cells. Because they are toxic to the cells that they are made in, one actually has to grow up a lot of these things. And the production of these things turns out to be relatively complicated, relatively costly.

So one of the things we're very interested in working on at Center for Biologics is how we can work with others to try to bring down the cost of production of these. That's not a total fix, but hopefully if it wasn't so expensive to make these products, people would be more willing to give them out on expanded access and companies would be more willing to have broader inclusion criteria for protocols besides their main protocol.

Again, I don't have a complete solution here, but I agree with you. We can't leave people

behind in this situation.

DR. JANET WOODCOCK: Yeah. And we've talked before. FDA I think is becoming more aware of this situation. It used to be we would hear people who were studied in a trial, and then we'd say who it was reasonable to also be included in the indication. And we would often have some special study saying renal failure or whatever so we can include those people and the right dosing.

But now that isn't the case. And we are having some work to raise awareness amongst the staff. Seminars are being held and everything about how the label effects coverage and access to treatment and reimbursement for treatment.

As Peter said, on the trial side, if there is enough material, then it's very reasonable to include other people, not maybe in the main trial if you're worried, or you can have an arm in that trial that isn't the randomized comparison arm, but it's actually to provide safety and additional types of people beyond the people, you know, that you have otherwise enrolled.

KHRYSTAL DAVIS: Yeah. And just to follow up. We are starting to see that being done. But also we need to advocate if possible that they are done contemporaneously so that that data can be included in the label packet as well. Thank you.

SANDY SIAMI: Sandy Siami, HealthCore. I have been doing research in rare diseases and orphan devices for about 25 years now, specifically in pediatrics to --

DR. JANET MAYNARD: We can't hear you very well.

SANDY SIAMI: Sorry. So my question is, because this population in rare diseases, they are rare, right? They're hard to find. What role do you think artificial intelligence or machine learning can play in clinical trials to help get these drugs and devices to the market?

DR. PETER MARKS: Some of this has to do with whether there could be more collaborative ways of finding patients. I think maybe that's part of this, is patient identification. One of this has been -- you know, the holy grail would be we have one

essentially wonderfully interchangeable electronic medical record in the United States instead of a balkanized version of hundreds of different medical records. And if you had, you could imagine that as part of entering your medical record, you could say, oh, I would want to be considered for clinical trials or not. And if that was checked that you wanted to be, you could imagine an artificial intelligence program that could probably search up so you could be on a list of things that -- a list of queries, you know, if the database was queried, an investigator could find everyone with Fragile X syndrome or everyone with SMA.

But currently the way we are working with our electronic medical records system, it does not work that way. And that is the nature of how things are. It's easier in some -- this is where some of the European countries have a one-up on us where they have a single medical records system in certain Nordic countries where you can use AI right now. And the issue here is maybe this is someplace we'll get to.

I think it does have to be done very carefully, because I think we want -- it's patient autonomy. You should be able to participate if you'd like and opt-out if you don't want to. But we're a little ways from getting there.

DR. JEFFREY SHUREN: And I think also there is the use of those technologies for going through information to developing better tools for identifying patients who have particular rare diseases as well.

DR. JANET MAYNARD: Good point. And I'll look over to see if there's questions from the web.

DR. NINA HUNTER: Yeah, sure. So this was brought up a little bit earlier. But we have seen some orphan drugs approved by FDA, but not EMA. Is there any collaboration and progress between the FDA and the EMA to harmonize the scientific and regulatory requirements for orphan drug development and registration?

DR. PETER MARKS: So I can start on the gene therapy end. There actually is a lot of dialogue

between EMA and FDA on trying to work together in this space. It's not perfect yet, but we have a dialogue that's ongoing and that will continue.

And more so even than just with EMA, I was at a meeting last week at the World Health Organization because there is a goal kind of more globally to try to harmonize what's going on, particularly in this rare disease space. Because everyone realizes that, again, we can't all have different expectations of what a submission will look like for a product that's only going to treat 50 people globally, or else it's just not going to work.

So are we there yet so that it's perfection? Maybe not yet. But I do think that the dialogue has been opened and it will hopefully progress in the not-too-distant future.

Just to be honest about what happens in life, the EMA had a move that they had to take because EMA previously was located in London. And something happened politically, geopolitically. They had to move to Amsterdam. That slowed things down a little bit. And right now we have an outbreak that's also

probably slowing things down a bit. But the dialogue is going on.

DR. JANET WOODCOCK: As far as small molecules, we do have a lot of harmonized standards. But it's clear that between the EU and FDA in U.S. and many other countries, we may not have the same approval decisions. And that is a matter of sort of national sovereignty. Usually we're working off the exact same data set.

And if things are approved in Europe, often the European folks will have more difficulty obtaining reimbursement even than in the United States. And we've already discussed some of the difficulties here. So a lot of this gets into how the healthcare systems are set up and what their standards are and so forth.

But we do work very closely with them. We are aware of all these things. We talk neurologist to neurologist and infectious disease doc to infectious disease doc and everything. But the approval decisions overall are taken up at a somewhat higher level.

DR. JANET MAYNARD: Great. Another question in the room?

DR. BARBARA GILLESPIE: I am Barbara Gillespie. I'm an adult nephrologist. I work at Covance as CRO that works with sponsors to run trials. And I'm here on behalf of the Kidney Health Initiative, which is a private-public partnership with the FDA.

So, Dr. Woodcock, you spoke at one of our meetings in the last few years about platform trials as one approach to innovative designs.

And I guess my question is I know the experience in oncology with I-SPY has been great. But our oncologists are years ahead of us with infrastructure and other kind of partnerships. So I wanted to hear from any of you on this stage or anyone in the room. What has the experience been with platform trials in other therapeutic areas? Like I said, I'm an adult nephrologist, but our kids who start off with things like nephrotic syndrome, IgA nephropathy and FSGS grow up to be adults, and we still don't have any approved drugs. And we've got

many sponsors looking at these trials. The efficiency of having a standard of care and a placebo arm that's shared is really wonderful, but there's a lot that goes into these survivals.

DR. JANET WOODCOCK: It's very frustrating to me, you know, to be very honest, there isn't funding, there isn't any kind of funding to set up networks for say pediatric nephrology problems or pediatric pulmonary diseases. So as you all know, the Cystic Fibrosis Foundation basically did this by establishing centers of excellence and by genotyping and following all their patients in a registry that Everybody came to those centers of excellence, which is most of the people.

Now, most rare diseases don't have the kind of funding to be able to set those things up, but they also have severely affected patients who would benefit from such a platform.

So I don't know. I think that we all probably need to think about the need for some stable funding to set up such networks, clinical trial platforms that could support clinical trials in a

variety of areas probably organized around experts, like pediatric nephrologists, pediatric neurologists. If there were some kind of funding made available that was stable, then I think that would go a long way. And then disease organizations could take the next steps to bring their patients together and try to work through something to set up a standing trial. But right now it's really, really hard.

I know a number of disease groups, and there are probably some people in this room that are trying to do this. So a number of disease groups are trying to set up master protocols for their disease.

DR. BARBARA GILLESPIE: Well, and I guess just to follow up, in addition to the finding, it's how do you incentivize sponsors to really collaborate, come together, the data sharing. I mean, we say that in many meetings, but the reality is -- and I'm sure there are sponsors in the room -- there's a lot of pushback. And it's just what kind of incentives are there, regulatory and otherwise, to try to help that conversation, too.

DR. JANET WOODCOCK: Well, I mean, sort

of chicken and the egg problem. If you had the centers of excellence and you had all the patients, then people would have to come to you. Right? And in my mind that would be better than setting up specific trials for specific drugs or gene therapies or whatever in development, to have them all evaluated in the same platform so we could see how they perform against each other. But there you have to have that m aster protocol in place and the centers of excellence in place. Then you've got some leverage.

DR. BARBARA GILLESPIE: Okay. Thank you.

DR. JANET MAYNARD: Great. Thank you.

CARRIE BARNHART: Hi. My name is Carrie Barnhart, and I have seven rare diseases. And I'm here today with a travel grant through Every Life Foundation. Not only do I have seven rare diseases, but I have 12 very painful conditions. And many of my diseases don't have any treatment. Or the one treatment there is causes anaphylaxis for me. So the overarching theme of why I'm here is I work with a lot of different disease groups. My son has four of my

diseases. And along with all of these diseases, like complex regional pain syndrome, Ehlers Danlos, lupus, all of these conditions cause a lot of massive pain.

And while it's never going to go away and there's no treatment for some of these diseases, what is the FDA going to do about treating pain until there is a treatment for the disease? With some of the pain treatments being taken off the market, a lot of pain patients are in agony. They're dying early. So I was just wondering what the FDA is going to do between here and finding the cure for the disease.

DR. JANET WOODCOCK: Well, I think we haven't taken that many pain treatments off the market. The problem is that people are becoming much more careful or cautious you might say about prescribing opioids in particular because of the opioid epidemic.

We are very aware that there are many people with chronic pain who need treatment. And FDA is continuing to try and balance that need against all the concerned people have about the loss of life and so forth that's coming on with opioid use disorder,

and overdose is consequent to that.

And we don't have a lot of good alternatives. We have acetaminophen, we have the non-steroidal anti-inflammatory agents, we have opioids. You know, our choices are kind of slim. And we have a few other special treatments for very special kind of pain.

We are working with the pharmaceutical industry to try and find new pain treatments that don't have the liabilities of many of the current analgesics that we have. But that's turning out to be pretty hard.

So I think the patients who are experiencing difficulty accessing pain medicine or having their pain adequately treated are probably experiencing some of the swinging of the pendulum from the opioid epidemic. And we have put out information to doctors and so forth warning people you shouldn't taper patients rapidly and you should individualize treatment. And other people have done that as well. But there's still -- because of the consequences of the epidemic, there is a tremendous concern about

prescribing opioids in particular. And of course some of the other medicines have their own liabilities. Many people, for example, can't take NSAIDS. It's very challenging.

CARRIE BARNHART: Just a follow-up. You had asked about patient advocate groups kind of doing the research. Well, there are a lot of pain advocate groups that have done the research on opioids for example and have found, you know, that it's actually a lot less damage from opioid use. Like people that are dependent on it to have quality of life, to be able to get out of bed, to be able to go to work, to be able to watch their kids. And it's staggering what the research shows versus what's actually told out there. So there's this fearmongering going on. And so a lot of patients like me have huge, huge barriers to be able to get management.

DR. JANET WOODCOCK: Yeah. We recognize that. There was even a little piece in the New England Journal of Medicine about this. I think they called it social toxicity or something like that,

where somebody was removed from his opioids, and he eventually lost his job because he couldn't get to work anymore, and then he got arrested because he was trying to get some pain medicine on the street. And these examples show that we really have to keep the patient in mind. It should be about the patient and what they need.

And of course these opioids are addictive. We know that. And we know some people can abuse them. But we know other people have their pain controlled very well by them and don't develop these problems. So it's really a matter of individualization again.

DR. JANET MAYNARD: Thank you. And I'll look to the web again to see if we have a web question. No web questions? Great. In the room?

SHEILA MIKHAIL: Hi. My name is Sheila Mikhail. I am the CEO and co-founder of AskBio. AskBio is a AAV gene therapy company that was founded back in 2001, way before it was popular to be in gene therapy. We were founded by researchers and parents who have children with devastating diseases. WE also

happen to be working on pain, just as a side note.

My comment relates to the SMA mother. Our technology is used in the AveXis therapeutic. It's the self-complementary vector. It breaks my heart to hear her comment.

We have worked very hard on manufacturing. We've spoken with Dr. Marks in the past. Our manufacturing system is we believe the highest-yielding gene therapy manufacturing technology. We put a certain portion of our capacity aside for non-profit purposes. We formed a foundation called Columbus Children's Foundation where we dedicate a portion of our technology, manufacturing capacity, and technology for the development of ultra-rare indications. To date we've treated 20 patients with ADC deficiency with no charge. Let me say that again, no cost to the patients.

So a lot of in biotech are not here just to make a lot of money; we remember our origins, and those are our patients and parents who have suffered. And we don't want to continue suffering.

So my question is, how do I help that

mother? How do I make our manufacturing and how digital enable our foundation to help that mother so that she can actually have access to therapeutics that are on the market and have been proven that they're effective.

I think there's no greater travesty than having a drug available that we know works and not having it available to a patient who is suffering.

DR. PETER MARKS: Well, I think there are a couple different things that can be done. I think first of all one of the questions that goes for some of the gene therapies is one of the simple things to do is to also ask the companies, which sometimes people don't do. But I think at this point for some of the companies, the easiest thing for a gene therapy that's already licensed is to try to go back to that company and see if that can be made available as part of an expanded access program. Because there the product is being made. One doesn't have to go after a new licensing process, one doesn't have to look at a different manufacturing process.

On the other hand, I think turning to

exactly what you're saying is one of the reasons why we, in collaboration with NCATS, National Center for Advancing Translational Sciences, are interested in seeing if we could put together some type of a public-private partnership to be able to use that capacity that -- we've had more than one. I think what you articulate is very nicely said by any number of gene therapy companies that want to use their excess capacity to help benefit people with ultra-rare and very rare diseases. And the question is how do you make that work.

And so putting together the infrastructure to make that work is part of what needs to happen. And so we're working towards that. And I hope we're not too far off. Thanks.

DR. JANET MAYNARD: Thank you. Any other questions from the audience in the room?

WOMAN: (inaudible) Foundation. Excellent panel. Thank you so much.

One quick thing I wanted to throw out there when this discussion was happening about our platform trials. So we are in fact now collaborating

with the Innovative Medicines Initiative, which is a European initiative. It's really a public-private partnership between industry and European Commission. And they have money, I just want to say.

So we are now developing a platform trial for four different diseases, of which NF is one of them. And we are also developing a platform trial in the U.S., which is more with a couple of centers. But I think the real maybe opportunity if we want to do something creative is maybe to start in Europe. Because of the public hospital system, we have released that political barrier. But it's so optimistic.

DR. JANET WOODCOCK: Agreed. And European Parliament is putting up the money for --

WOMAN: Exactly.

DR. JANET WOODCOCK: -- IMI initiatives. And that is very translational. It's not just basic science. And the industry is providing in the public-private partnership in kind activity.

WOMAN: Exactly.

DR. JANET WOODCOCK: So they have some

ownership as well that keeps it grounded in the practicalities of drug development. So we work with IMI very closely. And congratulations for getting some trials up and running.

WOMAN: Thank you. And the interesting thing is that in fact the next IMI is probably going to be called IHI. So Innovative Health Initiative, where standard devices and everything else will be included.

DR. JANET MAYNARD: Thank you. Are there other questions in the room? Other questions in the room? Okay. Well then why don't we break slightly early so that we'll have a 15-minute break instead of the initially planned ten-minute break. So we'll have a little bit of extra time. And we'll plan to reconvene at 2:00. Thank you.

(Break)

DR. JANET MAYNARD: -- individualized therapy, so if our panelists don’t mind coming on the stage, that would be great, please.

MAARIKA KIMBRELL: All right, everybody, so I guess we’re getting started. We’re on

Panel Number -- is it -- 4 this afternoon and we're going to be speaking about perspectives on individualized therapies. The goal of this session is to provide various perspectives on individualized therapies with an emphasis on regulatory considerations.

As with some of the other panels earlier today, I'll begin with some very brief introductions and then turn the floor over to our esteemed panelists to give a more -- a deeper introduction and some perspectives from them, and then we'll move on to questions. I have questions, but I also hope to hear questions both from you all here at White Oak as well as folks online.

So briefly, I'll introduce myself. My name is Maarika Kimbrell. I'm the deputy director of the Office of New Drug Policy which was a recently established office in the Office of New Drugs. It came about as a result of a recent reorganization and I'm serving as a panelist for the folks here. We've got a great group of people and I think we're going to have a very good discussion.

So we have Ella Basala, Petroula Smpokou, Julia Vitarello, Ciela Witten, and Timothy Yu. We're going to introduce folks not quite in the order that we're sitting, because we discussed this earlier and it wasn't alphabetical, but we're sitting alphabetically, so first, Julia.

JULIA VITARELLO: Hi. My name is Julia Vitarello and three years ago my daughter, Mila was given a death sentence. She was diagnosed with Batten disease which is a rare neurogenetive disease that's fatal. No treatments, no cures. This was the same little girl who was a typically little Colorado girl who was hiking and skiing. She was swimming and biking and rock climbing by the time she was two. She was advanced, normal, and singing all the words to her favorite songs, to "Puff, the Magic Dragon."

She was learning her ABCs. And at six years old, she lost her vision and she was diagnosed with Batten disease and I was told that she was going to lose very quickly her last words. She would say mommy for the last time. She would take her last steps. That we should buy a wheelchair, that her

brain would atrophy and eventually be an empty skull and that she would die in the next five years. As you can imagine, life as we knew it was over that day.

I was told that there are no tools in the toolbox. It was empty. There was nothing we could do. There was very little understood about this disease. So I started speaking with other rare disease parents who'd been fighting for their children across many diseases. I spoke with scientists and doctors around the world.

I read everything I could get my hands on around Batten disease, around lysosomal storage disease, and I learned pretty quickly what I needed to start a foundation, raise a lot of money. And I started doing that and telling Mila's story to anyone and everyone who would listen. At some point, I realized Mila was missing a mutation. She needed two. It was autosomal recessive and one of them was not able to be found.

So in my desperate plea to find a lab that would help me find the missing mutation so I could test my two-year-old son, who seemed completely

normal at the time, and to be 100 percent sure that my daughter, in fact, did have Batten CLN7, a rare form of a rare disease, I reached out on social media and crossed paths with Dr. Timothy Yu, and I will let him tell the story of -- he speaks about what happened after that, but in one year's time from when she was diagnosed, I was told that my child had never lived with that disease.

One year later, we were moving from Colorado to Boston and Mila was receiving a new drug tailored just to her called Milasen and she became the first person in the world to receive a drug tailored to one patient. And suddenly the no hope turned into a real second shot at life. Mila was seven years old when she was diagnosed -- I'm sorry, when she was treated and obviously, had lost quite a lot, so she, you know, is in a place where she's must better than where she should be right now and I'm incredibly grateful not only to Dr. Yu and his team, but to the FDA.

I was told the FDA was going to slow progress, and instead, they absolutely played an

instrumental role in making this making this treatment happen and collaborated with Dr. Yu and his team.

So thank you very much from myself, my daughter, my family for giving her this second chance at life and I just want to kind of end my thought here with, I stay up every night thinking about the millions of children that -- you know, I don’t know how it’s possible, but there are millions of children that have been diagnosed with rare diseases, enduring every day, and I think about the possibility that a treatment like Mila’s might be able to actually help some of those children.

The sum ends up being quite a big number when it adds up, and I see this as a real exciting time of opportunity and obligation to really explore a path of allowing treatments like Mila’s to be able to be accessible across many, many rare diseases and hope that there will one day be a tool in the toolbox for many of those families that otherwise would have no hope.

MAARIKA KIMBRELL: Thank you, Julia. I’ve heard you speak before, and I just wanted to say

that every time, it's almost more and more powerful, so thank you for joining us. So we've obviously heard from a parent and caregiver and an exceptional advocate, and so now, let's turn to the sponsor investigative perspective.

DR. TIMOTHY YU: Thank you, Maarika. And first of all, I want to thank all of you for the chance to come and participate in this Rare Disease Day here at the FDA. I'm sitting on this stage as an example of a physician scientist who's been able to take advantage of new tools that are available to us in 2020 -- or actually, beginning in 2017, but in this new age. They're really wonderful tools for drug development that are available to us, built off of many people's decades of hard work.

We are also in the privileged position of having wonderful diagnostic tools, being able to sequence genomes for patients and find the answers that were often so elusive in many people's diagnostic odysseys going up to this point. And thirdly, in addition to being -- having the privilege of having great therapeutic tools and diagnostic tools, really

benefitting from a time of renewed flexibility and innovation on the part of the FDA to think about creative ways to apply these tools.

I want to fill in some of the details as to how we came to develop what folks are saying is one of the first examples of a truly individualized genomic medicine for Julia's daughter, for Mila. We were fortunate to meet her off of social media in January 2017 and we were fortunate to be able to offer whole genome sequencing for her that not only established a diagnosis, not only named the rare disease that she had, but also pinpointed the exact mutation that Mila had.

It's an interesting time. It used to be that once we categorized the disease, that that was essentially where you stopped. You would be able to provide a diagnosis, a prognosis, and you would begin working on, say, a gene therapy or a small molecule approach. And I think it's an interesting time. The way -- the reason I say that is that now, being able to pinpoint the mutation, as in Mila's case, sometimes allows you opportunities that we didn't know existed

previously.

You've heard in earlier sessions how there are 7,000 different rare diseases and it's wonderful that we're able to name them and diagnose them, but tackling them one at a time is a daunting task.

Well, we were able to find in the instance of your daughter that she had an unusual type of mutation that's a type of splicing mutation that afforded a mechanism to potential treatment that didn't require us to know that much about the disease process, to know that much about the mechanism of this defective gene, and it allowed us to develop a drug for her modeled after a drug that you've already heard about called SPINRAZA for spinal muscular atrophy and customize it quickly for her, based on studies of her own tissue samples.

And with a lot of support from many people in academia and industry and from the regulatory space with the FDA, the Division of Gastroenterology and Inborn Errors, we have been treating her with this for the last few years, and to

what we believe is meaningful impact on her course of disease and improvement in her quality of life. So I'm up here to share a little bit of the story with you from the standpoint of a physician investigator who sees this as a wonderful opportunity to think of creative -- to develop creative different ways of tackling rare disease.

We've talked about finding the gene, about developing therapies, about understanding the natural history. Well, one other potential tool here is to develop treatments that might work across multiple different diseases that can be applied, depending on the type of mutation that you might have, in Mila's case, a particular type of splice mutation.

But our tools are increasing being matched not just to the disease, but to the type of mutation. Single-letter changes in the genome can be fixed, in principle, with crisper gene editing. Nonsense mutations have other approaches splicing mutations like Mila had can be addressed with yet other approaches.

So I'd like to just -- I'm using my

time on the stage here to encourage the room, folks in the room, advocates, industry representatives, and the FDA, to continue along this vein of flexibility and thinking about creative ways to apply these new opportunities.

MAARIKA KIMBRELL: Thank you, Dr. Yu. So now from an investigator to an actual patient. Ella, would you take the next turn?

ELLA BALASA: Sure. I received an individualized therapy called phage therapy in January last year. If you're not familiar, phage therapy is the use of a very specific virus to attack a specific bacterial host. I have cystic fibrosis and this disease is characterized by bacterial infections in the lungs, predominantly. And over time, these bacterial infections lead to lung damage, lung scarring, and then eventually, respiratory failure.

So over the past two to three years, I've been dealing with progressively more severe and more severe lung infections. I've been -- I had been using intravenous antibiotics to treat these infections and using longer courses of treatment and

for, obviously, more stronger therapies as well, and even though that this wasn't sustainable for the long term with antibiotic resistance.

And so I heard of phage therapy in November of 2018 and I saw a documentary of a patient with CF who was treated by Yale -- Yale University Researchers -- and I contacted these researchers and I was very interested in having this therapy. And I communicated directly with them and they were very receptive and willing to answer my questions about how this therapy might interact with my body and with the bacteria in my lungs, and I have a biology background and so I think that that was helpful and made me more confident in understanding this therapy and making the decision to receive the treatment.

I didn't have the support of my doctor at VCU, my pulmonologist, my CF doctor, because he wasn't familiar with phage. He, you know, wasn't -- didn't support that there's -- there's no evidence to it, right, it was an experimental therapy. It's not FDA approved. But I decided to go through with the therapy. So by January of 2019, I was very ill. I

had been dealing with a very resistant infection on multiple weeks, like, over five weeks of IV antibiotics and not seeing any relief from my symptoms.

I was on supplemental oxygen 24/7. I was having fevers. I was doing breathing treatments every two hours to try to clear out the lungs from just filing up with mucus. And so at that point, you know, I knew that the benefit would outweigh the risk of trying a treatment that really only a handful of patients had tried before me in modern history in the U.S.

And so, you know, it was kind of where I was in a dire situation and that was certainly a factor in my decision to pursue it, because I knew I needed an alternative. And so I traveled up to Yale University to receive treatment and Yale had offered for my doctor to deliver the medicine, to give the medicine to me at VCU, my home hospital, but because he was unwilling and unable, really, to navigate the INDE, IND process and finding the appropriate paperwork protocol process and as far as also the IRB

with the hospital at VCU, he was not able to do this for me.

So I traveled up to Yale and it was -- it was difficult, because I wasn't sure if I was even going to be able to physically make the trip; I was that ill. But, long story short, I received the therapy and within about a week's time, I started clearing the -- that particularly terrible infection that I had and because of my positive outcomes, I've really been an advocate for getting this therapy to a larger number of patients that are in need or that are facing, you know, antibiotic-resistant infections and are dire need.

MAARIKA KIMBRELL: Thank you. So I think listening to you, I was reminded of a couple of things from this morning. One is clearly being a patient scientist yourself, and the other was Dr. Marks' earlier mention of this being a good example of what is often thought of as a more common condition as -- once broken up become something rare, and in this case, truly individualized. So thank you.

So now, let's turn to hear some

perspectives of some esteemed American regulators. So why don't we start with Dr. Witten?

DR. CELIA WITTEN: Yes, thank you. I'm Celia Witten. I'm the deputy director of the Center for Biologics and FDA and as Dr. Marks said at the previous session, that's the center at FDA that regulates blood products, vaccines, and cellular gene therapy. So in particular, the area of individualized therapies, some of the products that we have under our oversight would include phage therapy, gene editing, gene therapy, and some vaccines for treatment of cancer.

And all of these therapies or potential therapies have an increasingly important potential role that they can play in the lives of patients. So we really need to try to pay attention to how we can facilitate their development and availability. And some of them, of the kind of therapies that I just mentioned, some of them may be made for a specific patient and some may be customized for a patient, but either way, they're really made for an individual patient or a small group of patients.

And a lot of these, the typical development path followed for -- it's not the traditional drug development pathway, which is development by a pharmaceutical company. But a lot of these products begin in an academic lab and a lot of the activity is in an academic lab and as I think we've just heard from the two patients or family members who've just spoken, and I don't know if the current system would like to, you know, work to try to facilitate availability for treatments for all patients who need it.

The regulatory framework that we have right now, I think, has the flexibility to accommodate these kinds of treatments as we just heard two examples of, and we have other examples in our center of things, even, that have gone through to licensure that maybe aren't quite individualized therapies but have had some similar kinds of aspects: CAR-T cells for certain kinds of cancers or cord blood would be examples where we've exercised considerable flexibility.

So what is needed to facilitate

development of these products and availability to patients? I think that's one of the things we're all interested in doing or hearing about. One thing, just make a couple observations. One is, there's a lot of different models of collaboration right now and some amazing individuals and organizations who are leading these collaborations to develop individualized therapeutics and also a number of models for data sharing.

I think we need to learn from these examples to find a way to develop these products as efficiently as possible, but I think it's possible that some new models of collaboration are -- may be needed, too, that include different stakeholders from who has traditionally been included. I mean, I'm struck not just at this meeting, other meetings I've been to, by the really heroic roles that have been played by family members and patients advocating for their families and their -- and themselves, but I don't -- I think we'd like to think, eventually, that there could be a system where you don't have to go to these heroic efforts to have a treatment available.

I mean, people shouldn't have a job of finding treatment for their family members or themselves. So that's -- should be a goal we all, you know, think about; although, there's certainly room for many kinds of models. So one thing Dr. Marks mentioned in the previous session and I'm just going to reiterate, that we're having a workshop. CBER is having a workshop on March 3rd to discuss some of these issues in further detail, both the technical issues related -- and these all echo themes that you've heard so far about manufacturing.

You know, we hear estimates of manufacturing capacity for AV vectors for all the projects that people would want to do at this time that we've heard from investigators, that they have to wait in line for availability of the vectors. And I've heard anywhere from we need tenfold more manufacturing capacity to a thousand-fold more manufacturing capacity just for AV vectors which is a promising area for gene therapy development.

So the manufacturing issues, preclinical testing, clinical testing, and

collaborations will all be discussed in this workshop, and I don't want to go on for too long, because I know we have another speaker and we want to take questions, but I just do want to mention one thing that is important also to keep in mind, which is that we have really -- when we think about these applications, we really think about that we should have two goals here.

One is, if there's an individual patient or a small number of patients who are in need, it's what is that patient or that small group of patients' need right now and how can we facilitate development of that product for that patient or that group. But a related question, and I think also important, is how can we leverage what we learn from that one patient or one program that will help us for the next patient and the next program?

Because many of our products and our product applications share something in common. If you develop a gene therapy with a AV vector for a disease or for related disease with the same mode of delivery, hopefully you will be able to learn something from one application that you can apply to

another. And there's a lot of challenges in doing this. I mean, phage therapy is a good example. How do you learn -- each patient may have a different resistant infection.

There may be a treatment developed on an individual basis for them. But still, I think we want to figure out as we go through this and as we keep in mind the needs of each patient and their family members, how are we going to also keep in mind the next patient and the next patient after that.

MAARIKA KIMBRELL: Thank you, Celia. Now we'll turn from CBER to -- back to CDER.

DR. PATROULA SMPOKOU: Hi. My name is Patroula Smpokou. I'm a clinical team leader in Division of GI and Inborn Errors Products in the Office of New Drugs in CDER. Thank you very much for the invitation to speak here. So by way of background, I'm a pediatric clinical genetics -- geneticist and I practice clinical genetics for several years and also I was involved in research before joining the agency and so I think from my perspective, the case of individualized or targeted

therapies is very, you know, dear and near to my heart and, of course, very, very fascinating.

So I was fortunate enough to be involved along with, you know, collaborate with team on the application for Milasen. This was a tremendous opportunity for both myself and the team to learn from both team members, group, from the family, from -- you know, we all were very invested in trying to figure out how can we best fill the gaps and truly pave a new and novel way of looking at this case.

So obviously, this individualized (inaudible) therapies is a very, very novel approach and I think, you know, what you're hearing today is really very good example of collaboration but also creative thinking and really being as flexible as one can be, keeping in mind the end goal and also the end result, right. So I guess first of all, I know the panel previously talked about natural history studies and (inaudible) the disease.

So in Batten disease, there are some natural history studies and there's, of course, observation in day-to-day clinical practice from

physicians in that case, you know, and of course Julia knows this better than anybody.

There was kind of a clear path of where this would lead and so the question, at least from our perspective and the team's perspective is what do we need at a minimum to make sure that we satisfy the regulatory requirements the way that FDA interprets the regulatory requirements, and of course place those in the context of this individualized therapy and the individual patient.

And so in that spirit, I think, from our clinical team, our toxicology team, our clinical pharmacology team, so everybody kind of came together and actually had very frequent interactions with Tim and his team and it was one of those times that I feel like I was just so excited to be involved with this, that as soon as update came from Tim about, you know, what's going on, how Mila is doing, and what dose should we do next, I would drop everything and just read it and, you know, try to figure out and email people and say, okay, here's what we have now, what should we do next.

And so it was great -- of course, very satisfying because for myself, I've seen those children, I've diagnosed those children and so I very well know how the patients and the families think. So I mean, from a regulatory perspective, you know, it can be very difficult. This is novel. We're not used to it. FDA is not used to it. (inaudible) it's a normal paradigm and the question becomes, do you fit this into your traditional paradigm or do you created a brand new paradigm, right, for those individualized therapies.

And the question is, we probably do a little bit of both, which is what our team also did. You know, you really have to understand the regulations deeply to really know why was it a regulatory climate. It's not only, okay, well, you make two studies or in two different species for toxicology, but why is that and what could we do, you know, to get the minimum amount of, let's say, toxicology data, right, to have some assurance of safety so that the patient can get treatment.

So I feel like our team really did a

fantastic job really coming together and thinking through this and not just saying, well, that's a requirement and that's the end of it. Because that just wouldn't work, and we knew that. So a lot of lessons learned, I would say, from this case and we continue to learn as we, and of course, Tim and Julia follow Mila and how she's doing.

It's been very inspiring for all of us and I'm sure everybody in the room would agree and I know that from a part of CDER and OND, there's active work being done to bring people together to think through the challenges and also think creatively and realistically about how we can help in this process to move those therapies forward.

MAARIKA KIMBRELL: Thank you. So listening to the five of you, I've got two questions that have come to mind. The first relates to, I think maybe each of you referenced the need for flexibility and responsiveness from a regulatory perspective in these areas, and what that brought to mind for me was considerations of benefit and risk when you have previously uncharted waters in a treatment.

And so could each of you sort of reflect on how you experiences with individualized therapies have brought -- how you've considered benefit and risk and how it might be different from other areas or may be similar, and from your various perspectives as patients, as parents, as regulators, and as physicians?

ELLA BALASA: Well, when I received the therapy, as I mentioned, I was in a dire need where I -- my life was at risk, and so I think that's an important consideration when deciding what is the appropriate time to do an individualized therapy or if at all, and weighing that benefit and risk analysis. For phage therapy, personally, it's something -- this is not -- it is a new therapy, but it's been around for a while and it had been tested in patients before, so I wasn't the first.

So I think that made me more comfortable with trying something that has been researched, has been shown to be effective; whereas, you know, with a case like Mila's, that would've been uncharted completely and so I think that that is a big

factor in determining whether, you know, or understanding the risks and the benefits.

DR. PATROULA SMPOKOU: So I guess I can go next. So that's a really important point and I guess it goes back to assessing the benefits versus the risks because the risks, of course, you cannot really assess by itself at any point in time, so from a regulatory perspective, I think every decision or almost every decision that we make and at least the way that I think about it is truly a benefit/risk assessment.

So the case -- in the case of individualized targeted therapies and in this particular case with Milasen, we're dealing with a neurodegenerative disease, very severe with quite clear trajectory, of course with variable progression, but we have a good idea of kind of what to expect in general, so I would say that in order to determine how much safety data, for example, you need to assess whether and IND is what we call safe to pursued, and also what dose to use, how to escalate the dose, but so a benefit/risk decision.

And also, you know, what data are emerging, how's the patient really responding to treatment, what toxicology information do we have from animals to maybe guide our safety monitoring to put in that benefit/risk determination and then, of course, how does the patient themselves report or if they're not able to self-report, what does the family think about how they're doing, either objectively, subjectively. And in that way, you can put kind of the picture together.

I do believe, though, that at the end of the day it's a truly benefit/risk decision from the patients' and the families' standpoint. I don't know that anybody else can make that decision, truly. That's something that at least, you know, and for Milasen, and I communicate that very clearly, you know, these are the requirements. This is what, at minimum, we want to see. We'll be in close collaboration, and we were, and we had a very open communication.

But in terms of tool making decisions about increasing the dose or, you know, or decreasing

the dose or making changes to the frequency or decisions about continuing or not continuing the treatment, I think in terms of providing all the information you have, it's really the family's ultimate decision to really weigh, what does the risk mean to them. Because, of course, patients with rare diseases, we know that very well, the definition of risk is very different that someone who may have more mild or more common disease with a very different trajectory.

And so we recognize that, that the risk threshold is very different and so I don't know that you can ever really truly appreciate that unless you're a patient with a rare disease, and so from a regulatory perspective, we can have an idea of what maybe the benefit is. We can have an idea of what maybe some of the side effects have been, but putting this together to actually make a decision in the case of a individualized therapy is really difficult and the patients and the families are truly the ones who can make that decision, so -- but just to point out that I think the risk, a lot of times, as you said,

can be defined very differently by different people.

JULIA VITARELLO: Thank you, Patroula. I feel like you said a lot of what's been on my mind. Leading up to Milasen -- to Mila receiving Milasen, I have to be honest that the risk/benefit analysis was pretty straightforward and black and white to me. When I faced it, was the risk of treating Mila versus the risk of not treating Mila. It was very specific to one person, to my daughter, and what was going to happen to her if she wasn't treated was very black and white. She was going to lose all of her abilities in a few years and she was going to die.

And the risk of treating her was an unknown, and Dr. Yu and I had a very good communication, on a daily basis, practically, and I was -- feel like I was educated as much as possible in what the possible risks were and we really didn't know. There was no other patient in the world receiving Milasen and there was actually almost no other patient in the world receiving a drug like hers.

And I have to be honest. I never spent more than one second questioning whether or not Mila

should start Milasen or not. There was no other option. There was no other treatment and Mila was losing her abilities rapidly, by the week, by the month. She was losing her -- down to two words and then the one word and down to no words in just a month. Taking five steps, one step, couldn't step at all by herself. And so for me, this was a great opportunity.

I was afraid that -- Mila was not having any pain, and so I was afraid that maybe, you know, Mila would start having excruciating pain and that was scary to think about; however, it absolutely did not influence my decision whatsoever, because the other option was, is that she was going to lose all her abilities and die. And so it was a pretty easy kind of risk/benefit analysis on my part.

I would just say that communication was really important in terms of being able to do my very best as a non-scientist, non-physician of understanding what Milasen entailed and believing that there was some reason to have hope that Mila could have a stable disease or potentially much less

quickly, I guess, declining as she was going at that moment in time. And so it did offer real hope. This was not voodoo, kind of wild stuff that, you know, it was an unknown. It was a legitimate hope that Mila was given, so I weighed this, too, and it was pretty black and white for me.

DR. CELIA WITTEN: I would like to reframe the question slightly the way that we think about it. But let me say it's obviously always case by case. I think the facts are different, but it's really a risk/benefit decision in the face of a certain amount of uncertainty or an amount of uncertainty.

And that amount of uncertainty may vary, depending on the application, and so to say who makes the decision or how you make the decision, I think it depends on a lot of things, but the uncertainty has to be taken into account. And there are other considerations, too. For example, if you look at the spectrum of the products that we've -- that I mentioned are addressed in our center from phage therapy to gene editing, gene editing can't be

withdrawn.

It’s not something where you can do a dosing study and then stop it or anything like that, so for these different situations, you -- and you may have a different understanding in different cases about how likely it is to be of benefit. Like, if you have a lot of uncertainty about risk but a fair amount of certainty about benefit, you might we willing in some circumstances to act on that.

So I think it would be hard to answer generally, except to say that I think the uncertainty about the information you have supporting the application is also important.

DR. TIMOTHY YU: So a little bit of background on how we thought about benefits and risks as we were considering whether to offer this therapy, whether we had done sufficient work, we were just -- had we done sufficient work to justify our offering this hope to Mila and her family. So just to level set so folks know what was done for this drug, we decided that we wanted to go after a splicing defect, a defect in the way that Mila’s gene was being

assembled.

And there are very simple but effective tools for looking and studying splicing if we wanted to, using patient-derived cells. So to be very concrete about it, we took a very small skin biopsy from Mila and then grew those in the laboratory and then studied her gene with and without the drug and were able to show that upon application of our drug, the splicing defect, the gene assembly defect would reverse itself upon application of this new investigational drug.

So that gave us some strong basis for thinking there could be a mechanistic improvement here. We took it a step further and we also shared with the FDA data showing that would her cells actually become healthier when you've given this drug, and we showed that this disease was known to change the way that cells recycle proteins and, in fact, in the absence of this gene working properly, cells would fill up with products that were meant to be recycled but never actually made it to be recycled.

And so they would build up and

accumulate trash, so to speak, and what we found was that treatment of her cells with those -- with that drug was sufficient to allow recycling to happen again and so they actually got healthier in front of our eyes. We could see this and you could -- we could build up a scientific rationale. This was not a shot in the dark. This was something that looked scientifically plausible.

All that being said, there were still many, many unknowns and that standard that I just described, while it was good in this particular instance, that's not always sufficient for a rare drug application to go through. But in this case, as we discussed, we were up against a disease where the natural history is very clear. The risks were very, very clear and we could talk about them with Julia and Mila's father and work through what exactly all of this meant to you all.

And it's a very individual discussion. I think that's the interesting part of this. Now, if we take an agency which holds great institutional knowledge about proper drug design and safety at the

level of populations, and now we throw in the application of that knowledge towards drugs that might just go to a single patient, the good news -- the decisions are so personal and so individualized, and they have to do with the physician-patient relationship and how one talks through our assessments of these risks and benefits.

But the good news is that the agency is populated with plenty of folks who have counseled patients on these exact issues in their own practices, and so I think the novel piece here is figuring out how the regulations that apply to protecting public health apply in the situation now where you're juxtaposing that onto individual decisions by individual families.

So I think that that's the part, you know, we're really grateful that you reached out on a limb to extend that paradigm to this case and looking for ways that we might continue doing that.

MAARIKA KIMBRELL: Great, thank you. I've got one more question and then I think we'll open it up to the audience, but we're, as we predicted,

eating up a lot of time, so maybe we could try to keep this one quick, but I do want to hit it.

So one of -- Celia, I think it was you, talked about these situations often being successful when there's somebody heroic in the mix gluing everything together or I tend to think of it as sort of the stars aligning in a particular situation, and I think our aim is that this shouldn't only be successful when the stars align perfectly or when we have heroic family members or investigators or whoever working to make something happen.

So what can we do, especially as regulators and -- to sort of ease that process, to ensure that these treatments are available to the less than amazingly heroic among us and then also what -- in that vein, what were your reflections on working with FDA and from the FDA or sort of with the investigators of what works well, what was successful, what comes to mind as important to keep in mind for an efficient process?

ELLA BALASA: So I didn't have any direct communications with the FDA in my treatment. I

really -- I really communicated with the investigator and -- but I think, you know, as far as my case, my doctor couldn't take on that role of being the investigator. And I think that this is quite common. You know, it can be, I think, a daunting and arduous process to find the appropriate IND, making sure your protocol is streamlined, and all the communications that come along with that with the FDA.

I think a lot of new providers or investigators aren't aware or aren't able to do this, and I think, really, part of the FDA to help and create guidelines and really walk -- help them walk through this process so that more patients are able to access these treatments, I think a lot -- you know, there's certainly roadblocks all along this, from -- honestly, I'm a patient that advocated for myself, but if I didn't have a provider that was willing to take on my case or if the communications with the FDA weren't streamlined, it wouldn't have happened. So that's really, like, the stars had to align, as you were saying.

And also, I think, to remember that

it’s a resource intensive experience or process for the investigator, too, because they have to communicate with the patient. I had to feel comfortable that he had my best interests in mind and my health in mind and -- when has to communicate with the FDA, and then along with the creation or the collaboration for the creation of the investigational therapies. So it’s quite a bit on an investigator to navigate all that.

JULIA VITARELLO: I was incredibly impressed with how Patroula and her team shifted from a paradigm that they were used to where there was one drug for thousands of people to entirely new paradigm that they had never faced before where the ripple effect was one. So it was Mila. No one else was taking Milasen and they were able to change, they were able -- faced the risk/benefit analysis and look at what the risk of treating Mila was versus the risk of not treating Mila and really treat her as one individual patient which reminded me a little bit of something like a brain tumor and removing a brain tumor and, you know, a doctor has a conversation with

me that says, you know, Mila has a brain tumor and we can take it out or we can leave it in, and, you know, having that kind of back and forth discussion of the risks of taking it out versus the risk of not taking it out for that specific patient.

And I really applaud Patroula and her team for shifting to a really different mentality that they were not used to and really thinking about Mila. And as we moved forward, now, this has opened up a potentially new field of medicine, of really truly personal medicines, and what I see is I see Mila and she was treated. And when I see potentially, you know, millions of children just with fatal diseases alone that could potentially -- we don't know yet -- could potentially benefit from a treatment like Mila's and how do we get from Mila to really, truly making a difference, not just treating another two or three Milas, but really offering a tool in the toolbox across many, many diseases, and that's going to require working off of this new entirety and thinking how do we face risk/benefit analysis when there's one child or two or three and it's not being given to

thousands of people.

And so I just hope that -- my hope is that we see more of this really out-of-the-box thinking and really realize that most people like me don't have any options and that this offers something exciting, but it needs very careful and very aggressive pushing forward and opening up a new potential field of medicine. So thank you for everything you've done. I hope it continues.

DR. TIMOTHY YU: Okay. I thought I would like to say that cases like Ella's, cases like Mila's, these individualized cases, they require thinking, in a way, very small. They require thinking about individual patients' needs, about their particular assessments of risks and benefits, and they require thinking about treating that one patient in the doctor-patient type of way.

But in a way, even though these individualized cases set a template and allow us to try something new, it's worth the walk only if we also figure out how to think big. And the question is, it's not that we want to convert drug therapists' and

drug developers' efforts towards now instead of treating whole classes of disease at once, now just treating single patients at once. That's not the point of that. That doesn't make sense, right.

The point is that how can we leverage these wonderfully advancing tools to develop individualized treatments and then figure out how to scale it? And the true measure of success, I think, in this space, if we do this right, is that these first examples will pave the way for further examples such that each example that follows it gets easier and easier, not more difficult and more difficult. I think that that should be the goal of what we try to do from this point doing forward, thinking about how -- the lessons that we draw. Well, if you focus one, you -- one patient, you can get amazing things done, and can we use that to develop policies that allow that to scale and so that each patient informs and makes the next patient's journey that much easier. I think that that's a really critical piece that I see coming from this.

DR. PATROULA SMPOKOU: Yeah, I wanted

to add, the one important piece that I thought was critical in this is the diagnosis, right, so Julia talked about how there was just mutation found and you kept looking and you kept looking and if you didn't do that, you wouldn't be here, right?

So and the diagnosis is many of the rare diseases and in the inborn errors metabolism which is the area that I work in is sometime actually quite challenging, even in this era of this, you know, genetic revolution and all the tools that we have and all the technologies, because even if you find on mutation or two, we still have to put it in context of the patient themselves.

What we see sometimes is that there's no specific guidelines of how the diagnosing of those patients or how to treat them, now to follow them over time, and that really becomes an obstacle when you try to really look at a specific patient's mutation, for example, and kind of inferring how the patient may, you know, progress with a disease over time.

So I think what we were discussing today about Mila's case and other cases, is actually a

great example of all the fundamental concepts that I think were discussed throughout the day today which basically is the diagnosis is really the most important step in the awareness of rare diseases, and really, the outreach to patients who may not otherwise have access to some of those technologies through some infrastructure and networks, but also a very delineated trajectory of disease.

So if we didn't know anything about Batten disease, right, then that would be a very different story and so the natural history of disease, we all talk about this, but it just becomes so critical because if you don't know the trajectory of the disease and you don't know what to follow, when to follow it, what to focus on, and so, you know and the other piece of that is really the collaboration, the communication that I know we touched upon and so at least from my perspective in my division, we're involved very much in outreach and engagement and so when I myself try to attempt meetings and really learn from the outside and so I think at least for me that becomes important because you realize, what is it that

the community wants.

But 00:53:25 also the gaps that there are there and how can we, you know, as FDA, maybe help in that way to fill those gaps or bridge those, you know, those gaps in some way. For example, I go to meetings and then I hear some investigators talking about, well, FDA doesn't know, you know, what we do and what we want and I'm kind of a fly on the wall and try to listen and say, okay, what is it that we're just really not getting across.

And some of those actually end up in guidances, and we wrote two guidances recently on inborn errors and this is where a lot of, kind of, the engagement comes in to try to tackle some of those and this actually trickled down to how to bring people together, really, to work together in this very mobile space and the trajectory of the space is going to be changing a lot and, of course, the basic principles will apply always, and I think we all need to be aware of what those are, but also how to apply them in a flexible way, in a creative way, and really a way that makes sense to kind of all parties involved.

DR. CELIA WITTEN: So one thing I'll just mention, that I know this comes up a lot in different contexts, but it's critically important here, and that's about sharing information so we can learn from what we've done.

And it seems like it's always a hard target to hit, but in this case, it's really important because we can talk about learning from our experience or people learning from their experience, working with FDA or us learning how to work with people to develop these, but if we really want to -- and I agree with what you said, if we want to scale this, then I think we have to think simultaneously about how we're going to learn from each of these experiences, not just about the process, but about what we saw -- what we saw from whatever preclinical testing that was done or bench testing and how that -- what we learn from the patients.

MAARIKA KIMBRELL: I think that takes us back to Dr. Yu's comment of focusing on both thinking small and thinking very big at the same time. So on that note, if there's any questions from the

audience, we'd be happy to take them.

AMY DAHM: Hello. My name is Amy Dahm. I'm with the Cushing's Support and Research Foundation. I myself am a Cushing's patient and I also have postoperative adrenal insufficiency. And Dr. Stratakis at the NIH has been research that's showing that there are some genetic mutations that can at least contribute to Cushing's. So given that and given CRISPR, my colleagues and I have been wondering what would that look like?

Like, what would it look like if you took CRISPR and Cushing's and -- would it be a complete prevention of it? Would it be a complete reversal of it? Like, would you have it one day and then the next, you wouldn't? Like, what does it look like?

DR. CELIA WITTEN: I think that it's -- I'm optimistic that in the long run we'll be able to figure out how to answer questions like that, but I think people are just starting to use -- you know, well, they have been under study for a couple years, but we're just starting to learn about how to make

gene editing tools useful. But the basic idea is to make a correction of the genetic defect in the cell in each cell.

The challenge -- well, there are many challenges, but one of many challenges is how to get it to the cell, how to -- if you can figure out how to correct the defect, how do you actually deliver it? So if you could perfectly deliver it and make these changes, then you would be good to go, but that -- there's a big different -- distance between where we are not and getting there, so I'm certainly optimistic that we'll get there, but that's the current state of things.

AMY DAHM: Thank you.

MAARIKA KIMBRELL: Do we have time for one more question? One more question.

CHRIS DEMARCO: Hi. My name is Chris DeMarco. I was diagnosed with a rare -- ultra, ultra rare disease. It's a one-in-a-million, back last year and very quickly found out there was no research, no patient registry, no foundation supporting the disease. We started a patient registry very much like

-- my world changed at that moment, you know, to try to create something that would actually, you know, look for a cure for this disease.

One thing I found, though, is it's interesting. As soon as we got the momentum going, that people are very interested in getting engaged and, you know, we've talked about a proof of concept for liver gene therapy, but a lot of it comes down to funding, you know, and so I'd be interested to know the -- from a individualized therapy, this is an ultra rare. It's like one in a million, so it's -- we found maybe about 20-some-odd patients around the world so far.

But being able to get someone interested in funding something like, if we got positive results from the liver gene therapy, you know, you're talking about individualized therapies, it's got to be significant amount of money.

DR. CELIA WITTEN: Yeah, I think that is a challenging area, which is why I think we're -- we have to discuss that collectively because I don't -- a lot of these, it's hard to see what the commercial

model, you know, what the model is for making these commercially viable efforts. So I don't think it's going to follow any kind of traditional pharmaceutical company supports it, kind of model. But I know you have probably -- Dr. Yu would have something to say.

DR. TIMOTHY YU: Thank you for ise that question. It's one of the biggest challenges in this space. I think that what we have are issues of drug design, drug testing, manufacturing, toxicology, and then administration. And we have standards that have evolved for how to do those things safely and effectively. By and large, many of those standards -- all of those standards have evolved with the best interests of patients in mind to protect their safety and to ensure the utility of the drugs that actually make it through the pipeline.

But I would -- I might argue personally that many of those standards have evolved in the area of big drugs like statins that might be given to tens of thousands of patients at a time. Now, I know that's an over simplification that that there are many forward-thinking ways about how to apply these

standards to smaller and smaller populations where that kind of investment can't be easily raised, but not take that drug development process and now apply it to a single patient for a family that's in dire need, and you've gone and blown up the problem even bigger.

These are really expensive projects and as -- I'd say, there's no norm. I'd say our first case, our one -- our first case of a brand new drug developed for a patient doesn't establish a norm. It just highlights an issue that needs to be solved, which is that it takes too much money to navigate all of those steps that I described and we just have to be creative about finding solutions.

I'll put in one brief plug. I'll say that for the particular route that we chose, we chose to use an antisense oligonucleotide drug approach, and that's an approach that has been around for about 30 years. The basic manufacturing process has -- it relies on chemistry that was developed 30 years ago -- actually, a lot more than 30 years ago, and as far as manufacturing processes go, I think arguably it's

among the simpler, much simpler than, say, gene therapies.

So you can mitigate the costs of manufacturing in a case like that, but on animal testing and toxicology, that's still extremely expensive, so finding ways to really make this work will require thinking about ways where we can leverage results from one experiment to another experiment of a close -- involving a closely related drug and another experiment involving another closely related drug.

If we're learning from each of those and the learnings bolster one another, we should be able to shrink that gap. I don't know if it will be sufficient, but we have to try.

MAARIKA KIMBRELL: Great, thank you. And I think we're about to be dragged off the stage. So let's -- I think Dr. Maynard's going to introduce the next panel, but thank you everyone and thanks to the panelists.

DR. JANET MAYNARD: Thank you so much, and if I could invite our last panelists, Panel 5, the Ecosystem of Rare Disease Product Development, on the

stage. If you don't mind sitting in the order on the screen, it will just make it easier as I put your name under. So Susan, you can sit here. Yep, then Martha.

DR. SUSAN MCCUNE: That's --

DR. JANET MAYNARD: Oh, no, I'm sorry. Chris.

DR. SUSAN MCCUNE: All right. Good afternoon, everyone. Wow. So we're bringing it home, guys.

DR. CHRISTOPHER AUSTIN: They're all still here.

DR. SUSAN MCCUNE: I know, and everybody wants to hear everything you have to say. So I'm really excited to be moderating this panel and I'm really excited because I'm not going to have to do much talking because I have real experts up here on stage.

So I'm Susan McCune. I'm the director of the Office of Pediatric Therapeutics in the Office of the Commissioner at the FDA and a little background on me is that I'm a pediatrician and my subspecialty is newborn intensive care, so we're going to the

extreme, young extreme for me and it's always an opportunity for me to think about how to move some of these therapies forward in the neonatology space.

And as I was talking to Janet, it's nice that I was going to help to focus some of the discussion today on pediatrics, but I don't need to because we've actually had a lot of really good discussion about pediatrics throughout the day in all of the panels.

So I know that we will continue to do that here as well, but I don't think we have to highlight it as much as I thought we were going to. So with that, we're going to talk about the ecosystem of rare disease product development, especially related to a lot of collaborations and we kind of talked about that sort of through the course of today. I'm going to let all of my august panel members kind of introduce themselves and as you're introducing yourself, tell us kind of a little bit about high level, what you think in terms of where we are in terms of the ecosystem and collaborations for rare disease product development and then I'll ask maybe

some specific questions as we go along and then we'll open it up for panel discussion after about half an hour. So, Chris, why don't we start with you?

DR. CHRISTOPHER AUSTIN: Yeah, sure. So thanks. I'm the person that the panel -- one of the panelists kept talking about, so I -- my ears were burning. I'm the director of a part of NIH you may never have heard of. It's called the National Center for Advancing Translational Sciences. It's one of the institutes at the NIH. If you were here for the panel this morning on natural history studies, you would have heard Ann Pariser. She runs our Office of Rare Diseases Research, which is part of NCATS.

I guess my perspective about the ecosystem is -- I guess I might summarize in two ways. First, the fact that we're having this meeting at all, I think we all need to celebrate and you need to congratulate yourselves for getting us here. Twenty years ago, when I was laboring away, as a lot of were then in this field, it felt very, very lonely and it doesn't anymore, and that's because of the efforts of a lot of people at the FDA, a lot of researchers, but

also a lot of patients like you.

And the only reason we've gotten here is because of the collaboration with all of you. At NCATS, we like to say that everything we do is a collaboration and, in fact, that is true, and that's because the field of translation, which we do, is, as we like to say, is a team sport. I don't care how smart you are, how motivated you are, you cannot successfully transform a fundamental discovery into an intervention that is shown to improve human health -- that's what translation means in medical parlance -- by yourself.

And I think one of the changes that we've seen which have enabled some of the remarkable things that we've seen in the last few years is this slow change toward teamwork. Scientists are not trained to be -- at least, traditionally they have not trained to be team members. My own well-meaning mentor when I was growing up told me never to collaborate with anybody, because all you're going to do is get scooped and, you know, you'll get hurt and all these things.

And she was very well meaning and looking out after my best -- what she thought was best for me, and I think in basic research, that can happen. But in translational research, you just can't get anywhere without doing this, so I think I'm really pleased about where we've gotten. You should know, however, that your academic colleagues are swimming upstream in this kind of behavior.

It is still not rewarded as it should be in the academic world. We're trying very hard at our place to change that and we need all the help we can get. And when I look at the limitations that we have to getting to the dream that we all have, so how do we take these extraordinary examples like Milasen that you just heard or the SMA example or others you probably know, and making that promise a reality for the many, many, many people for whom it is technically possible now -- which itself is a miracle -- what is that going to take?

It is going to take all of us to up our game another order of magnitude to working together and to realize that we have much more in common than

what separates us. We may have different disease names, but they're all rare diseases. They're all connected in one way or another. And what we see over and over and over again is the more -- we have a very diverse team of people who thought they had nothing to do with each other that gets together to work on a common problem.

That's when magic happens, and I think the more we do that and the more we pull together as a community, whether it's with data or looking for commonalities among diseases or platform technologies like we're been talking about or regulatory approaches like is all -- been talking about, the more we do that, the faster we'll make headway.

DR. SUSAN MCCUNE: Thank you. Martha?

DR. MARTHA DONOGHUE: Hi, good afternoon. Is this working?

DR. SUSAN MCCUNE: Mm hmm.

DR. MARTHA DONOGHUE: Excellent. My name is Martha Donohue. I am a pediatric oncologist and clinical team lead for the team that oversees the regulation of new cancer drugs to be developed for

gastrointestinal cancers and I also do quite a bit of work through the Oncology Center of Excellence on pediatric oncology initiatives and it's a pleasure to be here, so thank you so much for having me.

I guess to summarize sort of where I think the ecosystem is for development of rare -- of drugs to treat rare cancers, I think the ecosystems is alive and well. It's evolving and changing and is extraordinarily complex and it's exciting to be a part of it, even in a very small way.

And the field of oncology, I think, mirrors a lot of sort of what we're seeing for a lot of other diseases in that, with the advent of personalized medicine, we're seeing some amazing advances and potential for development and approval, actually, of drugs to treat a variety of diseases that heretofore we were having very limited success for. One example is the approval larotrectinib and entrectinib for NTRK fusion solid tumors and for one of the very first time, we were able to approve a drub not based upon sort of the histology of the tumor or where the tumor was in your body, but rather the

molecular underpinnings of that tumor and what was driving that tumor.

And while these are amazing success stories, they also highlight the challenges of development of drugs to treat rare cancers, so while we were able to give a relatively broad indication for these two drugs based upon a biomarker and tumor, at the same time these biomarkers were extraordinarily rare for almost every cancer, so less than 0.1 percent to 0.2 percent of all types of adult cancers would have this biomarker and on the other hand, you'd have some very, very rare pediatric tumors such as infantile fibrosarcoma that would have this biomarker, but those cases would only be a handful.

And so looking at the drug development paradigm for -- those particular drugs highlighted a lot of the challenges for rare disease drug development. How do you find the patients, particularly when you're thinking about clinical trials for a drug? How do you enroll patients where there only may be a handful of sites, and yet the patient may be thousands of miles away? And how do we

assess effectiveness of a drug when we don't do a randomized clinical trial and certainly where placebo control would not be ethical?

And so when we're looking at specific cases like that, it kind of helps us to kind of innovate and drive collaboration and communication with one another and be flexible and creative and all those other attributes that I'm hearing a lot of other people speak about on this panel. And it's, you know, examples like this and our increased understanding of the molecular biology of cancers that's transforming the way we look at cancer drug development, where we typically would have the luxury of large trials and big development programs for lung cancer and colon cancer, for example.

Now, we're seeing smaller and smaller pieces of pie within those large cancers and we're having to figure out, how do we develop drugs efficiently and get these drugs to patients faster? You know, at the same time, we're looking at not just developing drugs. We're looking at developing the technologies to identify patients who could benefit

from these drugs, and so that adds a degree of -- an additional degree of complexity to drug development.

So in order to address these challenges and many opportunities that we have to get drugs to patients more quickly, collaboration, communication, working together becomes even more imperative that it once was. It's always been important, but as we're seeing more and more things become rare diseases, it's forcing us in many good ways to work together. And so what I've seen, at least, in the area that I work in at the agency over the past five to 10 years, is increased energy being spent toward this collaborative process.

We have the Oncology Center of Excellence forum in the Office of the Commissioner, and the reason for the Oncology Center of Excellence is for us to collaborate with one another more closely across centers so that we have a better understanding of what's going on with cancer drug development in the Center for Biologics, the Center for Devices and Radiologic Health, and the Center for Drug Evaluation and Research so we can work together to streamline

things to the extent possible and to share information.

We're also seeing increased emphasis on working outside of our own organization, working -- reaching across the pond to work with European regulators, for instance, and we're seeing true tangible success from some of these efforts.

We're just piloting a program now whereby we're reviewing drug applications in a coordinated way with other regulatory authorities and I think that we're early stages for that, but that provides us with an opportunity to talk to one another more, maybe streamline evaluation of a specific application to benefit patients, but also learn from one another in the long term so that we can learn to work together even early in the drug development process.

So I guess I'll end there, but I do think it's an exciting time to be in this environment, rare disease development. I think there's a lot of energy being applied to it and a lot to learn and a lot to do.

DR. SUSAN MCCUNE: Sheila?

SHEILA MIKHAIL: Hi. My name is Sheila Mikhail. I'm the CEO and co-founder of AskBio. AskBio is an AV gene therapy company. It started off as a collaboration, so collaborations are at our roots. It was started by parents who had children with devastating disease. Traditional medicine didn't provide them with any answers, so they reached out to researchers.

These were very educated research patients -- research scientist's patients. They read every single paper. They looked at all different types of alternative medicines and they were extreme advocates for their children, really admirable people. They reached out to Jude Samulski who was the first to clone AAV for therapeutic purposes. He's the scientific founder of our company. And if it wasn't for those parent collaborators, we wouldn't be here today.

For a long time, gene therapy was not seen in the best of light. People thought it was too risky and it was too much science fiction. I would go

to different investor conferences with all the Wall Street crowd and they would just walk away from me. It was almost like I had the Coronavirus written on my forehead.

Today, it's a different era, but again, I think the number one thing that I want to say is you really have to collaborate with patients because that's what makes your effort sustainable. They can't walk away, in many instances, from their endeavors and their money is short of a short-term goal. But having -- making treatments that have benefit for patients is a much more long-term, sustainable objective. Over the years, we have developed treatments for Duchenne's and in a second I'm going to talk about that and how we use collaborations to advance that drug.

We also developed treatments for giant axonal neuropathy, and in that case, we had parents who had Relay for Life races and bake sales, but on the basis of those grass roots fundraising efforts, we actually have treated several patients and with the collaboration of NIH and the support of NIH.

We have also advanced treatments for

hemophilia which are now being advanced by Takeda. We're in the clinic right now for a Pompe and heart failure -- late stage heart failure. We'll be in the clinic hopefully by the end of the year for MMA and limb-girdle 2i. We're also working on Huntington's which we hope to be in the clinic next year. Gene therapy is exciting.

It has a lot of potential and it's giving a lot of hope to patients, and I'm very fortunate to be part of this change in making history. The example that I want to give is in the treatment of -- the development of the treatment for Duchenne's muscular dystrophy. As I mentioned, we started our efforts at a time when gene therapy was perceived as science fiction. We could not get funding for the product.

We had parents who literally put in their own money, did bake sales, did a lot of things to advance a therapeutic. GSK, this is another example of a collaboration, gave us access to a capsid that they just had sitting on the shelf and that allowed us to use what we thought was going to be the

best capsid available.

We collaborated with academics who had the dog models, the Golden Retriever dog models and didn't have a lot of money, so people are just -- are kicking into this effort. We went into the clinic with the support of the Muscular Dystrophy Association. If it wasn't for their support, we wouldn't have gone into the first -- into the clinic the first time. At that time, it was in the last 2000s.

People were very skeptical of gene therapy, so we could only inject in the muscle and in very small area, only put a small amount of virus into little boys the size of an eraser. Not -- knew it wasn't going to have therapeutic effect, but we had to demonstrate that it was safe, baseline safety. We were successful there.

Again, we went back up to Wall Street. We had dogs out nine years showing that we could correct the dog model. Could not get funding. Everybody said, it would not work. (inaudible) stepped up, helped us -- another collaboration -- with

the funding to do all the I&D enabling studies. We ran out of money, but we had the opportunity to collaborate again with Pfizer. Pfizer has taken the drug into the clinic.

They now own all rights to it, but we're very happy because we have met many of the boys in that clinical trial and they should be in wheelchairs today but instead, they're playing Little League baseball and they're enjoying swimming lessons, and that's why most of us in this space do what we do. We get up in the mornings because we want to make a difference in patients' lives and we have had had the satisfaction of ASPIRE, of having that impact on patients.

The other thing I want to mention is our foundation, because it's equally important to me as the for-profit part of our business. Columbus Children's Foundation was founded -- again, we were very patient motivated to address the needs of ultra rare indications that can be treated by gene therapy. We do this through a nonprofit structure. These are indications with 100 or so or fewer patients.

We don’t have a hard stop, but we know that those are not commercially viable indications, and so we donate our technology, our manufacturing capacity, our (inaudible), our regulatory, our legal support to the advancement of these drugs. Today, we’re working on AADC, amino acid decarboxylase deficiency. That’s a mouthful. And we have treated 20 patients free of charge. I think we’re one of the few groups that has done that.

We’re also -- have in our pipeline for the foundation (inaudible). So those are the diseases we’re working on. Thank you.

DR. SUSAN MCCUNE: Vasum?

DR. VASUM PEIRIS: Thank you. Mic’s on. Perfect. First of all, thank you very much for everybody for continuing to stay here. This is a very important cause and it’s wonderful that as we’ve talked about before, that the meeting is happening. I just want to thank Janet and the entire OOPD team that has put this together and all of the people that have worked to get this to happen, so it’s wonderful to see so much registration and so much interest across the

country and across the globe in these issues where rare diseases.

Very simply put, in terms of introductions, I'm going to build on what Jeff, Dr. Shuren, the center director mentioned. For the purposes of this panel, I am the gizmo guy, so I'm the chief medical officer for pediatrics and special populations at the Center for Device and Radiological Health. My clinical background is in pediatrics, (inaudible) pediatrics, pediatric cardiology, and adult congenital cardiology.

So I really had an opportunity in private practice to see everything from the fetus, prenatal, perinatal medicine all the way through the hundred-year-old and you can imagine in a field like congenital heart disease, it's extremely device rich, but certainly very much also dependent on medications and I'm sure to (inaudible) share great deal of insights with Susie with respect to any neonatology as well.

There's a lot of topics to address, but I'll try to focus on that you brought us towards, as,

you know, what is the ecosystem, what is the state of the ecosystem and where are we going, really. I think it is wonderful that we are coming together and that there again, there's so much interest. There is a great deal of work that's being done, I think, in the biologics and drug space.

There continues to be great potential in the device space and I think as we move forward, we recognize how much devices and advancing technologies will make a difference in patient lives and the difference that they make every single day in patient encounters. If you really think about it, when you go to a doctor and you have a doctor visit, there's a higher likelihood that you actually might engage with a medical device -- you know, a thermometer, a dipstick, a blood pressure cuff -- than you might with a drug.

That that's something to be cognizant of as we think about how technologies are affecting lives and especially with respect to small populations and rare diseases. We -- a couple of the earlier panels alluded to this a little bit, but I think

there’s necessity to really work -- maybe focus on this a little bit more, but with respect to how we can begin to advance technologies to truly serve the purposes of small populations, pediatrics, and rare diseases, we have to begin the potential of the ecosystem together.

And the issue around collaboration that Chris mentioned, I think is an important one. I’ll just highlight one point around that very historical notion that people were told back in the day, perhaps, don’t collaborate because your academic careers really are based off of you being the leader, you being the thought leader, you taking forward research.

It’s wonderful to see that medical schools across the country in their mission statements now are putting in that they -- one of their purposes is to develop collaborative professions. And that collaboration over time can make a significant difference.

And from where we are right now, when you think about how do we optimize the potential of the ecosystem, we’ve got to bring together issues not

just in the regulatory space, not just in the clinical space, but in the economic space as well because we recognize that there are a great deal of efforts that could be considered perhaps one-offs, a great deal of philanthropic investment in certain area, either certain aspects of Milasen or a specific disease or a specific drug or a specific medical product.

What we want to get towards is a platform that allows anybody with great ideas, great potential, to be able to invest in the development of medical products for rare diseases, especially in the pediatric population. One of the things that Dr. Shuren mentioned earlier is the SHIP Program. That's the System of Hospitals for Innovation in Pediatrics. It is a program and a framework that we've put together to really consider what is the next step in an ecosystem that truly works for the benefits of small populations and pediatrics.

How do we begin to bring together individuals and organizations across the ecosystem and across the spectrum to truly begin to think differently around investment in pediatrics so that we

can actually get to a point where when technologies are being developed, pediatrics, rare diseases, small populations are considered as part of the deal. It's going to be an afterthought. It's not going to be done years later.

It's not going to be considered as a potential and perhaps never get there because there's additional costs and legal issues afterwards, but it's going to be done from the beginning. So I'll stop there. Lot more to talk about, but hopefully that gives you a little bit of introduction of where we're headed.

DR. SUSAN MCCUNE: Rhiannon.

RHIANNON PERRY: My name is Rhiannon Perry. I was born with sickle cell and lupus. For about 13 years, I was in and out of the hospital working on fixing the issues that both the combination of sickle cell and lupus have caused. Around four years ago, I took part in an experimental haploidentical bone marrow transplant to cure both diseases and now that I'm cured, I'm working with organizations like Hope for Henry and the ICAN

Initiative to help bring awareness to those rare diseases and the causes.

ICAN and being part of the Hope for Henry patient and team board collaboration is a really important step to bring more awareness to these diseases and to start a communication and collaboration with patients and the environment and the community around and to better educate more people about the things that are going on with those diseases.

DR. SUSAN MCCUNE: So thank you all very much. I think as you all have seen, we have pretty much representatives of most of the stakeholders either in your past life or your current life up on the stage in terms of patient advocates, academia, industry, and government entities. And round five years ago, we started the International Neonatal Consortium and really thrilled at that time. It was one of the first consortia efforts that were undertaken and I'm thrilled today that every panel had talked -- has been talking about public-private partnerships and consortia efforts and I'm going to go

back to Rhiannon to start the conversation.

Rhiannon mentioned ICAN, which is the International Children's Advocacy Network, and has been very, very important in understanding what end points and what clinical trials are meaningful for pediatric patients. And so my question to the folks on the panel is, all of us have been involved in consortia efforts. Clearly, we not have -- we're now getting an experience that's in -- upwards of years, and now we probably have a good deal of insight into what has worked really well and where there's some challenges associated with consortia efforts.

So I'm going to open it up and start maybe with Rhiannon at the end, just talking about what are the -- what are some of the examples of successful efforts from the consortia perspective, what are done well, and then where are -- where do we have some challenges.

RHIANNON PERRY: So like I said before, I work with Hope for Henry and so we have a patient advisory council and then we also have a teen board where teens in the community can come take part of

programs and fundraisers for Hope for Henry to better provide incentive programs for patients and so we did -- collided those two programs or groups to take part in the ICAN chapter and so with the ICAN chapter, we do a lot of community work.

There are two important parts. There's education incentive and then there's also the feedback incentive and so the education incentive part is where we go into Children's National Medical Center and we talk with researchers and doctors and those who are in the field who can explain what they do, why they do it, and how they do it and better educate us on the importance of their role in the community.

And then we also, what the feedback initiative is, a lot of the patients are able to look at these programs that are implemented to help them and to kind of discuss what's good and what's bad about it. So the ICAN program is great because we are able to collaborate with the community and we're able to spread awareness about these diseases and illnesses that really need to be brought up. And one thing that we can definitely work more on is our outreach in

reaching other communities, other areas in the world to bring more awareness to that.

DR. SUSAN MCCUNE: Thank you. So we're going to go right back -- right back the way we came.

DR. VASUM PEIRIS: Oh, I thought we were going to go hand written here. Your focus is really around what is -- what's working well in consortia, perhaps what's not, how do we improve, that type of...

DR. SUSAN MCCUNE: Yes.

DR. VASUM PEIRIS: Yeah.

DR. SUSAN MCCUNE: You know, what's the experience, because now we've been -- each of the panels before us has really talked about public-private partnerships and consortia efforts and everyone has some experience with that. And what have we learned that works or that people know kind of from your experience what's worked, and then what are some challenges that maybe other folks can help in -- address some of those challenges?

DR. VASUM PEIRIS: Yeah. So thanks. It's a great question and I think something that

absolutely makes a difference for the types of initiatives that are necessary to really move forward in the field of rare diseases. I know that there have been a number of different consortia efforts that have some together in an attempt, in their own spheres to break down silos.

And what you recognize sometimes is that perhaps there are still silos within those consortia and so how do we begin to get to a point again where we truly are beginning to take a look at this from a very global standpoint where the entire ecosystem is being optimized, truly, for the benefits of patients and that is a little bit of the work, I think, that we're trying to do right now with the consortia that we're developing for around SHIP.

We wanted to ensure that stakeholders across the ecosystem are involved, patients included, but that also includes, again, not just that regulatory world like I mentioned before. It also brings into play the individuals that invest in the development of these medical products, like (inaudible) Funds, Angel Funds, all of that, because

without creating a system that brings together all of those different players, it's really difficult to make a -- to develop a platform and a system that truly makes a difference for patients.

So making sure that when we do develop consortia that all the right individuals are -- and organizations and perspectives are represented. It is, I think, very simply put, naively put, important. But making that take effect, that sometimes is a challenge and how do we truly continue momentum and bring all of those individuals together in a collaborative community type atmosphere to be able to move this field forward.

DR. SUSAN MCCUNE: Sheila?

SHEILA MIKHAIL: I find that people are usually more cooperative in collaborations when they have something to gain and little to lose. And what I mean by that is often, they work much better when there's not competing interests, but when there's synergistic interests or new opportunities. So I think of, for example, a lot of the collaborations that -- and consortiums I'm involved in, where there's

a complement of gene editing technology with AV delivery technology, that works extremely well vis-à-vis to AV companies working maybe on the same diseases, that works less well.

Where there's a new use of a technology, for example we discovered that a Doggybone technology -- Doggybone DNA technology that's used for vaccines can be used to produce plasmoid without big bioreactors and E. coli, so it's safer for patients, it's quicker. I will reduce manufacturing costs. That was a good collaboration because there was something for everybody to get out of it, right, nothing was being taken away. There was only upside.

Where there's safety issues that affect technology, it's to everybody's interest to make sure that patients have the highest level of safety and that we address these as an industry. So for example, in our space, it's well known that there is often transaminitis associated with the delivery of AV therapeutics, so many of us come together to try to address those issues, share data, try to make sure that we optimize the safety of our therapeutics for

patients.

Where there's industry standards that affect everybody, once again, titering is a big issue, titering of our material -- AV material in the manufacturing process. That's another area where people come together because there's a common interest. So I think there's many places where people can play nicely together, but I think we all have to be knowledgeable that sometimes there are tensions because we're also forced to compete.

DR. SUSAN MCCUNE: Martha?

DR. MARTHA DONOGHUE: Hi. I guess I'll speak a little bit to an example in pediatric oncology and I think of rare disease drug development, drug development to treat rare cancers, really need to be a global enterprise and because of the issues relating to the rarity of pediatric cancers or pediatric diseases in general, there are sometimes complimentary or competing regulations in various countries that will either mandate clinical trials in pediatric patients or offer incentives.

And for the most part, I think these

regulations are wonderful and important, but they also have the potential to cause differences and they way we're applying these regulations that can scuttle or certainly make drug development for children more difficult and we were running into that a little bit in the past with respect to oncology with varying regulations in in Europe requiring one thing and then the timing of our incentive process sort of being a mismatch.

And so companies who are looking to develop drugs globally, it puts them in a bind, frankly, I think some of the time, because they're getting different advice and really what we want is one clinical trial that's going to answer a scientific question rather than something more distinctive than that, so a new regulation that's going to come in effect in August whereby the U.S. we're going to be able to require certain pediatric investigations for cancer therapeutics being developed in adult patients that have a mechanism of action that's applicable to oncology and in children -- to cancers in children.

And it's very exciting and I think it's

really going to help move drug development forward for children, but we're in a circumstance -- will be in a circumstance soon where we're thinking about, okay, well we have lots of drugs, maybe four, five, six drugs with a particular mechanism of action but yet we have a very small pool of patients and so how do we figure out how best to study these drugs in children so that we're not duplicating our efforts and certainly not competing with one another?

And if so -- they developed in Europe back -- starting in about 2013 an organization called Accelerate and what's unique about this organization is that it brings together patient advocacy groups, international regulators, companies developing drugs for cancer, and scientists all together in a pretty competitive space on a regular basis to take on certain issue and try -- and really encourage free flow of information to help everyone make the best decisions possible to develop drugs more efficiently for kids.

And while it started in Europe, recently, over the past year-and-a-half to two years,

they've been increasing involving in the -- with the U.S. as well with the help of an advocacy group called (inaudible). We had our first meeting in the United States this fall and this particular one was on development of a particular class of drugs called epigenetic modifying agents for patients with cancer, for pediatric patients with cancer.

And because of the ability to have this informal communication with one another, I think we all walked away with a better understanding of what was important to patients, which drugs within that class might have the most promise for treating pediatric cancers, and while we didn't come away with any definitive decisions, I think we all came away with increased understanding of one another and better -- to make the best decisions that we could for patients.

So I think that's one excellent example of sort of a new way to collaborate in a pretty competitive way. We're all sort of having the same goals, but I think also respecting the competition piece of it as well. And I think we still have a lot

of challenges. I think we need to bring in other regulators into this conversation, not just Europe and U.S.

I think at this particular meeting, we had representative from Australia as well, but I think the more people we can bring to the table to have these discussions, the better and, of course, sometimes the ability of our infrastructure to handle complexities can be really tested when we're thinking about how quickly science evolves and changes, so we may come up with a plan that we think is perfectly reasonable and wonderful to move something forward and then something new can come up and in science that may make us need to relook at things and shift trajectories. So I'll stop there.

DR. SUSAN MCCUNE: Chris?

DR. CHRISTOPHER AUSTIN: I'm going to take Martha's example and up her 10. So, sort of think of -- it's hard for me to pick one of these. Everything we do is a collaboration, but I decided, like a lot of scientists, you learn the most from the extreme phenotype which is... So I decided in a fit

of collaboration to become the chair for three years of something called the International Rare Disease Research Consortium. It is a consortium of about 65 organizations from 22 countries on five continents. It includes all the major funders: NIH, you know, European Commission, Japan, Canada, Australia, China, you name it, as well as about 15 companies 15 patient groups, and a whole bunch of scientists.

And they literally speak 40 different languages. They come from the entire spectrum of research from genetics to public health and regulation, everything in between, and they were brought together -- we were all brought together by a common enemy and one of my points has got to be, you got to keep the focus on the common enemy because if you don't, everybody starts focusing on the other guy who's there enemy.

And so the common enemy here is the enormity of the rare disease problem. Those of you who've heard me talk will know that I am fond of saying where -- unfortunate truth, that at the current rate of progress, which is really quite remarkable,

but at the current state of progress it will be 2,000 years before there is a treatment for all rare diseases.

So we have to do things differently. That is just not an acceptable answer. And it doesn't have to be, but all of these folks were brought together by this common desire to say, well, if we coordinate what we do internationally and so the NIH knows what the European Commission is doing, would know what AMED is doing in Japan. We know we're working on the same thing. We can divide and conquer. The genome project was done that way, if you remember this.

And so what are the lessons from this absolutely scarring experience, I must say, of three years? It was actually an enormous pleasure, but what I learned was that first of all, it is critical that leadership -- leadership's really important in this case -- keep articulating what the goal is, what -- why are we all here. And it -- that sounds sort of obvious, but it's easy to lose track in the nitty-gritty of individual projects, why we're doing this.

I just imagine Bill Belichick used to do before he started losing football games. To anticipate that there will be different languages and people will misinterpret each other, they will misinterpret each other, so you have to have the translators amidst the sort of senior people who look out for this at meetings and when something like that happens, say, what they probably meant is -- they're like -- it's like a marriage counselor, which I think we've all experienced where -- so that's really important.

Third, you got to be really up front about the money, because in the end, it always comes down to money. Things always come down to money, no matter how much people say, oh, well, kumbaya, we're all in this together; everybody's got their budgets. Everybody's got issues they got to deal with, so be up front about that. And fourthly, be up front about the credit issue, so we all love to work together and all that stuff, but we all have a boss, too, and that boss, frankly, doesn't care what Joe Schmo in Japan got valued -- the value out of what you did.

You know, he or she wants to know where's the beef, from you, and so you have to design what you do to have more than enough credit to go around, or else the thing is toing to fall apart and people are going to leave because they're going to have to choose between their own job and that they really want to do. And that's a false choice they shouldn't have to make, and it's manageable, but you have to do it -- you have to do it prospectively.

And so I guess my lesson from this was that with good proactive leadership and people who are sort of like-minded, which these kinds of consortia tend to attract, and proactive management of the problems that you know are going to appear, these can be extremely effective and so I'd urge you to realize that they can be done, but you can't just let it -- think that it's going to work on its own, because it really won't.

DR. SUSAN MCCUNE: So on that note, with about 15 minutes left in the session, I'm going to open it up for questions here in the room, and while people are coming to the microphones, I didn't

know if there's anyone online that had a particular question for us. No. Okay. It's late in the afternoon. Dr. Epps is moving to the microphone.

DR. EPPS: At the microphone. I wanted -- I had a question. I want to circle back to something that Rhiannon had mentioned as a challenge, which is bringing in all communities. We know that rare diseases affect folks in every community. I wanted to ask the panel, starting with Rhiannon, any thoughts she had on how to bring other -- folks in other communities in to this process and to ask other panelists what sort of activities or actions they have been doing up to this point to try to make that happen.

RHIANNON PERRY: So to start, with the Hope for Henry, Children's National Medical Center chapter of ICAN, we've reached out to many different hospitals to implement those programs there and to try to gather people and a group of people who are willing to go out and speak about these issues and hold conferences for others to come in and speak about it and communicate, share their thoughts and things like

that. So that's one of the efforts that we're really trying to take now.

DR. EPPS: Are you guys using a lot in terms of social media to reach out to other folks?

RHIANNON PERRY: Definitely.

DR. CHRISTOPHER AUSTIN: I guess the only thing I would say is if you think about a sports team, so I was in Boston for 20 years and the Red Sox would be pathetic to being really good. When they were pathetic, I was like one of, like, four people at the ballpark. And when they started winning, all of a sudden everybody was a Red Sox fan. So having some -- people love to be part of the winning team. And so I think all of us have experienced this, that we all have long-term goals but you've got to start winning individual baseball games, and that will bring in more people so there's this adage that we all have.

You know, got to have some short-term confidence building measures. That's really important. And it's -- and all of us say, well, gosh, you know, that's just -- it's such a small step and it doesn't really matter because it's not -- it's

infinitesimal the way we want to go. It really matters because it will bring other people in who will make your team bigger and stronger.

SHEILA MIKHAIL: Just to build on that, sometimes, too, it's -- the team maybe isn't your company or your organization, but it's a field. I feel like for AV gene therapy, we had to do that. In the early days, we gave out a lot of our technology. AveXis uses our technology and that's a major -- almost every single company out there uses some form of our technology.

We're making our manufacturing process available and we're doing that because the industry is still very vulnerable and we need to have some more wins. So when the SMA drug was approved, that was really good and now, hopefully, the DMD drug will be approved and the hemophilia drugs look. But there's, you know, like you mentioned, 7,000 diseases, rare diseases, and we're still hopeful that we can go into the main pathway diseases.

With Medtronic's help, we're not in heart failure and that's a pretty big step. At least

with monogenetic diseases, you know what the drug is. The drug is basically replacing the defective genes, the good gene that's going to do the work that the defective one can't. We get to pathway diseases, and there's a lot of different targets and you hope you get the right one. So, anyway, for us, I agree with that, but I think our team is much bigger. For us, it's an evolving field.

DR. VASUM PEIRIS: And I'd just build on that team concept, since you laid it out so well. For the Red Sox, it was probably the four people that knew plus my entire pediatric EPT. They were always there. That's all we talked about during rounds. But on the team concept, there's a big team that can do a great deal of great work. You know what that team is? HHS, the government. Right.

That team is doing a lot of work. What if -- again, to Susie's question -- what if there is better collaboration, NIH, CMS, FDA, and others that came together to try to begin to truly address this across the spectrum? How do we begin to develop more of a collaborative environment within those teams?

Those teams can make a huge difference and create platforms and systems that can help everybody to have better success.

All the individual projects, all the individual areas that people are working on right now, that team can come together and help all of those other individuals.

DR. SUSAN MCCUNE: We have three more questions lined up.

ANNA CHRISMAN: Hello everyone. Good afternoon. My name is Anna Chrisman and I am from Genentech. My question was really about standardization, so this was mentioned a lot throughout the different panels and there's also, in context of consortium, I'd imagine that's important as well. So the panel earlier had discussed the rare disease accelerator and (inaudible) best practices from NIH and the need for standardization from that perspective. Is anything similar envisions for investigator sponsors' studies, and if so, do the panelists have any feedback on lessons learned they could share regarding standardization of data there

and how sponsors and investigators could get that type of feedback?

DR. CHRISTOPHER AUSTIN: Go for it.

DR. VASUM PEIRIS: I'll start you off. I don't have another good story about teams, but standardizing data, right. One of the areas that CDRH has been working on for quite some time is an actual evaluation system for health technology. How do we begin to get to a point where hubs across the country and potentially across the world have access to certain levels of data and can actually share that data in a secure way?

Very simply put, the way that I naively look at it is, there is data that we acquire every single day in EHRs and that is put into patient management. That data can be refined. Certain data elements can be developed, and it can get to a point where that data is so refined where -- and abstracted, that you have a specific data element that can make a difference for both regulatory and public health decisions across the entire country or potentially across the world.

But ultimately, from a regulatory standpoint, if you want to look at it that way, you can get to a point where that information can be aggregated and potentially help facilitate and accelerate development of medical products.

DR. MARTHA DONOGHUE: Yeah, in our space, we've talked about having a drug master file for capsids. Right now, we have that for manufacturing, so anybody who uses our system, right, they can refer back to our master file that's filed with the FDA. But we could envision a world where a lot of the capsids that are now coming off patent like AV8 and 9, which are used in a lot of products, if there was a master file filed at the FDA that investigators could refer to, it might accelerate drug development.

The capsids have a certain tropism, right. They're always going to have a certain tropism. The thing that's changing is the drug that you're putting and essentially it's the gene that you want to express. And so it could simplify and accelerate getting I&Ds filed.

DR. SUSAN MCCUNE: So moderator's prerogative. I'm going to say that we have three last questions and everybody has to keep their answer short. So we're going to go one, two, three and then we'll be done.

WOMAN 1: Okay, I'm Anna (inaudible) the president of the Children's (inaudible) Foundation. I have two things that I would like. I want -- I'm going to start with hope and then I have a request. So hope is that we've had some very large collaborative initiatives and -- within the NF community and they have really delivered, and NCATS to say that Chris puts his axe where his words are, NCATS was a big part of that collaborative effort and the drug that was identified through that (inaudible) is now ready to go into clinical trial, so that's the hope.

The request is that collaboration is really hard and I will say it's a combination of stick and carrot and I don't know whether I should start hitting with the carrot as well, but I'm not sure. But the thing that I -- we have discovered over the

last five years that we've really had this big collaborative consortia is that there's two elements, I think, to successful collaborations.

One, is an incentive. Try to understand why people don't want to collaborate and try to pull them over to the side where you want them to be. But the second thing, and this is a request, I think there is also something where we really need help from federal agencies and that's around policies. It is unacceptable, Mr. and Mrs. Hospital Service that you are competing between hospitals and yet there not one shared place where everybody shares their clinical information, especially in the rare disease community.

It is not acceptable, Mrs. and Mr. Researcher that you develop animal models with taxpayer dollars and that these animals are not available for drug testing. Here, we need help. Here, we need policies. Chris, I see you smile because I know... I'm looking, but I see --

DR. CHRISTOPHER AUSTIN: You're speaking my language. Yeah.

WOMAN 1: But I see -- I think we need

to start thinking. Really, there we need you guys because we as patient associations, patient organizations, and with our patients, especially in the rare disease community, it's really, hard because the patients are going to be activists but then they're going to be activists against their treating clinicians, which is really not a good thing to do. So we need policies. So this is my request. So my hope is it works and Chris helped. My request is, please help us with policies. And I would like to get a reaction.

DR. CHRISTOPHER AUSTIN: A great point, and I'm just going to maybe just build on that and hopefully augment this. Since (inaudible) pediatrics. That's what we're trying to do, right? We are trying to overcome a number of different issues in the system that isn't necessarily optimally supporting device innovation for pediatrics and small populations. But one of those issues, right, is that notion of small, geographically disbursed heterogenous populations that we just can't get all the information for. Well, where do all those populations get care? Those

populations get care at the pediatric academic medical centers across the country, right, and across the globe. So if we can bring those systems together --

WOMAN 1: Yep.

DR. CHRISTOPHER AUSTIN: -- and ensure that there is a method by which to aggregate that the information and the data that's being developed plus a system that accounts and accommodates for a number of other legal issues, regulatory issues, economic issues, then perhaps we will have a system that truly supports innovation for small populations and if you can support innovation for small populations, you will accelerate innovation for all populations.

WOMAN 1: Yeah, exactly. Exactly. Yeah.

DR. SUSAN MCCUNE: All right, off to the left over here.

WOMAN 1: Okay. Eric (inaudible) research foundation. This question is probably for Dr. Austin.

Having worked with your international consortium for as long as you have, one of the things

that we have encountered as we get closer -- we're in Phage 3 on one of our trials, is it turns out we are beginning to realize that we need to build a network of patient advocates that can speak within the countries, whether it's the European Union or even Australia, places like that, that we need a network of advocates that are going to be ready on our own behalf to go before their own regulators, even after it's gotten approved here in order to be able to argue the importance of this treatment within those individual countries. Is that the case?

DR. CHRISTOPHER AUSTIN: Yeah. Oh, yeah, definitely. And I would say -- so what we did within IRDRC, is because it was an umbrella organization, in order to be a patient advocacy group within IRDRC, you had to be representing an entire country. So for instance, NORD was a member and URS and Europe and those kinds of things. And -- but they of course, then have a relationship with each -- they all have member organizations and in more ways it was -- what was wonderful about that experience was that (inaudible) is, I think, ahead of almost everybody and

NORD'S pretty good, but then we had a patient organization from Botswana that was significantly smaller and had significantly less experience and so what this allowed was this sort of big brother/big sister relationship.

But you're absolutely right. That's what these countries needed. But what we discovered was that U.S. and Europe, we lose track of how far the culture has come to take the patient seriously. In Japan, for instance, which is a very hierarchical culture and is still quite male dominated, male oriented, most of the patients are moms, like they are here, not all, but a lot of them are and so that is a very hard thing for the culture to deal with.

How do you overcome those two big cultural barriers? And so we do a lot of work and continue to with the other countries and say, well, that was once the case in the United States, too, and so how have we overcome that? But yes, this is absolutely essential. The other thing that the -- each of the countries has to do which the United States hasn't done yet, of course, but we managed to

get around it anyway because we have the Orphan Drug Act and other things, is to have a national rare disease policy and those national rare disease policies are almost always run from the patient groups. They make it possible.

MAN 1: Thank you.

DR. SUSAN MCCUNE: Last question.

WOMAN 2: It's not so much a question as a statement. I'm the proud mom of that young lady right there and, you know, we have been through quite a journey listening to some of the other people in here, so I definitely sympathize with everyone here. But I feel like I'm in a room of geniuses with big hearts who are overlooking on major thing and that's your basic, most profitable equity, your biggest equity is your patients.

And I feel like I've been sitting here and I've been listening to humongous words, huge terminology that is way above me, and I'm the biggest commodity. What we're doing with ICAN and Children's Hospital and some of these other -- on Be The Match and doing all these other kind of things to kind of,

like, bring wellness and give back to all of you, who have given so much to us, is that it's so 30,000 feet up there that John Q. Public can't join you to be a part of your consortium.

And the reason why and the only way that you will get a consortium is if John Q. Public jumps on board to what you are doing and sees your vision the same way that you see the vision. So I'm excited to be here. I'm so happy that we get the opportunity to come and share our experiences with you. But from a patient, from a parent, and from John Q. Public just sitting out there, I have no idea what you're talking about.

And if I don't have an idea of what you're talking about, I can't advocate on Capitol Hill the way I am with Be The Match to bring some of the initiatives that you want to happen. If you want us to work with Japan and China and all that, it's going to take 10,000 Americans to jump on board to say, hey, John Q. Government, this is what we, the American public, want. We want you to bring down the walls and the barriers that prevent us from working together,

country to country, community to community to community to community.

And you're losing -- your biggest advocacy here is your patients. It is the people with the rare diseases and all of your little subgroups coming together and saying, we are the rare disease community. It's not just us. It's our families who are affected by it and that's where you grow your consortium. So I applaud each and every one of you for that, but we got to bring it from here back down to the grass roots if you want to see improvement.

DR. SUSAN MCCUNE: So I think that's the best last word for our panel, and with that I'd like to really thank the panel for all your comments.

DR. JANET MAYNARD: Thank you so much to our panelists. We really appreciated that session. So now, we will transition to the open public comment period and Catherine Park will introduce that period. Thank you.

CATHERINE PARK: Well, hello everyone. Thank you so much for being here and for such a great meeting. We are now doing to start the open public

comment portion of the meeting. Today, we have nine speakers registered and each of them will have three minutes to speak. If a speaker finishes early, we intend to move on to the next speaker. We ill call each speaker by their name.

If there is additional time after, we will open the mic up to the room. When it is your turn, please approach the podium to your left to provide your comments. For transparency purposes, we ask you please disclose if you're affiliated with an organization, if your travel has been funded, or if you have significant financial interest in rare disease medical product development.

As you are speaking, you'll notice you have a timing light to guide you. The green light will indicate when you can begin speaking. It will turn yellow when you have 30 second left in your time. The timer will turn red when your time has come to an end. If you have not concluded your remarks by the end of your allotted time, I will ask you to do so kindly.

As a reminder, you also have the option

to submit comments to the docket which will remain open until Sunday, March 29th. Again, you can find additional information about this in the Federal Register Notice. If you are signed up for an open public comment slot, you are welcome to make your way to the first two rows in front of the podium at this time. Over there. If you would prefer to use a hand-held microphone and remain in your seat, please raise your hand when I call your name and will bring the mic to you.

I am now calling the first speaker in the open public comment period, Mary McGowan.

MARY MCGOWAN: Good afternoon. I'm Mary McGowan, executive director of Myositis Association. I have no travel stipend to be here and no financial interests. I would like to thank the FDA for this public hearing and for allowing me to speak. Again, my name is Mary McGowan. I'm the executive director of the Myositis Association. We are an international umbrella organization for numerous rare artery, muscle degenerative diseases including dermatomyositis, polymyositis, necrotizing myopathy,

and inclusion body myositis among others.

In my brief comments, I will address challenges across many chronic rare diseases. These include diagnosis, clinical trial participation, unique needs of women, and underserved populations, and the important of support systems.

Delay to diagnosis is a great concern. Those living with artery diseases see on average eight doctors and take five to seven years to receive the proper diagnosis. This has significant impact on patients' health and risks of mortality, mental health, and eligibility for future clinical trials. With such a significant delay in diagnosis, patients miss the window of opportunity for early treatment and symptom management which my result in progression of disease that is often irreversible and requires more complex treatments, some with harsh side effects, to address the damages done.

Additionally, repeated misdiagnosis creates a mistrust of the medical community. Finally, delay to diagnosis means that the time patients receive their diagnosis complications they have

incurred may make them ineligible for clinical trials.

Clinical trials are the beacon of hope for patients and their loved ones. We need to do better to ensure that clinical trials are for all individuals. Women make up 80 percent of all autoimmune diseases; yet it has been shown that women participate in clinical trials at a lower rate than met, something the FDA has already been working on to address through policy changes and the Women in Clinical Trials campaign.

In considering trial design and patient engagement, it behooves us to hear the unique challenges that women with rare diseases face, including future fertility, balancing family, job, and the increased likelihood of being caregivers for others with health problem. These issues are compounded by the complexities of their own rare disease. For women with myositis seeking to have children, concerns about participation in clinical trials are multiplied by the knowledge that increased flares can make it more challenging for them to care for their children and the stress of a regimen of an

autoimmune disease trial increases the risk for autoimmune disease flares.

Additionally, women with a rare disease are at a more significant risk of financial and mental health challenges. Creating support systems for women living with rare diseases like myositis is virtually important to improve opportunities for clinical trial participation for women, in order to ensure that all treatment options meet the differing biological needs of both genders.

Similarly, we must consider the unique challenges for those in underserved and diverse populations living with a rare disease like myositis. Women of color have the highest prevalence of dermatomyositis and polymyositis. They also tend to be diagnosed younger with more severe disease and have a higher mortality rate. It is crucial to have significant representation for this population in clinical trials, but there are a number of barriers.

Again, these patients tend to be sicker at the time of diagnosis which means that they often do not meet eligibility criteria for many clinical

trials. Additionally, most individuals from underserved populations are distrusting of experimental treatments and clinical trials due to historic breaches of trust. The population --

CATHERINE PARK: Thank you so much for sharing. Thank you.

MARY MCGOWAN: Thank you very much for your attention, in particular to the FDA for your extraordinary work. Appreciate it.

CATHERINE PARK: Thank you. Next we have Matt Buck.

MATT BUCK: Thank you. I'm Matt Buck. I'm vice president of regulatory affairs at Ionis Pharmaceuticals. I'm here today representing the n-Lorem Foundation which is a nonprofit, so I have both industry in here, representing nonprofit. I guess we're industry then. Yes, I have a financial disease in rare disease drug development.

So the mission of the n-Lorem Foundation is to charitably provide investigational, antisense oligonucleotides to treat patients with ultra rare disease which affect about one to 10

patients. The foundation was established at the end of 2019 and our mission, of course -- sorry, our goal and who we work with is Ionis Pharmaceuticals and the Undiagnosed Disease Network, the UDN, to provide these individual therapeutics.

We were just established at the end of 2019 and we've already identified our first case, our first patient for an individualized therapeutic. In the coming months, we will have more cases, so here today, I am here to emphasize some of the recommendations that we've already shared with the FDA. We've already had the opportunity to speak with key personnel at CDER and we appreciate that opportunity.

And we recognize that there are two FDA draft guidances on individual therapeutics, and we appreciate that work. But knowing that there will be cases for us to bring forward to FDA in the coming months, I just want to emphasize our recommendations. One of those is that, ideally, CDER would have a sole division within the FDA that would manage individual therapeutic INDs. And that is so that a single

philosophy or standard can be uniformly applied to all of the evidentiary requirements.

Second, with respect to evidentiary requirements, when it comes to ASOs that are well characterized, that we would be able to utilize what we know about that platform to establish more minimal data standards which we believe would be -- examples are a single-species tox study such as single-species rodent tox package and of course an abbreviated stability program.

And finally, just the identification of one or two FDA project managers that might be assigned to individual therapeutic INDs would be extremely helpful as we come to the FDA in the next couple of months with several of these cases. So with that, I provide my recommendations and we will, of course, follow up with the written recommendations to be provided to the docket at the end of the month, and thank you for your time.

CATHERINE PARK: Thank you, Matt. Next we have Michelle Adams.

MICHELLE ADAMS: Hi, I'm Michelle

Adams. I'm with the National Organization of Rare Disorders and I don't have any disclosures. Thank you. On behalf of the 25 to 30 million Americans with one of the over 7,000 rare disease, would like to thank the FDA for holding this meeting today to commemorate and celebrate rare disease week.

NORD is a unique federation of health organizations dedicated to helping people with rare diseases through educations, advocacy, research, and patient services programs. NORD is proud to serve as the host and sponsor of Rare Disease Day and the United States as we have been doing each year since 2009 with our partner organization (inaudible) invited us to join the campaign they had started in Europe the previous year.

Rare Disease Day is observed in community settings, governmental legislative offices, school classrooms, college campuses, and hospitals, all to make the voices of rare disease patients heard. It is truly inspiring to know that people around the country are coming together at events like this one with the shared goal to promote awareness and improves

the lives of all people living with rare diseases.

As I mentioned, it is estimated that are over 7,000 rare diseases and over 90 percent of rare diseases still don't have an FDA-approved treatment indicated to treat their disease. As we heard from Dr. Hahn today, FDA shares NORD's goal of ensuring that more effective and safe treatments for rare diseases become available. All the panels today have been incredibly informative and what is especially clear is that FDA focus in part on natural history registries.

As we heard this morning, natural history registries offer a unique, exciting opportunity to collect and share information about the progression and health impact of a rare disease. NORD is thrilled to be partnered with C-Path, a rare disease cures accelerator as both Dr. Woodcock and Dr. (inaudible) mentioned earlier today also.

Thank you, FDA, for providing this opportunity. NORD is a leader in this space. In 2014, NORD launched the IAMRARE Registry Program. It also launched (inaudible) today. The platform is

designed with extensive input from FDA, NIH, patient advocacy organizations, and other health experts. The IAMRARE hosts over 40 rare diseases, natural history study partnerships, and 20 of which were developed in part through a cooperative agreement with FDA. The IAMRARE Registry Program works in collaboration with patient and advocacy organization and industry partners to capture natural history data. Importantly, the emphasis is on input from the patient and caregivers' perspective.

And to the point where this morning, (inaudible) to our registry, but patients bear no cost for participating. With better information about a rare disease natural history registers will also allow for more effective treatment targets, more specific end points, and more efficient clinical trials. We're hopeful as it is that rare disease patients will get better, more effective treatment sooner. Thank you.

CATHERINE PARK: Thank you. Nest we have Tisha Wang.

TISHA WANG: Hi. My name is Tisha Wang. I'm a pulmonary physician and clinician at

UCLA. I thank you for the opportunity to speak today. As the clinical director and vice president of the Pulmonary Alveolar Proteinosis or PAP Foundation. My travel was funded, but I have no financial interest here.

PAP is a rare disease without any approved therapy in which patients drown in their own surfactant proteins and develop shortness of breath and respiratory failure. In 2005, I was a trainee and I met a woman in her 20s with severe PAP. She was obese, in a wheelchair, on oxygen, and she came monthly for (inaudible) out the protein. She was so sick that I became convinced that she was going to die of this disease.

Based on what we knew about the cause of PAP which is that her cells and her lung were broken because they didn’t have access to her protein, it made sense to me to try this protein and it is called GM-CSF. We tried it off label. In hindsight, we were both so young, but we trusted each other. We took a chance together and I gave her the protein and over the next six months, we actually cured. She was

dramatically cured.

Fifteen years later, she is still cured. She's now a therapist with a master's degree. She's an athlete and witnessing her recovery has been one of the most meaningful moments in my career. Over the next decade, I accumulated a large number of PAP patients and began collaborating with Dr. Bruce Trapnell at the Rare Lung Disease Consortium to do research.

I continued using off-label GM-CSF for many of my PAP patients with success, and learned that Dr. Trapnell and others were doing the same. In 2016, with one of my PAP patients in Los Angeles, we reinvigorated the PAP Foundation, a patient advocacy organization with the mission of getting an FDA-approved therapy and ultimately a cure for this devastating disease.

We've been able to connect with hundreds of patients in the meantime and hear about their experiences of being told they have no options for therapy. Some have since died or required lung transplant. Through the foundation, however, we've

been able to hear a number of success stories of individual patients using GM-CSF with improved quality of life and exercise tolerance and decreased need for whole-lung lavage and oxygen.

In fact, a number of patients improved on GM-CSF and stopped, only to have their disease recur off therapy. Fortunately, the research has progressed in the last decade. We have a Phase 1 trial in the U.S., two recently completed randomized control trials, all using inhaled GM-CSF and available results from the patient and (inaudible) trials indicate that this medicine improves several outcomes in PAP, pulmonary function tests, oxygen in the blood, the amount of abnormal surfactant present, and the quality of life of these patients.

We at the foundation find these results encouraging and consistent with the experience of our patient community. So we at the PAP Foundation remain steadfast around a mission to become one of the few rare diseases to have an FDA approved therapy for our patients. We’re committed to working very closely with the FDA to achieve this and applaud the FDA for

granting breakthrough therapy designation for Molgradex, which is a formulation of inhaled GM-CSF. What is striking about this meeting and being her all day today is that everybody in this room is on a mission.

The missing is slightly different for all of us and it's inspired by different things, but we're all on a mission. And so I think my last statement to the FDA probably mirrors the sentiment in this room which is that our patient and our physician community is more than willing to commit our time, our knowledge, our personal experiences, our resources, really whatever is necessary to move us forward in conjunction with the FDA.

Thank you again for the opportunity to speak on behalf of the PAP Foundation, the PAP patient community today.

CATHERINE PARK: Thank you. Next, we have Jen McNary.

JEN MCNARY: Hi, thank you. I'm Jen McNary, a rare disease advocate, mom of three sons with rare disease. I'm the founder of One Rare, a

board member of various organizations, and a consultant in the rare space, but for these purposes, I don't believe I have any relevant financial disclosures. I self-paid for my travel.

The end of one discussion today was incredibly important to me and it's been discussed at other venues this year, such as JPMorgan, in thinking about this concept a little broader throughout the day, as we realize the benefits of precision genetic medicine and end of a few will become increasingly more common. It is imperative that the agency adapt and implement a more consistent approach, however, to ensure the same standards are being applied across divisions and across disease states, assuming that it's a monogenic disease and that the therapy is replacing missing genes.

I recently wrote a blog where I spoke about my conversations with Dr. Peter Marks regarding this topic and while I am increasingly confident that the top officials such as Dr. Marks, Janet Woodcock, et cetera, appreciate and understand the importance of flexibility when reviewing these types of data, I want

to continue to ensure that this trickles down throughout the entire agency to allow a visible path forward for good science.

Switching gears, in the spirit of being wholly supportive of faster FDA approvals, I would be remiss in not also mentioning a troubling situation in the access and reimbursement landscape that's going to affect us all. I'm aware that in order for innovation to best serve patients in this room, two things need to happen, clear pathways for development and ultimately access and reimbursement.

Several organizations have recently published concerns about ICR, its utilization of the quality to determine the value of a new therapy for rare disease, but in my opinion the most effective was that published by the National Council of Disabilities. They found sufficient evidence of the discriminatory nature of qualities to warrant concern, including concerns raised by bioethicists, patient rights groups, and disability rights advocates about limiting access to life-saving medications.

In a recent article, the Pink Sheet,

ICR calls itself an expert to help the FDA understand the importance of patient relevant outcomes and consistent end points. ICR says that its work could advance greater use of patient relevant outcomes in drug development. As the commissioner mentioned, the FDA is doing an amazing job of incorporating the patient voice into drug development and uses rigorous methods to evaluate and approve new innovative therapies.

Yet ICR attempts to play at the same evaluation of already approved drugs. I would urge that the agency consider decline this offer to partner with this self-appointed and blatantly discriminatory organization in favor of working with foundations, some of which are in this room: EveryLife Foundation, ARM, IGT, (inaudible). They all have a proven track record of supporting patient needs and so I would encourage the agency to instead look to them. Thank you.

CATHERINE PARK: Thank you. Next, we have Khrystal Davis.

KHRYSTAL DAVIS: I'm Khrystal K. Davis.

I'm an SMA mom, founder of Texas Rare Alliance, and I received a grant from the EveryLife Foundation that covered my travel today. We cannot treat what we do not diagnose. Commissioner Hahn recognized the innovations are coming fast and furious and that we need to do more, faster, to meet unmet needs.

I believe this is especially true in access to the diagnosis. We are undeniably failing in the timely diagnosis of rare disease patients. It takes an average of five to seven years to accurately diagnose rare disease patients. Sadly, many children with rare diseases will not survive to their fifth birthday. Many of these children will not survive to receive a diagnosis. We can and must do better in diagnosing rare disease patients.

When we fail at diagnosing rare disease patients, that failure impacts everything in the process that follows. Undiagnosed patients cannot participate in patient registries and natural history studies which then fails to include the true spectrum of rare disease patients, especially diverse and underserved patients.

Undiagnosed patients cannot drive research. Undiagnosed patients cannot inform the design of clinical trials and they cannot participate in clinical trials. Undiagnosed patients cannot follow the appropriate standards of care for a better chance of survival to see an approved treatment. Undiagnosed patients cannot access approved treatments and this is unacceptable.

Dr. Marks discussed the advantage of leveraging existing resources in responding to the anticipated number of individualized gene therapies. We must also leverage existing resources to drastically reduce the diagnostic odyssey for rare disease patients. Whole genome sequencing offers the opportunity to identify thousands of known rare diseases and plays an invaluable role in discovering new rare diseases.

Project Baby Bear Data from the work of Dr. Stephen Kingsmore in Rady Children’s Genomic Institute for Genomic Medicine shows that rapid whole genome sequencing improved health outcomes while decreasing healthcare spending for California NICU and

PICU critically ill patients with unknown etiologies. This impressive and actional model needs to be adopted in all states. Whole genome sequencing not only improves access to the diagnosis, it also improves access to treatments by helping develop potential treatments, identify patients for clinical trials, and determine proper treatments for rare disease patients utilizing personalized medicine.

Whole genome sequencing offers an opportunity to move from failing at diagnosing rare disease patients to excelling at diagnosing rare disease patients. We must work to change the culture to leverage genomic data. We need funding to improve access to whole genome sequencing and improved health literacy for genomic medicine for providers, patients, and caregivers. Access begins with the diagnosis.

CATHERINE PARK: Khrystal --

KHRYSTAL DAVIS: We cannot treat what we did not diagnose.

CATHERINE PARK: Thank you.

KHRYSTAL DAVIS: Thank you.

CATHERINE PARK: Next we have Kelly

Thornton.

KELLY THORNTON: Hello. My name is Kelly Thornton and I am with an organization, Pain Advocate Warriors and they're financially funding me and the American Pain and Disability Foundation. Hello. So the FDA needs to follow existing FDA protocols and stop being driven by the prevailing winds from political forces. I am on behalf of chronic pain patients.

So, okay. The CDC is trying to drive policy based on their poorly written and poorly understood 2016 opiate prescribing guidelines, providing themselves incompetent and not ground in the best interest in U.S. public, especially not in the best interest of chronic pain patients who depend on analgesics for quality of life.

The FDA -- excuse me. The FDA alone is in authority, yet we now have the CDC, 50 state governments, U.S. Congress, U.S. Senate, President of the United States, and even certain members of the media all trying to force additional overlapping, burdensome, contradictory political motivated,

unscientific regulations on opiates.

The U.S. government needs to get out of the doctor's office and leave it 100 percent up to the FDA to regulate and approve what medicines are on the market. The FDA's full prescribing information already contains limits and conditions and guidelines tailored to all drugs, and that is all that is needed. All other parties need to, frankly, get out because not only are the misinformed of the facts, their politicalize guidelines have cause as much death and misery for chronic pain patients while not helping addicts whatsoever.

Sheriffs, which in the report, they are not seeing prescription drugs found on deceased overdose victims, but instead see illicit fentanyl, heroin, and other illegal drugs such as methamphetamines, for at least the last eight years now. Can't CDC and others outside the FDA see their own data doesn't add up? A recent study said 1.3 percent of overdose fatalities were caused by patients taking their own prescribed opioids, so 98.7 percent are due to illicit or illegal activities. Pounding

that 1.3 percent down to zero percent is more likely to kill hundreds or thousands of times more as disabled and elderly patients are suddenly on the street buying heroin for pain relief and getting God knows what in their cartel-provided medicine.

How about we do something right for a change instead of driving good people to end their lives via suicide or become criminals? If that is what our society has decided to become, perhaps our nation needs to dissolve and let each state become independent, because our federal system is not helping people who need help the most. It is, in fact, crucifying, torturing, and driving people who've worked their entire lives to support this nation into --

CATHERINE PARK: Kelly --

KELLY THORNTON: -- a state of insanity because --

CATHERINE PARK: Thank you so much.

KELLY THORNTON: -- regulation.

CATHERINE PARK: Thank you.

KELLY THORNTON: Please stop their

perpetrating going into circles. Please. Thank you. I didn't get to finish it.

CATHERINE PARK: Next, we have Amanda Proctor. Okay. Then next, we have Bonita Talotti.

BONITA TALOTTI: Good job.

CATHERINE PARK: Thank you.

BONITA TALOTTI: Hello. Good afternoon. Thank you so much for having all of us here. My name is Bonita Talotti. I'm a patient living with Ehlers-Danlos syndrome. I'm here today on my own representing our organization as one of the volunteers local EDS -- Metro EDS and HSD support group. No one's funded my travel. I'm just coming from Virginia.

I'm here today to talk about access, one of the few things that was not talked about throughout the day. I heard a lot today about patient focused, patient centered, individualized treatment, but very little to no discussion on access. I found out about Ehlers-Danlos syndrome four years ago, after I'd been taking ciprofloxacin for three years and finally connected the dots and recognized cipro did

something to me. It turns out, cipro is actually a fluroquinolone antibiotic that is contraindicated for patients with Ehlers-Danlos syndrome and unfortunately for me, FDA did not connect the dogs and come up with the black box warning until 2018 about two years after I was diagnosed.

I'm here today to point out that we, as patients, deserve and need to have the full facts of the drugs that are being prescribed to us. I didn't know at the time that I was given cipro that it can lead to tendinitis or tendinosis. My shoulder, which has been hurting throughout the day, is a result of EDS as well as ciprofloxacin. I didn't know that ciprofloxacin could destroy my gut. Indeed, I was never informed that I should even take a probiotic.

I didn't know that amitriptyline would result in orthostatic intolerance. I didn't know that naproxen which is what's been prescribed for me for my shoulder could result in GI risks of bleeding. None of this was ever informed to me or disclosed to me, rather. I had to find that out from various other sources.

As patients, we need to know exactly what it is that we're taking. We need to know the benefits as well as the risks. We also have another access issue that's really never talked about in any public meeting I've ever gone to, at FDA or at any other event, and that's financial. We as patients don't have access financially to all the latest technologies or treatments, the new drugs, the new devices, CRISPR, gene editing, gene therapies.

What good does all the innovations do if we as patients can't even afford them? I would urge industry, FDA, and other stakeholders to recognize that we have a serious financial access issue. If our payors aren't covering these things, we can't access them, plain and simple. I won't get into the opioid debate, but I will say this. We as patients don't have access to alternatives to opioids as well. What good does anything do if we don't have access to anything?

We as patients need access, first and foremost. Thank you.

CATHERINE PARK: Thank you so much.

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. JANET MAYNARD: So we're going to transition to closing remarks, because unfortunately we're out of time for the open public comment period. So on behalf of FDA, I'd like to thank all of the panel participants, speakers, and everyone in the audience here in the Great Room and also on the webcast for participating in today's meeting. We greatly appreciate your attention and your interest in these topics.

This has been a very important meeting to all the participants including FDA, patients, researchers, and the industry representatives. We greatly appreciate perspectives and personal experiences that were shared with us today. Today, we heard that patients are at the heart of all that we do. There are exciting opportunities in rare disease product development, and great unmet needs of patients and families living with rare diseases. In the

morning, we heard about natural history and registry studies. Key points included the importance of patients and patient advocates in these studies and the need to think globally and evolve over time.

In the afternoon, we heard about the importance of collaboration, leveraging data, and learning from each other. This was a very informative meeting for us here at FDA. Rare diseases have enormous impacts on patients and families and the need to develop new therapies for rare diseases is immense. We look forward to incorporating what we have learned today into the agency's thinking on rare disease product development. Your perspectives and voices were heard today.

Working together, we can support optimal development of safe and effective products for patients with rare diseases. I want to let you know that just because the meeting is over, it doesn't mean that this is the last or only opportunity to interact with FDA. Today you heard from FDA's staff and the agency who want to hear from you and learn about your experiences. If you don't know where to start, the

patient affairs staff can help. You can send them an email at PatientAffairs@FDA.gov. They can help you stay connected with other activities at FDA or address future questions.

You can also connect with the Office of Orphan Products Development at Orphan@FDA.gov. As mentioned earlier today, we strongly encourage you to submit comments to the docket which will be open until March 29th, 2020. Details on how to submit comments to the docket can be found on the Federal Register Notice for the meeting. On your chair, we have placed a short survey that we hope you will complete so that we can continue to improve our public meetings.

When you are done with the survey, you can give it to the registration desk or to the FDA staff working at this meeting, and those are the folks who are wearing the nametags. For those on the web, we will be sending you the same survey via the email address that you registered with. And on that note, I am closing this public meeting. Thank you. Safe travels and have a wonderful evening.

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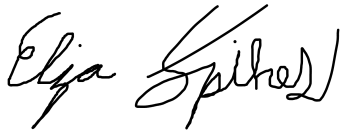

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Rule 30

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(A) to review the transcript or recording; and

(B) if there are changes in form or substance, to sign a statement listing the changes and the reasons for making them.

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