

1 FOOD AND DRUG ADMINISTRATION (FDA)

2 FDA Rare Disease Day 2020:

3 Supporting the Future of Rare Disease

4 February 24, 2020

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1 DR. JANET MAYNARD: Good morning and
2 welcome to this public meeting, FDA Rare Disease Day
3 2020, Supporting the Future of Rare Disease Product
4 Development. My name is Janet Maynard. I am the
5 director of the Office of Orphan Products Development
6 at FDA, and I am excited to have this opportunity to
7 engage directly with you to help support the future of
8 rare disease product development.

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

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

22 Developing a treatment for a rare

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

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

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

1 kiosk outside of the conference room. The pre-ordered
2 lunches need to be purchased by 3:30. Thus, if you
3 have not pre-ordered your lunch but would like to, we
4 recommend you pre-order now.

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

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

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

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

1 discretion.

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

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


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

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

22 We will now review today's agenda. The

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

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

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

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

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

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

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

22 For those on the webcast, please type

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

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

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

22 Now we will briefly cover a few rules

1 of engagement for our discussion today.

2 We encourage all individuals to
3 contribute to the dialogue, either today in the
4 meeting or through the public docket. We appreciate
5 the opportunity to hear your perspectives. The views
6 expressed today are personal opinions. Please be
7 respectful of others and allow participants to finish
8 sharing their experiences without interrupting.

9 Participants in the room should use microphones so the
10 webcast attendees can hear their remarks. And please
11 complete an evaluation form to let us know how the
12 meeting went today.

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

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

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

4 So our introductory remarks will be
5 given by Dr. Amy Abernethy, who should be arriving
6 shortly, or is here. Great. Thank you, Dr.
7 Abernethy. So Dr. Amy Abernethy, MD, PhD, is an
8 oncologist and internationally-recognized clinical
9 data expert and clinical researcher. As the Principal
10 Deputy Commissioner of Food and Drugs, Dr. Abernethy
11 helps oversee FDA's day-to-day functioning and directs
12 special and high-priority cross-cutting initiatives
13 that impact the regulation of drugs, medical devices,
14 foods, and tobacco.

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

22 Dr. Abernethy received her MD at Duke

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

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

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

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

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

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

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

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

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

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

1 scleroderma. These are rare lung conditions.

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

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

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

22 Given that rare diseases are rare by

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

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

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


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

1 variable across patients.

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

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

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

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

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

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

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

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

1 support and satisfy post-approval study requirements.

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

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

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

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

1 efficient development of safe and effective medical
2 products.

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

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

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

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

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

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

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

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

22 I just wanted to introduce myself. My

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 for a national evaluation system for health
2 technologies.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 there can be a fair appraisal of these evidence
2 systems.

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

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

1 infrastructure and collaborating with the stakeholder
2 community.

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

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

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

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

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

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

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

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

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

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

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

1 important point. Very often when scientists dive into
2 trying to identify the genetic background and
3 understand the biology of the disease and begin to
4 work on targeting it, there is very little known.

5 There is often case reports and case series that are
6 highly selective and don't necessarily collect all of
7 the background information on the heterogeneity of the
8 disease or its course, or really what are the more
9 common complications or its rate of progression.

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

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

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

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

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

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

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

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

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

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


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

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

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

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

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

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

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

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

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

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

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

15 DR. ERIKA TORJUSEN: Thank you for that
16 comment.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 DR. ANNETTE BAKKER: Exactly.

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

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

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

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

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

1 the framework for medical devices.

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


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

16 DR. ERIKA TORJUSEN: Thank you.

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

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

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

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

1 from the online community.

2 DR. ERIKA TORJUSEN: The first comment.
3 Yes.

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

6 DR. ERIKA TORJUSEN: Yeah.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 DR. PETER STEIN: Just as another
2 opportunity, is we have a biomarker qualification
3 program both for C08 patient-reported outcomes as well
4 as biomarkers, which is many patient groups that are
5 looking to find endpoints and measures that they can
6 develop so that will facilitate drug development
7 interact with us in that way as well. That's another
8 opportunity.

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

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

15 DR. ERIKA TORJUSEN: Yes.

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

1 that can make use of their information?

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

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

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

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

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

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

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

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

22 DR. PETER STEIN: Just to underline

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

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

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

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

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

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

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

14 **WOMAN:** Yes. Thank you.

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

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

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

6 (Break)

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

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

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

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

1 depth, rich depth and insight from these folks.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

18 DR. THERESA MULLIN: Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 So we do this through some of our

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

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

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

1 trials from industry.

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

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

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

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

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

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

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

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

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

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

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

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

22 And so sort of going to your point

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

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

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

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

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

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

1 disease.

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

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

1 the community and really get a program together.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 to meet the needs.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 to collect. And that's a question about standards of
2 data. And this doesn't mean that all of the sudden
3 we're going to start telling people what to do.

4 That's not the case. But what we're saying is that
5 whatever you do, this is the kind of information that
6 you need to collect so that it becomes ensured that
7 whatever you collected becomes reproducible.

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

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

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

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

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

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

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

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

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

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

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

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

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

22 JEN FARMER: So sustainability is a

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

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

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

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

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

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

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

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

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

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

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

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

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

22 DR. THERESA MULLIN: Who would like to

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

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

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

1 DR. THERESA MULLIN: Thank you. Yes?

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

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

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

1 groups did not.

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

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

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

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

9 DR. THERESA MULLIN: Thank you.

10 ERIC HARTMAN: Hi, I'm Eric Hartman.
11 I'm the director of advocacy for the Choroideremia
12 Research Foundation. And we are fortunate enough to
13 have two gene therapy trials underway, and a third
14 about to begin. One of the challenges that we have
15 found in our disease is one in 50,000, supposedly
16 6,000 in the United States, is we believe 70 percent
17 of our patient population hasn't been genotyped to
18 actually know they have that disease. So our
19 challenge right now is our known patient population,
20 we may only have 30 percent. But on a global basis,
21 we are trying to find our patient population. We
22 started our own patient registry, but it's just a

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

17 DR. THERESA MULLIN: Anne?

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

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

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

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

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

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

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

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

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

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

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

22 So the sustainability is essentially

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

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

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

11 (Break)

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

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

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

5 Before joining MD Anderson, he served
6 as chair of the Radiation Oncology Department at the
7 University of Pennsylvania School of Medicine from
8 2005 to 2014.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 But what I can promise you is that in

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

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

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

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

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

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

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

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

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

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

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

1 clinical research. This is the tragic irony. Because
2 as you've heard time and again, the underlying
3 challenge of rare diseases is that while they are rare
4 individually, collectively they are not. There were
5 7,000 of them listed by us as rare diseases. Our
6 priority at FDA is to help find and support the
7 development of new treatments and cures -- yes, cures
8 -- for rare diseases, and to do everything we can to
9 advance this agenda through approvals, new and
10 creative trials, funding of new research programs, and
11 in other ways. And with your help, I believe we'll
12 get there.

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

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

1 to do that. Thank you very much.

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

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

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

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

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

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

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

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

22 DR. JEFFREY SHUREN: Hello, I am Jeff

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

3 DR. JANET MAYNARD: I like that,
4 gizmos.

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

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

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

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

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

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

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

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

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

11 DR. PETER MARKS: That's right.

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

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

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

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

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

1 challenges that you're seeing?

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

1 outcome assessments. What are all these?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 And so those types of things are things

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 provide those pathways.

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

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

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

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

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

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

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

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

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

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

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

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

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

1 collect that information.

2 And I'll put a plug in, by the way.

3 While not a tiny, tiny population, but it is rare
4 disease. Friday we did approve the very first test
5 for Fragile X syndrome and carriers.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 be international, not just in one country.

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

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

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

1 DR. JANET MAYNARD: Great point.

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

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

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

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

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

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

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

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

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

1 behind in this situation.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 DR. JANET WOODCOCK: Well, I mean, sort

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

11 DR. BARBARA GILLESPIE: Okay. Thank
12 you.

13 DR. JANET MAYNARD: Great. Thank you.

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

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

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

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

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

1 and overdose is consequent to that.

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

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

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

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

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

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

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

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

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

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

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

2 My comment relates to the SMA mother.

3 Our technology is used in the AveXis therapeutic.

4 It's the self-complementary vector. It breaks my
5 heart to hear her comment.

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

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

22 So my question is, how do I help that

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

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

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

22 On the other hand, I think turning to

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

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

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

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

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

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

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

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

16 WOMAN: Exactly.

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

21 WOMAN: Exactly.

22 DR. JANET WOODCOCK: So they have some

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

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

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

17 (Break)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 previously.

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

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

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

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

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

15 But our tools are increasingly being
16 matched not just to the disease, but to the type of
17 mutation. Single-letter changes in the genome can be
18 fixed, in principle, with crispr gene editing.
19 Nonsense mutations have other approaches splicing
20 mutations like Mila had can be addressed with yet
21 other approaches.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 So now, let's turn to hear some

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

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

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

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

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

22 So what is needed to facilitate

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 So I feel like our team really did a

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 can be defined very differently by different people.

2 JULIA VITARELLO: Thank you, Patroula.

3 I feel like you said a lot of what's been on my mind.

4 Leading up to Milasen -- to Mila receiving Milasen, I

5 have to be honest that the risk/benefit analysis was

6 pretty straightforward and black and white to me.

7 When I faced it, was the risk of treating Mila versus

8 the risk of not treating Mila. It was very specific

9 to one person, to my daughter, and what was going to

10 happen to her if she wasn't treated was very black and

11 white. She was going to lose all of her abilities in

12 a few years and she was going to die.

13 And the risk of treating her was an

14 unknown, and Dr. Yu and I had a very good

15 communication, on a daily basis, practically, and I

16 was -- feel like I was educated as much as possible in

17 what the possible risks were and we really didn't

18 know. There was no other patient in the world

19 receiving Milasen and there was actually almost no

20 other patient in the world receiving a drug like hers.

21 And I have to be honest. I never spent

22 more than one second questioning whether or not Mila

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

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

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

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

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

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

1 withdrawn.

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

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

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

1 assembled.

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

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

22 And so they would build up and

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

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

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

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

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

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

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

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

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

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

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

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

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

22 And also, I think, to remember that

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

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

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

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

1 thousands of people.

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

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

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

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

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

22 DR. PATROULA SMPOKOU: Yeah, I wanted

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

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

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

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

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

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

1 the community wants.

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

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

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

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

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

1 audience, we'd be happy to take them.

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

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

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

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

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

14 AMY DAHM: Thank you.

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

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


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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4 DR. SUSAN MCCUNE: That's --

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

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

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

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

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

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

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

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

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

4 DR. CHRISTOPHER AUSTIN: Yeah, sure.

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

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

1 also a lot of patients like you.

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

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

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

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

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

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

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

15 DR. SUSAN MCCUNE: Thank you. Martha?

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

18 DR. SUSAN MCCUNE: Mm hmm.

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

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

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

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

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

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

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

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

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

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

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

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

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

1 things to the extent possible and to share
2 information.

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

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

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

1 DR. SUSAN MCCUNE: Sheila?

2 SHEILA MIKHAIL: Hi. My name is Sheila
3 Mikhail. I'm the CEO and co-founder of AskBio.
4 AskBio is an AV gene therapy company. It started off
5 as a collaboration, so collaborations are at our
6 roots. It was started by parents who had children
7 with devastating disease. Traditional medicine didn't
8 provide them with any answers, so they reached out to
9 researchers.

10 These were very educated research
11 patients -- research scientist's patients. They read
12 every single paper. They looked at all different
13 types of alternative medicines and they were extreme
14 advocates for their children, really admirable people.
15 They reached out to Jude Samulski who was the first to
16 clone AAV for therapeutic purposes. He's the
17 scientific founder of our company. And if it wasn't
18 for those parent collaborators, we wouldn't be here
19 today.

20 For a long time, gene therapy was not
21 seen in the best of light. People thought it was too
22 risky and it was too much science fiction. I would go

1 to different investor conferences with all the Wall
2 Street crowd and they would just walk away from me.
3 It was almost like I had the Coronavirus written on my
4 forehead.

5 Today, it's a different era, but again,
6 I think the number one thing that I want to say is you
7 really have to collaborate with patients because
8 that's what makes your effort sustainable. They can't
9 walk away, in many instances, from their endeavors and
10 their money is short of a short-term goal. But having
11 -- making treatments that have benefit for patients is
12 a much more long-term, sustainable objective. Over
13 the years, we have developed treatments for Duchenne's
14 and in a second I'm going to talk about that and how
15 we use collaborations to advance that drug.

16 We also developed treatments for giant
17 axonal neuropathy, and in that case, we had parents
18 who had Relay for Life races and bake sales, but on
19 the basis of those grass roots fundraising efforts, we
20 actually have treated several patients and with the
21 collaboration of NIH and the support of NIH.

22 We have also advanced treatments for

1 hemophilia which are now being advanced by Takeda.
2 We're in the clinic right now for a Pompe and heart
3 failure -- late stage heart failure. We'll be in the
4 clinic hopefully by the end of the year for MMA and
5 limb-girdle 2i. We're also working on Huntington's
6 which we hope to be in the clinic next year. Gene
7 therapy is exciting.

8 It has a lot of potential and it's
9 giving a lot of hope to patients, and I'm very
10 fortunate to be part of this change in making history.
11 The example that I want to give is in the treatment of
12 -- the development of the treatment for Duchenne's
13 muscular dystrophy. As I mentioned, we started our
14 efforts at a time when gene therapy was perceived as
15 science fiction. We could not get funding for the
16 product.

17 We had parents who literally put in
18 their own money, did bake sales, did a lot of things
19 to advance a therapeutic. GSK, this is another
20 example of a collaboration, gave us access to a capsid
21 that they just had sitting on the shelf and that
22 allowed us to use what we thought was going to be the

1 best capsid available.

2 We collaborated with academics who had
3 the dog models, the Golden Retriever dog models and
4 didn't have a lot of money, so people are just -- are
5 kicking into this effort. We went into the clinic
6 with the support of the Muscular Dystrophy
7 Association. If it wasn't for their support, we
8 wouldn't have gone into the first -- into the clinic
9 the first time. At that time, it was in the last
10 2000s.

11 People were very skeptical of gene
12 therapy, so we could only inject in the muscle and in
13 very small area, only put a small amount of virus into
14 little boys the size of an eraser. Not -- knew it
15 wasn't going to have therapeutic effect, but we had to
16 demonstrate that it was safe, baseline safety. We
17 were successful there.

18 Again, we went back up to Wall Street.
19 We had dogs out nine years showing that we could
20 correct the dog model. Could not get funding.
21 Everybody said, it would not work. (inaudible)
22 stepped up, helped us -- another collaboration -- with

1 the funding to do all the I&D enabling studies. We
2 ran out of money, but we had the opportunity to
3 collaborate again with Pfizer. Pfizer has taken the
4 drug into the clinic.

5 They now own all rights to it, but
6 we're very happy because we have met many of the boys
7 in that clinical trial and they should be in
8 wheelchairs today but instead, they're playing Little
9 League baseball and they're enjoying swimming lessons,
10 and that's why most of us in this space do what we do.
11 We get up in the mornings because we want to make a
12 difference in patients' lives and we have had had the
13 satisfaction of ASPIRE, of having that impact on
14 patients.

15 The other thing I want to mention is
16 our foundation, because it's equally important to me
17 as the for-profit part of our business. Columbus
18 Children's Foundation was founded -- again, we were
19 very patient motivated to address the needs of ultra
20 rare indications that can be treated by gene therapy.
21 We do this through a nonprofit structure. These are
22 indications with 100 or so or fewer patients.

1 We don't have a hard stop, but we know
2 that those are not commercially viable indications,
3 and so we donate our technology, our manufacturing
4 capacity, our (inaudible), our regulatory, our legal
5 support to the advancement of these drugs. Today,
6 we're working on AADC, amino acid decarboxylase
7 deficiency. That's a mouthful. And we have treated
8 20 patients free of charge. I think we're one of the
9 few groups that has done that.

10 We're also -- have in our pipeline for
11 the foundation (inaudible). So those are the diseases
12 we're working on. Thank you.

13 DR. SUSAN MCCUNE: Vasum?

14 DR. VASUM PEIRIS: Thank you. Mic's
15 on. Perfect. First of all, thank you very much for
16 everybody for continuing to stay here. This is a very
17 important cause and it's wonderful that as we've
18 talked about before, that the meeting is happening. I
19 just want to thank Janet and the entire OOPD team that
20 has put this together and all of the people that have
21 worked to get this to happen, so it's wonderful to see
22 so much registration and so much interest across the

1 country and across the globe in these issues where
2 rare diseases.

3 Very simply put, in terms of
4 introductions, I'm going to build on what Jeff, Dr.
5 Shuren, the center director mentioned. For the
6 purposes of this panel, I am the gizmo guy, so I'm the
7 chief medical officer for pediatrics and special
8 populations at the Center for Device and Radiological
9 Health. My clinical background is in pediatrics,
10 (inaudible) pediatrics, pediatric cardiology, and
11 adult congenital cardiology.

12 So I really had an opportunity in
13 private practice to see everything from the fetus,
14 prenatal, perinatal medicine all the way through the
15 hundred-year-old and you can imagine in a field like
16 congenital heart disease, it's extremely device rich,
17 but certainly very much also dependent on medications
18 and I'm sure to (inaudible) share great deal of
19 insights with Susie with respect to any neonatology as
20 well.

21 There's a lot of topics to address, but
22 I'll try to focus on that you brought us towards, as,

1 you know, what is the ecosystem, what is the state of
2 the ecosystem and where are we going, really. I think
3 it is wonderful that we are coming together and that
4 there again, there's so much interest. There is a
5 great deal of work that's being done, I think, in the
6 biologics and drug space.

7 There continues to be great potential
8 in the device space and I think as we move forward, we
9 recognize how much devices and advancing technologies
10 will make a difference in patient lives and the
11 difference that they make every single day in patient
12 encounters. If you really think about it, when you go
13 to a doctor and you have a doctor visit, there's a
14 higher likelihood that you actually might engage with
15 a medical device -- you know, a thermometer, a
16 dipstick, a blood pressure cuff -- than you might with
17 a drug.

18 That that's something to be cognizant
19 of as we think about how technologies are affecting
20 lives and especially with respect to small populations
21 and rare diseases. We -- a couple of the earlier
22 panels alluded to this a little bit, but I think

1 there's necessity to really work -- maybe focus on
2 this a little bit more, but with respect to how we can
3 begin to advance technologies to truly serve the
4 purposes of small populations, pediatrics, and rare
5 diseases, we have to begin the potential of the
6 ecosystem together.

7 And the issue around collaboration that
8 Chris mentioned, I think is an important one. I'll
9 just highlight one point around that very historical
10 notion that people were told back in the day, perhaps,
11 don't collaborate because your academic careers really
12 are based off of you being the leader, you being the
13 thought leader, you taking forward research.

14 It's wonderful to see that medical
15 schools across the country in their mission statements
16 now are putting in that they -- one of their purposes
17 is to develop collaborative professions. And that
18 collaboration over time can make a significant
19 difference.

20 And from where we are right now, when
21 you think about how do we optimize the potential of
22 the ecosystem, we've got to bring together issues not

1 just in the regulatory space, not just in the clinical
2 space, but in the economic space as well because we
3 recognize that there are a great deal of efforts that
4 could be considered perhaps one-offs, a great deal of
5 philanthropic investment in certain area, either
6 certain aspects of Milasen or a specific disease or a
7 specific drug or a specific medical product.

8 What we want to get towards is a
9 platform that allows anybody with great ideas, great
10 potential, to be able to invest in the development of
11 medical products for rare diseases, especially in the
12 pediatric population. One of the things that Dr.
13 Shuren mentioned earlier is the SHIP Program. That's
14 the System of Hospitals for Innovation in Pediatrics.
15 It is a program and a framework that we've put
16 together to really consider what is the next step in
17 an ecosystem that truly works for the benefits of
18 small populations and pediatrics.

19 How do we begin to bring together
20 individuals and organizations across the ecosystem and
21 across the spectrum to truly begin to think
22 differently around investment in pediatrics so that we

1 can actually get to a point where when technologies
2 are being developed, pediatrics, rare diseases, small
3 populations are considered as part of the deal. It's
4 going to be an afterthought. It's not going to be
5 done years later.

6 It's not going to be considered as a
7 potential and perhaps never get there because there's
8 additional costs and legal issues afterwards, but it's
9 going to be done from the beginning. So I'll stop
10 there. Lot more to talk about, but hopefully that
11 gives you a little bit of introduction of where we're
12 headed.

13 DR. SUSAN MCCUNE: Rhiannon.

14 RHIANNON PERRY: My name is Rhiannon
15 Perry. I was born with sickle cell and lupus. For
16 about 13 years, I was in and out of the hospital
17 working on fixing the issues that both the combination
18 of sickle cell and lupus have caused. Around four
19 years ago, I took part in an experimental
20 haploidentical bone marrow transplant to cure both
21 diseases and now that I'm cured, I'm working with
22 organizations like Hope for Henry and the ICAN

1 Initiative to help bring awareness to those rare
2 diseases and the causes.

3 ICAN and being part of the Hope for
4 Henry patient and team board collaboration is a really
5 important step to bring more awareness to these
6 diseases and to start a communication and
7 collaboration with patients and the environment and
8 the community around and to better educate more people
9 about the things that are going on with those
10 diseases.

11 DR. SUSAN MCCUNE: So thank you all
12 very much. I think as you all have seen, we have
13 pretty much representatives of most of the
14 stakeholders either in your past life or your current
15 life up on the stage in terms of patient advocates,
16 academia, industry, and government entities. And
17 round five years ago, we started the International
18 Neonatal Consortium and really thrilled at that time.
19 It was one of the first consortia efforts that were
20 undertaken and I'm thrilled today that every panel had
21 talked -- has been talking about public-private
22 partnerships and consortia efforts and I'm going to go

1 back to Rhiannon to start the conversation.

2 Rhiannon mentioned ICAN, which is the
3 International Children's Advocacy Network, and has
4 been very, very important in understanding what end
5 points and what clinical trials are meaningful for
6 pediatric patients. And so my question to the folks
7 on the panel is, all of us have been involved in
8 consortia efforts. Clearly, we not have -- we're now
9 getting an experience that's in -- upwards of years,
10 and now we probably have a good deal of insight into
11 what has worked really well and where there's some
12 challenges associated with consortia efforts.

13 So I'm going to open it up and start
14 maybe with Rhiannon at the end, just talking about
15 what are the -- what are some of the examples of
16 successful efforts from the consortia perspective,
17 what are done well, and then where are -- where do we
18 have some challenges.

19 RHIANNON PERRY: So like I said before,
20 I work with Hope for Henry and so we have a patient
21 advisory council and then we also have a teen board
22 where teens in the community can come take part of

1 programs and fundraisers for Hope for Henry to better
2 provide incentive programs for patients and so we did
3 -- collided those two programs or groups to take part
4 in the ICAN chapter and so with the ICAN chapter, we
5 do a lot of community work.

6 There are two important parts. There's
7 education incentive and then there's also the feedback
8 incentive and so the education incentive part is where
9 we go into Children's National Medical Center and we
10 talk with researchers and doctors and those who are in
11 the field who can explain what they do, why they do
12 it, and how they do it and better educate us on the
13 importance of their role in the community.

14 And then we also, what the feedback
15 initiative is, a lot of the patients are able to look
16 at these programs that are implemented to help them
17 and to kind of discuss what's good and what's bad
18 about it. So the ICAN program is great because we are
19 able to collaborate with the community and we're able
20 to spread awareness about these diseases and illnesses
21 that really need to be brought up. And one thing that
22 we can definitely work more on is our outreach in

1 reaching other communities, other areas in the world
2 to bring more awareness to that.

3 DR. SUSAN MCCUNE: Thank you. So we're
4 going to go right back -- right back the way we came.

5 DR. VASUM PEIRIS: Oh, I thought we
6 were going to go hand written here. Your focus is
7 really around what is -- what's working well in
8 consortia, perhaps what's not, how do we improve, that
9 type of...

10 DR. SUSAN MCCUNE: Yes.

11 DR. VASUM PEIRIS: Yeah.

12 DR. SUSAN MCCUNE: You know, what's the
13 experience, because now we've been -- each of the
14 panels before us has really talked about public-
15 private partnerships and consortia efforts and
16 everyone has some experience with that. And what have
17 we learned that works or that people know kind of from
18 your experience what's worked, and then what are some
19 challenges that maybe other folks can help in --
20 address some of those challenges?

21 DR. VASUM PEIRIS: Yeah. So thanks.
22 It's a great question and I think something that

1 absolutely makes a difference for the types of
2 initiatives that are necessary to really move forward
3 in the field of rare diseases. I know that there have
4 been a number of different consortia efforts that have
5 some together in an attempt, in their own spheres to
6 break down silos.

7 And what you recognize sometimes is
8 that perhaps there are still silos within those
9 consortia and so how do we begin to get to a point
10 again where we truly are beginning to take a look at
11 this from a very global standpoint where the entire
12 ecosystem is being optimized, truly, for the benefits
13 of patients and that is a little bit of the work, I
14 think, that we're trying to do right now with the
15 consortia that we're developing for around SHIP.

16 We wanted to ensure that stakeholders
17 across the ecosystem are involved, patients included,
18 but that also includes, again, not just that
19 regulatory world like I mentioned before. It also
20 brings into play the individuals that invest in the
21 development of these medical products, like
22 (inaudible) Funds, Angel Funds, all of that, because

1 without creating a system that brings together all of
2 those different players, it's really difficult to make
3 a -- to develop a platform and a system that truly
4 makes a difference for patients.

5 So making sure that when we do develop
6 consortia that all the right individuals are -- and
7 organizations and perspectives are represented. It
8 is, I think, very simply put, naively put, important.
9 But making that take effect, that sometimes is a
10 challenge and how do we truly continue momentum and
11 bring all of those individuals together in a
12 collaborative community type atmosphere to be able to
13 move this field forward.

14 DR. SUSAN MCCUNE: Sheila?

15 SHEILA MIKHAIL: I find that people are
16 usually more cooperative in collaborations when they
17 have something to gain and little to lose. And what I
18 mean by that is often, they work much better when
19 there's not competing interests, but when there's
20 synergistic interests or new opportunities. So I
21 think of, for example, a lot of the collaborations
22 that -- and consortiums I'm involved in, where there's

1 a complement of gene editing technology with AV
2 delivery technology, that works extremely well vis-à-
3 vis to AV companies working maybe on the same
4 diseases, that works less well.

5 Where there's a new use of a
6 technology, for example we discovered that a Doggybone
7 technology -- Doggybone DNA technology that's used for
8 vaccines can be used to produce plasmoid without big
9 bioreactors and E. coli, so it's safer for patients,
10 it's quicker. I will reduce manufacturing costs.
11 That was a good collaboration because there was
12 something for everybody to get out of it, right,
13 nothing was being taken away. There was only upside.

14 Where there's safety issues that affect
15 technology, it's to everybody's interest to make sure
16 that patients have the highest level of safety and
17 that we address these as an industry. So for example,
18 in our space, it's well known that there is often
19 transaminitis associated with the delivery of AV
20 therapeutics, so many of us come together to try to
21 address those issues, share data, try to make sure
22 that we optimize the safety of our therapeutics for

1 patients.

2 Where there's industry standards that
3 affect everybody, once again, titering is a big issue,
4 titering of our material -- AV material in the
5 manufacturing process. That's another area where
6 people come together because there's a common
7 interest. So I think there's many places where people
8 can play nicely together, but I think we all have to
9 be knowledgeable that sometimes there are tensions
10 because we're also forced to compete.

11 DR. SUSAN MCCUNE: Martha?

12 DR. MARTHA DONOGHUE: Hi. I guess I'll
13 speak a little bit to an example in pediatric oncology
14 and I think of rare disease drug development, drug
15 development to treat rare cancers, really need to be a
16 global enterprise and because of the issues relating
17 to the rarity of pediatric cancers or pediatric
18 diseases in general, there are sometimes complimentary
19 or competing regulations in various countries that
20 will either mandate clinical trials in pediatric
21 patients or offer incentives.

22 And for the most part, I think these

1 regulations are wonderful and important, but they also
2 have the potential to cause differences and they way
3 we're applying these regulations that can scuttle or
4 certainly make drug development for children more
5 difficult and we were running into that a little bit
6 in the past with respect to oncology with varying
7 regulations in in Europe requiring one thing and then
8 the timing of our incentive process sort of being a
9 mismatch.

10 And so companies who are looking to
11 develop drugs globally, it puts them in a bind,
12 frankly, I think some of the time, because they're
13 getting different advice and really what we want is
14 one clinical trial that's going to answer a scientific
15 question rather than something more distinctive than
16 that, so a new regulation that's going to come in
17 effect in August whereby the U.S. we're going to be
18 able to require certain pediatric investigations for
19 cancer therapeutics being developed in adult patients
20 that have a mechanism of action that's applicable to
21 oncology and in children -- to cancers in children.

22 And it's very exciting and I think it's

1 really going to help move drug development forward for
2 children, but we're in a circumstance -- will be in a
3 circumstance soon where we're thinking about, okay,
4 well we have lots of drugs, maybe four, five, six
5 drugs with a particular mechanism of action but yet we
6 have a very small pool of patients and so how do we
7 figure out how best to study these drugs in children
8 so that we're not duplicating our efforts and
9 certainly not competing with one another?

10 And if so -- they developed in Europe
11 back -- starting in about 2013 an organization called
12 Accelerate and what's unique about this organization
13 is that it brings together patient advocacy groups,
14 international regulators, companies developing drugs
15 for cancer, and scientists all together in a pretty
16 competitive space on a regular basis to take on
17 certain issue and try -- and really encourage free
18 flow of information to help everyone make the best
19 decisions possible to develop drugs more efficiently
20 for kids.

21 And while it started in Europe,
22 recently, over the past year-and-a-half to two years,

1 they've been increasing involving in the -- with the
2 U.S. as well with the help of an advocacy group called
3 (inaudible). We had our first meeting in the United
4 States this fall and this particular one was on
5 development of a particular class of drugs called
6 epigenetic modifying agents for patients with cancer,
7 for pediatric patients with cancer.

8 And because of the ability to have this
9 informal communication with one another, I think we
10 all walked away with a better understanding of what
11 was important to patients, which drugs within that
12 class might have the most promise for treating
13 pediatric cancers, and while we didn't come away with
14 any definitive decisions, I think we all came away
15 with increased understanding of one another and better
16 -- to make the best decisions that we could for
17 patients.

18 So I think that's one excellent example
19 of sort of a new way to collaborate in a pretty
20 competitive way. We're all sort of having the same
21 goals, but I think also respecting the competition
22 piece of it as well. And I think we still have a lot

1 of challenges. I think we need to bring in other
2 regulators into this conversation, not just Europe and
3 U.S.

4 I think at this particular meeting, we
5 had representative from Australia as well, but I think
6 the more people we can bring to the table to have
7 these discussions, the better and, of course,
8 sometimes the ability of our infrastructure to handle
9 complexities can be really tested when we're thinking
10 about how quickly science evolves and changes, so we
11 may come up with a plan that we think is perfectly
12 reasonable and wonderful to move something forward and
13 then something new can come up and in science that may
14 make us need to relook at things and shift
15 trajectories. So I'll stop there.

16 DR. SUSAN MCCUNE: Chris?

17 DR. CHRISTOPHER AUSTIN: I'm going to
18 take Martha's example and up her 10. So, sort of
19 think of -- it's hard for me to pick one of these.
20 Everything we do is a collaboration, but I decided,
21 like a lot of scientists, you learn the most from the
22 extreme phenotype which is... So I decided in a fit

1 of collaboration to become the chair for three years
2 of something called the International Rare Disease
3 Research Consortium. It is a consortium of about 65
4 organizations from 22 countries on five continents.
5 It includes all the major funders: NIH, you know,
6 European Commission, Japan, Canada, Australia, China,
7 you name it, as well as about 15 companies 15 patient
8 groups, and a whole bunch of scientists.

9 And they literally speak 40 different
10 languages. They come from the entire spectrum of
11 research from genetics to public health and
12 regulation, everything in between, and they were
13 brought together -- we were all brought together by a
14 common enemy and one of my points has got to be, you
15 got to keep the focus on the common enemy because if
16 you don't, everybody starts focusing on the other guy
17 who's there enemy.

18 And so the common enemy here is the
19 enormity of the rare disease problem. Those of you
20 who've heard me talk will know that I am fond of
21 saying where -- unfortunate truth, that at the current
22 rate of progress, which is really quite remarkable,

1 but at the current state of progress it will be 2,000
2 years before there is a treatment for all rare
3 diseases.

4 So we have to do things differently.
5 That is just not an acceptable answer. And it doesn't
6 have to be, but all of these folks were brought
7 together by this common desire to say, well, if we
8 coordinate what we do internationally and so the NIH
9 knows what the European Commission is doing, would
10 know what AMED is doing in Japan. We know we're
11 working on the same thing. We can divide and conquer.
12 The genome project was done that way, if you remember
13 this.

14 And so what are the lessons from this
15 absolutely scarring experience, I must say, of three
16 years? It was actually an enormous pleasure, but what
17 I learned was that first of all, it is critical that
18 leadership -- leadership's really important in this
19 case -- keep articulating what the goal is, what --
20 why are we all here. And it -- that sounds sort of
21 obvious, but it's easy to lose track in the nitty-
22 gritty of individual projects, why we're doing this.

1 I just imagine Bill Belichick used to
2 do before he started losing football games. To
3 anticipate that there will be different languages and
4 people will misinterpret each other, they will
5 misinterpret each other, so you have to have the
6 translators amidst the sort of senior people who look
7 out for this at meetings and when something like that
8 happens, say, what they probably meant is -- they're
9 like -- it's like a marriage counselor, which I think
10 we've all experienced where -- so that's really
11 important.

12 Third, you got to be really up front
13 about the money, because in the end, it always comes
14 down to money. Things always come down to money, no
15 matter how much people say, oh, well, kumbaya, we're
16 all in this together; everybody's got their budgets.
17 Everybody's got issues they got to deal with, so be up
18 front about that. And fourthly, be up front about the
19 credit issue, so we all love to work together and all
20 that stuff, but we all have a boss, too, and that
21 boss, frankly, doesn't care what Joe Schmo in Japan
22 got valued -- the value out of what you did.

1 You know, he or she wants to know
2 where's the beef, from you, and so you have to design
3 what you do to have more than enough credit to go
4 around, or else the thing is toing to fall apart and
5 people are going to leave because they're going to
6 have to choose between their own job and that they
7 really want to do. And that's a false choice they
8 shouldn't have to make, and it's manageable, but you
9 have to do it -- you have to do it prospectively.

10 And so I guess my lesson from this was
11 that with good proactive leadership and people who are
12 sort of like-minded, which these kinds of consortia
13 tend to attract, and proactive management of the
14 problems that you know are going to appear, these can
15 be extremely effective and so I'd urge you to realize
16 that they can be done, but you can't just let it --
17 think that it's going to work on its own, because it
18 really won't.

19 DR. SUSAN MCCUNE: So on that note,
20 with about 15 minutes left in the session, I'm going
21 to open it up for questions here in the room, and
22 while people are coming to the microphones, I didn't

1 know if there's anyone online that had a particular
2 question for us. No. Okay. It's late in the
3 afternoon. Dr. Epps is moving to the microphone.

4 DR. EPPS: At the microphone. I wanted
5 -- I had a question. I want to circle back to
6 something that Rhiannon had mentioned as a challenge,
7 which is bringing in all communities. We know that
8 rare diseases affect folks in every community. I
9 wanted to ask the panel, starting with Rhiannon, any
10 thoughts she had on how to bring other -- folks in
11 other communities in to this process and to ask other
12 panelists what sort of activities or actions they have
13 been doing up to this point to try to make that
14 happen.

15 RHIANNON PERRY: So to start, with the
16 Hope for Henry, Children's National Medical Center
17 chapter of ICAN, we've reached out to many different
18 hospitals to implement those programs there and to try
19 to gather people and a group of people who are willing
20 to go out and speak about these issues and hold
21 conferences for others to come in and speak about it
22 and communicate, share their thoughts and things like

1 that. So that's one of the efforts that we're really
2 trying to take now.

3 DR. EPPS: Are you guys using a lot in
4 terms of social media to reach out to other folks?

5 RHIANNON PERRY: Definitely.

6 DR. CHRISTOPHER AUSTIN: I guess the
7 only thing I would say is if you think about a sports
8 team, so I was in Boston for 20 years and the Red Sox
9 would be pathetic to being really good. When they
10 were pathetic, I was like one of, like, four people at
11 the ballpark. And when they started winning, all of a
12 sudden everybody was a Red Sox fan. So having some --
13 people love to be part of the winning team. And so I
14 think all of us have experienced this, that we all
15 have long-term goals but you've got to start winning
16 individual baseball games, and that will bring in more
17 people so there's this adage that we all have.

18 You know, got to have some short-term
19 confidence building measures. That's really
20 important. And it's -- and all of us say, well, gosh,
21 you know, that's just -- it's such a small step and it
22 doesn't really matter because it's not -- it's

1 infinitesimal the way we want to go. It really
2 matters because it will bring other people in who will
3 make your team bigger and stronger.

4 SHEILA MIKHAIL: Just to build on that,
5 sometimes, too, it's -- the team maybe isn't your
6 company or your organization, but it's a field. I
7 feel like for AV gene therapy, we had to do that. In
8 the early days, we gave out a lot of our technology.
9 AveXis uses our technology and that's a major --
10 almost every single company out there uses some form
11 of our technology.

12 We're making our manufacturing process
13 available and we're doing that because the industry is
14 still very vulnerable and we need to have some more
15 wins. So when the SMA drug was approved, that was
16 really good and now, hopefully, the DMD drug will be
17 approved and the hemophilia drugs look. But there's,
18 you know, like you mentioned, 7,000 diseases, rare
19 diseases, and we're still hopeful that we can go into
20 the main pathway diseases.

21 With Medtronic's help, we're not in
22 heart failure and that's a pretty big step. At least

1 with monogenetic diseases, you know what the drug is.
2 The drug is basically replacing the defective genes,
3 the good gene that's going to do the work that the
4 defective one can't. We get to pathway diseases, and
5 there's a lot of different targets and you hope you
6 get the right one. So, anyway, for us, I agree with
7 that, but I think our team is much bigger. For us,
8 it's an evolving field.

9 DR. VASUM PEIRIS: And I'd just build
10 on that team concept, since you laid it out so well.
11 For the Red Sox, it was probably the four people that
12 knew plus my entire pediatric EPT. They were always
13 there. That's all we talked about during rounds. But
14 on the team concept, there's a big team that can do a
15 great deal of great work. You know what that team is?
16 HHS, the government. Right.

17 That team is doing a lot of work. What
18 if -- again, to Susie's question -- what if there is
19 better collaboration, NIH, CMS, FDA, and others that
20 came together to try to begin to truly address this
21 across the spectrum? How do we begin to develop more
22 of a collaborative environment within those teams?

1 Those teams can make a huge difference and create
2 platforms and systems that can help everybody to have
3 better success.

4 All the individual projects, all the
5 individual areas that people are working on right now,
6 that team can come together and help all of those
7 other individuals.

8 DR. SUSAN MCCUNE: We have three more
9 questions lined up.

10 ANNA CHRISMAN: Hello everyone. Good
11 afternoon. My name is Anna Chrisman and I am from
12 Genentech. My question was really about
13 standardization, so this was mentioned a lot
14 throughout the different panels and there's also, in
15 context of consortium, I'd imagine that's important as
16 well. So the panel earlier had discussed the rare
17 disease accelerator and (inaudible) best practices
18 from NIH and the need for standardization from that
19 perspective. Is anything similar envisions for
20 investigator sponsors' studies, and if so, do the
21 panelists have any feedback on lessons learned they
22 could share regarding standardization of data there

1 and how sponsors and investigators could get that type
2 of feedback?

3 DR. CHRISTOPHER AUSTIN: Go for it.

4 DR. VASUM PEIRIS: I'll start you off.
5 I don't have another good story about teams, but
6 standardizing data, right. One of the areas that CDRH
7 has been working on for quite some time is an actual
8 evaluation system for health technology. How do we
9 begin to get to a point where hubs across the country
10 and potentially across the world have access to
11 certain levels of data and can actually share that
12 data in a secure way?


13 Very simply put, the way that I naively
14 look at it is, there is data that we acquire every
15 single day in EHRs and that is put into patient
16 management. That data can be refined. Certain data
17 elements can be developed, and it can get to a point
18 where that data is so refined where -- and abstracted,
19 that you have a specific data element that can make a
20 difference for both regulatory and public health
21 decisions across the entire country or potentially
22 across the world.

1 But ultimately, from a regulatory
2 standpoint, if you want to look at it that way, you
3 can get to a point where that information can be
4 aggregated and potentially help facilitate and
5 accelerate development of medical products.

6 DR. MARTHA DONOGHUE: Yeah, in our
7 space, we've talked about having a drug master file
8 for capsids. Right now, we have that for
9 manufacturing, so anybody who uses our system, right,
10 they can refer back to our master file that's filed
11 with the FDA. But we could envision a world where a
12 lot of the capsids that are now coming off patent like
13 AV8 and 9, which are used in a lot of products, if
14 there was a master file filed at the FDA that
15 investigators could refer to, it might accelerate drug
16 development.

17 The capsids have a certain tropism,
18 right. They're always going to have a certain
19 tropism. The thing that's changing is the drug that
20 you're putting and essentially it's the gene that you
21 want to express. And so it could simplify and
22 accelerate getting I&Ds filed.

1 DR. SUSAN MCCUNE: So moderator's
2 prerogative. I'm going to say that we have three last
3 questions and everybody has to keep their answer
4 short. So we're going to go one, two, three and then
5 we'll be done.

6  MAN 1: Okay, I'm Anna (inaudible)
7 the president of the Children's (inaudible)
8 Foundation. I have two things that I would like. I
9 want -- I'm going to start with hope and then I have a
10 request. So hope is that we've had some very large
11 collaborative initiatives and -- within the NF
12 community and they have really delivered, and NCATS to
13 say that Chris puts his axe where his words are, NCATS
14 was a big part of that collaborative effort and the
15 drug that was identified through that (inaudible) is
16 now ready to go into clinical trial, so that's the
17 hope.

18 The request is that collaboration is
19 really hard and I will say it's a combination of stick
20 and carrot and I don't know whether I should start
21 hitting with the carrot as well, but I'm not sure.
22 But the thing that I -- we have discovered over the

1 last five years that we've really had this big
2 collaborative consortia is that there's two elements,
3 I think, to successful collaborations.

4 One, is an incentive. Try to
5 understand why people don't want to collaborate and
6 try to pull them over to the side where you want them
7 to be. But the second thing, and this is a request, I
8 think there is also something where we really need
9 help from federal agencies and that's around policies.
10 It is unacceptable, Mr. and Mrs. Hospital Service that
11 you are competing between hospitals and yet there not
12 one shared place where everybody shares their clinical
13 information, especially in the rare disease community.

14 It is not acceptable, Mrs. and Mr.
15 Researcher that you develop animal models with
16 taxpayer dollars and that these animals are not
17 available for drug testing. Here, we need help.
18 Here, we need policies. Chris, I see you smile
19 because I know... I'm looking, but I see --

20 DR. CHRISTOPHER AUSTIN: You're
21 speaking my language. Yeah.

22 WOMAN 1: But I see -- I think we need

1 to start thinking. Really, there we need you guys
2 because we as patient associations, patient
3 organizations, and with our patients, especially in
4 the rare disease community, it's really, hard because
5 the patients are going to be activists but then
6 they're going to be activists against their treating
7 clinicians, which is really not a good thing to do.
8 So we need policies. So this is my request. So my
9 hope is it works and Chris helped. My request is,
10 please help us with policies. And I would like to get
11 a reaction.

12 DR. CHRISTOPHER AUSTIN: A great point,
13 and I'm just going to maybe just build on that and
14 hopefully augment this. Since (inaudible) pediatrics.
15 That's what we're trying to do, right? We are trying
16 to overcome a number of different issues in the system
17 that isn't necessarily optimally supporting device
18 innovation for pediatrics and small populations. But
19 one of those issues, right, is that notion of small,
20 geographically disbursed heterogenous populations that
21 we just can't get all the information for. Well,
22 where do all those populations get care? Those


1 populations get care at the pediatric academic medical
2 centers across the country, right, and across the
3 globe. So if we can bring those systems together --

4 WOMAN 1: Yep.

5 DR. CHRISTOPHER AUSTIN: -- and ensure
6 that there is a method by which to aggregate that the
7 information and the data that's being developed plus a
8 system that accounts and accommodates for a number of
9 other legal issues, regulatory issues, economic
10 issues, then perhaps we will have a system that truly
11 supports innovation for small populations and if you
12 can support innovation for small populations, you will
13 accelerate innovation for all populations.

14 WOMAN 1: Yeah, exactly. Exactly.
15 Yeah.

16 DR. SUSAN MCCUNE: All right, off to
17 the left over here.

18  N 1: Okay. Eric (inaudible)
19 research foundation. This question is probably for
20 Dr. Austin.

21 Having worked with your international
22 consortium for as long as you have, one of the things

1 that we have encountered as we get closer -- we're in
2 Phage 3 on one of our trials, is it turns out we are
3 beginning to realize that we need to build a network
4 of patient advocates that can speak within the
5 countries, whether it's the European Union or even
6 Australia, places like that, that we need a network of
7 advocates that are going to be ready on our own behalf
8 to go before their own regulators, even after it's
9 gotten approved here in order to be able to argue the
10 importance of this treatment within those individual
11 countries. Is that the case?

12 DR. CHRISTOPHER AUSTIN: Yeah. Oh,
13 yeah, definitely. And I would say -- so what we did
14 within IRDRC, is because it was an umbrella
15 organization, in order to be a patient advocacy group
16 within IRDRC, you had to be representing an entire
17 country. So for instance, NORD was a member and URS
18 and Europe and those kinds of things. And -- but they
19 of course, then have a relationship with each -- they
20 all have member organizations and in more ways it was
21 -- what was wonderful about that experience was that
22 (inaudible) is, I think, ahead of almost everybody and

1 NORD'S pretty good, but then we had a patient
2 organization from Botswana that was significantly
3 smaller and had significantly less experience and so
4 what this allowed was this sort of big brother/big
5 sister relationship.

6 But you're absolutely right. That's
7 what these countries needed. But what we discovered
8 was that U.S. and Europe, we lose track of how far the
9 culture has come to take the patient seriously. In
10 Japan, for instance, which is a very hierarchical
11 culture and is still quite male dominated, male
12 oriented, most of the patients are moms, like they are
13 here, not all, but a lot of them are and so that is a
14 very hard thing for the culture to deal with.

15 How do you overcome those two big
16 cultural barriers? And so we do a lot of work and
17 continue to with the other countries and say, well,
18 that was once the case in the United States, too, and
19 so how have we overcome that? But yes, this is
20 absolutely essential. The other thing that the --
21 each of the countries has to do which the United
22 States hasn't done yet, of course, but we managed to

1 get around it anyway because we have the Orphan Drug
2 Act and other things, is to have a national rare
3 disease policy and those national rare disease
4 policies are almost always run from the patient
5 groups. They make it possible.

6 MAN 1: Thank you.

7 DR. SUSAN MCCUNE: Last question.

8 WOMAN 2: It's not so much a question
9 as a statement. I'm the proud mom of that young lady
10 right there and, you know, we have been through quite
11 a journey listening to some of the other people in
12 here, so I definitely sympathize with everyone here.
13 But I feel like I'm in a room of geniuses with big
14 hearts who are overlooking on major thing and that's
15 your basic, most profitable equity, your biggest
16 equity is your patients.

17 And I feel like I've been sitting here
18 and I've been listening to humongous words, huge
19 terminology that is way above me, and I'm the biggest
20 commodity. What we're doing with ICAN and Children's
21 Hospital and some of these other -- on Be The Match
22 and doing all these other kind of things to kind of,

1 like, bring wellness and give back to all of you, who
2 have given so much to us, is that it's so 30,000 feet
3 up there that John Q. Public can't join you to be a
4 part of your consortium.

5 And the reason why and the only way
6 that you will get a consortium is if John Q. Public
7 jumps on board to what you are doing and sees your
8 vision the same way that you see the vision. So I'm
9 excited to be here. I'm so happy that we get the
10 opportunity to come and share our experiences with
11 you. But from a patient, from a parent, and from John
12 Q. Public just sitting out there, I have no idea what
13 you're talking about.

14 And if I don't have an idea of what
15 you're talking about, I can't advocate on Capitol Hill
16 the way I am with Be The Match to bring some of the
17 initiatives that you want to happen. If you want us
18 to work with Japan and China and all that, it's going
19 to take 10,000 Americans to jump on board to say, hey,
20 John Q. Government, this is what we, the American
21 public, want. We want you to bring down the walls and
22 the barriers that prevent us from working together,



country to country, community to community to

2 community to community.

3 And you're losing -- your biggest
4 advocacy here is your patients. It is the people with
5 the rare diseases and all of your little subgroups
6 coming together and saying, we are the rare disease
7 community. It's not just us. It's our families who
8 are affected by it and that's where you grow your
9 consortium. So I applaud each and every one of you
10 for that, but we got to bring it from here back down
11 to the grass roots if you want to see improvement.

12 DR. SUSAN MCCUNE: So I think that's
13 the best last word for our panel, and with that I'd
14 like to really thank the panel for all your comments.

15 DR. JANET MAYNARD: Thank you so much
16 to our panelists. We really appreciated that session.
17 So now, we will transition to the open public comment
18 period and Catherine Park will introduce that period.
19 Thank you.

20 CATHERINE PARK: Well, hello everyone.
21 Thank you so much for being here and for such a great
22 meeting. We are now doing to start the open public

1 comment portion of the meeting. Today, we have nine
2 speakers registered and each of them will have three
3 minutes to speak. If a speaker finishes early, we
4 intend to move on to the next speaker. We ill call
5 each speaker by their name.

6 If there is additional time after, we
7 will open the mic up to the room. When it is your
8 turn, please approach the podium to your left to
9 provide your comments. For transparency purposes, we
10 ask you please disclose if you're affiliated with an
11 organization, if your travel has been funded, or if
12 you have significant financial interest in rare
13 disease medical product development.

14 As you are speaking, you'll notice you
15 have a timing light to guide you. The green light
16 will indicate when you can begin speaking. It will
17 turn yellow when you have 30 second left in your time.
18 The timer will turn red when your time has come to an
19 end. If you have not concluded your remarks by the
20 end of your allotted time, I will ask you to do so
21 kindly.

22 As a reminder, you also have the option

1 to submit comments to the docket which will remain
2 open until Sunday, March 29th. Again, you can find
3 additional information about this in the Federal
4 Register Notice. If you are signed up for an open
5 public comment slot, you are welcome to make your way
6 to the first two rows in front of the podium at this
7 time. Over there. If you would prefer to use a hand-
8 held microphone and remain in your seat, please raise
9 your hand when I call your name and will bring the mic
10 to you.

11 I am now calling the first speaker in
12 the open public comment period, Mary McGowan.

13 MARY MCGOWAN: Good afternoon. I'm
14 Mary McGowan, executive director of Myositis
15 Association. I have no travel stipend to be here and
16 no financial interests. I would like to thank the FDA
17 for this public hearing and for allowing me to speak.
18 Again, my name is Mary McGowan. I'm the executive
19 director of the Myositis Association. We are an
20 international umbrella organization for numerous rare
21 artery, muscle degenerative diseases including
22 dermatomyositis, polymyositis, necrotizing myopathy,

1 and inclusion body myositis among others.

2 In my brief comments, I will address
3 challenges across many chronic rare diseases. These
4 include diagnosis, clinical trial participation,
5 unique needs of women, and underserved populations,
6 and the important of support systems.

7 Delay to diagnosis is a great concern.
8 Those living with artery diseases see on average eight
9 doctors and take five to seven years to receive the
10 proper diagnosis. This has significant impact on
11 patients' health and risks of mortality, mental
12 health, and eligibility for future clinical trials.
13 With such a significant delay in diagnosis, patients
14 miss the window of opportunity for early treatment and
15 symptom management which my result in progression of
16 disease that is often irreversible and requires more
17 complex treatments, some with harsh side effects, to
18 address the damages done.

19 Additionally, repeated misdiagnosis
20 creates a mistrust of the medical community. Finally,
21 delay to diagnosis means that the time patients
22 receive their diagnosis complications they have

1 incurred may make them ineligible for clinical trials.

2 Clinical trials are the beacon of hope
3 for patients and their loved ones. We need to do
4 better to ensure that clinical trials are for all
5 individuals. Women make up 80 percent of all
6 autoimmune diseases; yet it has been shown that women
7 participate in clinical trials at a lower rate than
8 met, something the FDA has already been working on to
9 address through policy changes and the Women in
10 Clinical Trials campaign.

11 In considering trial design and patient
12 engagement, it behooves us to hear the unique
13 challenges that women with rare diseases face,
14 including future fertility, balancing family, job, and
15 the increased likelihood of being caregivers for
16 others with health problem. These issues are
17 compounded by the complexities of their own rare
18 disease. For women with myositis seeking to have
19 children, concerns about participation in clinical
20 trials are multiplied by the knowledge that increased
21 flares can make it more challenging for them to care
22 for their children and the stress of a regimen of an

1 autoimmune disease trial increases the risk for
2 autoimmune disease flares.

3 Additionally, women with a rare disease
4 are at a more significant risk of financial and mental
5 health challenges. Creating support systems for women
6 living with rare diseases like myositis is virtually
7 important to improve opportunities for clinical trial
8 participation for women, in order to ensure that all
9 treatment options meet the differing biological needs
10 of both genders.

11 Similarly, we must consider the unique
12 challenges for those in underserved and diverse
13 populations living with a rare disease like myositis.
14 Women of color have the highest prevalence of
15 dermatomyositis and polymyositis. They also tend to
16 be diagnosed younger with more severe disease and have
17 a higher mortality rate. It is crucial to have
18 significant representation for this population in
19 clinical trials, but there are a number of barriers.

20 Again, these patients tend to be sicker
21 at the time of diagnosis which means that they often
22 do not meet eligibility criteria for many clinical

1 trials. Additionally, most individuals from
2 underserved populations are distrusting of
3 experimental treatments and clinical trials due to
4 historic breaches of trust. The population --

5 CATHERINE PARK: Thank you so much for
6 sharing. Thank you.

7 MARY MCGOWAN: Thank you very much for
8 your attention, in particular to the FDA for your
9 extraordinary work. Appreciate it.

10 CATHERINE PARK: Thank you. Next we
11 have Matt Buck.

12 MATT BUCK: Thank you. I'm Matt Buck.
13 I'm vice president of regulatory affairs at Ionis
14 Pharmaceuticals. I'm here today representing the n-
15 Lorem Foundation which is a nonprofit, so I have both
16 industry in here, representing nonprofit. I guess
17 we're industry then. Yes, I have a financial disease
18 in rare disease drug development.

19 So the mission of the n-Lorem
20 Foundation is to charitably provide investigational,
21 antisense oligonucleotides to treat patients with
22 ultra rare disease which affect about one to 10

1 patients. The foundation was established at the end
2 of 2019 and our mission, of course -- sorry, our goal
3 and who we work with is Ionis Pharmaceuticals and the
4 Undiagnosed Disease Network, the UDN, to provide these
5 individual therapeutics.

6 We were just established at the end of
7 2019 and we've already identified our first case, our
8 first patient for an individualized therapeutic. In
9 the coming months, we will have more cases, so here
10 today, I am here to emphasize some of the
11 recommendations that we've already shared with the
12 FDA. We've already had the opportunity to speak with
13 key personnel at CDER and we appreciate that
14 opportunity.

15 And we recognize that there are two FDA
16 draft guidances on individual therapeutics, and we
17 appreciate that work. But knowing that there will be
18 cases for us to bring forward to FDA in the coming
19 months, I just want to emphasize our recommendations.
20 One of those is that, ideally, CDER would have a sole
21 division within the FDA that would manage individual
22 therapeutic INDs. And that is so that a single

1 philosophy or standard can be uniformly applied to all
2 of the evidentiary requirements.

3 Second, with respect to evidentiary
4 requirements, when it comes to ASOs that are well
5 characterized, that we would be able to utilize what
6 we know about that platform to establish more minimal
7 data standards which we believe would be -- examples
8 are a single-species tox study such as single-species
9 rodent tox package and of course an abbreviated
10 stability program.

11 And finally, just the identification of
12 one or two FDA project managers that might be assigned
13 to individual therapeutic INDs would be extremely
14 helpful as we come to the FDA in the next couple of
15 months with several of these cases. So with that, I
16 provide my recommendations and we will, of course,
17 follow up with the written recommendations to be
18 provided to the docket at the end of the month, and
19 thank you for your time.

20 CATHERINE PARK: Thank you, Matt.
21 Next we have Michelle Adams.

22 MICHELLE ADAMS: Hi, I'm Michelle

1 Adams. I'm with the National Organization of Rare
2 Disorders and I don't have any disclosures. Thank
3 you. On behalf of the 25 to 30 million Americans with
4 one of the over 7,000 rare disease, would like to
5 thank the FDA for holding this meeting today to
6 commemorate and celebrate rare disease week.

7 NORD is a unique federation of health
8 organizations dedicated to helping people with rare
9 diseases through educations, advocacy, research, and
10 patient services programs. NORD is proud to serve as
11 the host and sponsor of Rare Disease Day and the
12 United States as we have been doing each year since
13 2009 with our partner organization (inaudible) invited
14 us to join the campaign they had started in Europe the
15 previous year.

16 Rare Disease Day is observed in
17 community settings, governmental legislative offices,
18 school classrooms, college campuses, and hospitals,
19 all to make the voices of rare disease patients heard.
20 It is truly inspiring to know that people around the
21 country are coming together at events like this one
22 with the shared goal to promote awareness and improves

1 the lives of all people living with rare diseases.

2 As I mentioned, it is estimated that
3 are over 7,000 rare diseases and over 90 percent of
4 rare diseases still don't have an FDA-approved
5 treatment indicated to treat their disease. As we
6 heard from Dr. Hahn today, FDA shares NORD's goal of
7 ensuring that more effective and safe treatments for
8 rare diseases become available. All the panels today
9 have been incredibly informative and what is
10 especially clear is that FDA focus in part on natural
11 history registries.

12 As we heard this morning, natural
13 history registries offer a unique, exciting
14 opportunity to collect and share information about the
15 progression and health impact of a rare disease. NORD
16 is thrilled to be partnered with C-Path, a rare
17 disease cures accelerator as both Dr. Woodcock and Dr.
18 (inaudible) mentioned earlier today also.

19 Thank you, FDA, for providing this
20 opportunity. NORD is a leader in this space. In
21 2014, NORD launched the IAMRARE Registry Program. It
22 also launched (inaudible) today. The platform is

1 designed with extensive input from FDA, NIH, patient
2 advocacy organizations, and other health experts. The
3 IAMRARE hosts over 40 rare diseases, natural history
4 study partnerships, and 20 of which were developed in
5 part through a cooperative agreement with FDA. The
6 IAMRARE Registry Program works in collaboration with
7 patient and advocacy organization and industry
8 partners to capture natural history data.
9 Importantly, the emphasis is on input from the patient
10 and caregivers' perspective.

11 And to the point where this morning,
12 (inaudible) to our registry, but patients bear no cost
13 for participating. With better information about a
14 rare disease natural history registers will also allow
15 for more effective treatment targets, more specific
16 end points, and more efficient clinical trials. We're
17 hopeful as it is that rare disease patients will get
18 better, more effective treatment sooner. Thank you.

19 CATHERINE PARK: Thank you. Next we
20 have Tisha Wang.

21 TISHA WANG: Hi. My name is Tisha
22 Wang. I'm a pulmonary physician and clinician at

1 UCLA. I thank you for the opportunity to speak today.
2 As the clinical director and vice president of the
3 Pulmonary Alveolar Proteinosis or PAP Foundation. My
4 travel was funded, but I have no financial interest
5 here.

6 PAP is a rare disease without any
7 approved therapy in which patients drown in their own
8 surfactant proteins and develop shortness of breath
9 and respiratory failure. In 2005, I was a trainee and
10 I met a woman in her 20s with severe PAP. She was
11 obese, in a wheelchair, on oxygen, and she came
12 monthly for (inaudible) out the protein. She was so
13 sick that I became convinced that she was going to die
14 of this disease.

15 Based on what we knew about the cause
16 of PAP which is that her cells and her lung were
17 broken because they didn't have access to her protein,
18 it made sense to me to try this protein and it is
19 called GM-CSF. We tried it off label. In hindsight,
20 we were both so young, but we trusted each other. We
21 took a chance together and I gave her the protein and
22 over the next six months, we actually cured. She was

1 dramatically cured.

2 Fifteen years later, she is still
3 cured. She's now a therapist with a master's degree.
4 She's an athlete and witnessing her recovery has been
5 one of the most meaningful moments in my career. Over
6 the next decade, I accumulated a large number of PAP
7 patients and began collaborating with Dr. Bruce
8 Trapnell at the Rare Lung Disease Consortium to do
9 research.

10 I continued using off-label GM-CSF for
11 many of my PAP patients with success, and learned that
12 Dr. Trapnell and others were doing the same. In 2016,
13 with one of my PAP patients in Los Angeles, we
14 reinvigorated the PAP Foundation, a patient advocacy
15 organization with the mission of getting an FDA-
16 approved therapy and ultimately a cure for this
17 devastating disease.

18 We've been able to connect with
19 hundreds of patients in the meantime and hear about
20 their experiences of being told they have no options
21 for therapy. Some have since died or required lung
22 transplant. Through the foundation, however, we've

1 been able to hear a number of success stories of
2 individual patients using GM-CSF with improved quality
3 of life and exercise tolerance and decreased need for
4 whole-lung lavage and oxygen.

5 In fact, a number of patients improved
6 on GM-CSF and stopped, only to have their disease
7 recur off therapy. Fortunately, the research has
8 progressed in the last decade. We have a Phase 1
9 trial in the U.S., two recently completed randomized
10 control trials, all using inhaled GM-CSF and available
11 results from the patient and (inaudible) trials
12 indicate that this medicine improves several outcomes
13 in PAP, pulmonary function tests, oxygen in the blood,
14 the amount of abnormal surfactant present, and the
15 quality of life of these patients.

16 We at the foundation find these results
17 encouraging and consistent with the experience of our
18 patient community. So we at the PAP Foundation remain
19 steadfast around a mission to become one of the few
20 rare diseases to have an FDA approved therapy for our
21 patients. We're committed to working very closely
22 with the FDA to achieve this and applaud the FDA for

1 granting breakthrough therapy designation for
2 Molgradex, which is a formulation of inhaled GM-CSF.
3 What is striking about this meeting and being her all
4 day today is that everybody in this room is on a
5 mission.

6 The missing is slightly different for
7 all of us and it's inspired by different things, but
8 we're all on a mission. And so I think my last
9 statement to the FDA probably mirrors the sentiment in
10 this room which is that our patient and our physician
11 community is more than willing to commit our time, our
12 knowledge, our personal experiences, our resources,
13 really whatever is necessary to move us forward in
14 conjunction with the FDA.

15 Thank you again for the opportunity to
16 speak on behalf of the PAP Foundation, the PAP patient
17 community today.

18 CATHERINE PARK: Thank you. Next, we
19 have Jen McNary.

20 JEN MCNARY: Hi, thank you. I'm Jen
21 McNary, a rare disease advocate, mom of three sons
22 with rare disease. I'm the founder of One Rare, a

1 board member of various organizations, and a
2 consultant in the rare space, but for these purposes,
3 I don't believe I have any relevant financial
4 disclosures. I self-paid for my travel.

5 The end of one discussion today was
6 incredibly important to me and it's been discussed at
7 other venues this year, such as JPMorgan, in thinking
8 about this concept a little broader throughout the
9 day, as we realize the benefits of precision genetic
10 medicine and end of a few will become increasingly
11 more common. It is imperative that the agency adapt
12 and implement a more consistent approach, however, to
13 ensure the same standards are being applied across
14 divisions and across disease states, assuming that
15 it's a monogenic disease and that the therapy is
16 replacing missing genes.

17 I recently wrote a blog where I spoke
18 about my conversations with Dr. Peter Marks regarding
19 this topic and while I am increasingly confident that
20 the top officials such as Dr. Marks, Janet Woodcock,
21 et cetera, appreciate and understand the importance of
22 flexibility when reviewing these types of data, I want

1 to continue to ensure that this trickles down
2 throughout the entire agency to allow a visible path
3 forward for good science.

4 Switching gears, in the spirit of being
5 wholly supportive of faster FDA approvals, I would be
6 remiss in not also mentioning a troubling situation in
7 the access and reimbursement landscape that's going to
8 affect us all. I'm aware that in order for innovation
9 to best serve patients in this room, two things need
10 to happen, clear pathways for development and
11 ultimately access and reimbursement.

12 Several organizations have recently
13 published concerns about ICR, its utilization of the
14 quality to determine the value of a new therapy for
15 rare disease, but in my opinion the most effective was
16 that published by the National Council of
17 Disabilities. They found sufficient evidence of the
18 discriminatory nature of qualities to warrant concern,
19 including concerns raised by bioethicists, patient
20 rights groups, and disability rights advocates about
21 limiting access to life-saving medications.

22 In a recent article, the Pink Sheet,

1 ICR calls itself an expert to help the FDA understand
2 the importance of patient relevant outcomes and
3 consistent end points. ICR says that its work could
4 advance greater use of patient relevant outcomes in
5 drug development. As the commissioner mentioned, the
6 FDA is doing an amazing job of incorporating the
7 patient voice into drug development and uses rigorous
8 methods to evaluate and approve new innovative
9 therapies.

10 Yet ICR attempts to play at the same
11 evaluation of already approved drugs. I would urge
12 that the agency consider decline this offer to partner
13 with this self-appointed and blatantly discriminatory
14 organization in favor of working with foundations,
15 some of which are in this room: EveryLife Foundation,
16 ARM, IGT, (inaudible). They all have a proven track
17 record of supporting patient needs and so I would
18 encourage the agency to instead look to them. Thank
19 you.

20 CATHERINE PARK: Thank you. Next, we
21 have Khrystal Davis.

22 KHRYSTAL DAVIS: I'm Khrystal K. Davis.

1 I'm an SMA mom, founder of Texas Rare Alliance, and I
2 received a grant from the EveryLife Foundation that
3 covered my travel today. We cannot treat what we do
4 not diagnose. Commissioner Hahn recognized the
5 innovations are coming fast and furious and that we
6 need to do more, faster, to meet unmet needs.

7 I believe this is especially true in
8 access to the diagnosis. We are undeniably failing in
9 the timely diagnosis of rare disease patients. It
10 takes an average of five to seven years to accurately
11 diagnose rare disease patients. Sadly, many children
12 with rare diseases will not survive to their fifth
13 birthday. Many of these children will not survive to
14 receive a diagnosis. We can and must do better in
15 diagnosing rare disease patients.

16 When we fail at diagnosing rare disease
17 patients, that failure impacts everything in the
18 process that follows. Undiagnosed patients cannot
19 participate in patient registries and natural history
20 studies which then fails to include the true spectrum
21 of rare disease patients, especially diverse and
22 underserved patients.

1 Undiagnosed patients cannot drive
2 research. Undiagnosed patients cannot inform the
3 design of clinical trials and they cannot participate
4 in clinical trials. Undiagnosed patients cannot
5 follow the appropriate standards of care for a better
6 chance of survival to see an approved treatment.
7 Undiagnosed patients cannot access approved treatments
8 and this is unacceptable.

9 Dr. Marks discussed the advantage of
10 leveraging existing resources in responding to the
11 anticipated number of individualized gene therapies.
12 We must also leverage existing resources to
13 drastically reduce the diagnostic odyssey for rare
14 disease patients. Whole genome sequencing offers the
15 opportunity to identify thousands of known rare
16 diseases and plays an invaluable role in discovering
17 new rare diseases.

18 Project Baby Bear Data from the work of
19 Dr. Stephen Kingsmore in Rady Children's Genomic
20 Institute for Genomic Medicine shows that rapid whole
21 genome sequencing improved health outcomes while
22 decreasing healthcare spending for California NICU and

1 PICU critically ill patients with unknown etiologies.
2 This impressive and actional model needs to be adopted
3 in all states. Whole genome sequencing not only
4 improves access to the diagnosis, it also improves
5 access to treatments by helping develop potential
6 treatments, identify patients for clinical trials, and
7 determine proper treatments for rare disease patients
8 utilizing personalized medicine.

9 Whole genome sequencing offers an
10 opportunity to move from failing at diagnosing rare
11 disease patients to excelling at diagnosing rare
12 disease patients. We must work to change the culture
13 to leverage genomic data. We need funding to improve
14 access to whole genome sequencing and improved health
15 literacy for genomic medicine for providers, patients,
16 and caregivers. Access begins with the diagnosis.

17 CATHERINE PARK: Khrystal --

18 KHRYSTAL DAVIS: We cannot treat what
19 we did not diagnose.

20 CATHERINE PARK: Thank you.

21 KHRYSTAL DAVIS: Thank you.

22 CATHERINE PARK: Next we have Kelly

1 Thornton.

2 KELLY THORNTON: Hello. My name is
3 Kelly Thornton and I am with an organization, Pain
4 Advocate Warriors and they're financially funding me
5 and the American Pain and Disability Foundation.
6 Hello. So the FDA needs to follow existing FDA
7 protocols and stop being driven by the prevailing
8 winds from political forces. I am on behalf of
9 chronic pain patients.

10 So, okay. The CDC is trying to drive
11 policy based on their poorly written and poorly
12 understood 2016 opiate prescribing guidelines,
13 providing themselves incompetent and not ground in the
14 best interest in U.S. public, especially not in the
15 best interest of chronic pain patients who depend on
16 analgesics for quality of life.

17 The FDA -- excuse me. The FDA alone is
18 in authority, yet we now have the CDC, 50 state
19 governments, U.S. Congress, U.S. Senate, President of
20 the United States, and even certain members of the
21 media all trying to force additional overlapping,
22 burdensome, contradictory political motivated,

1 unscientific regulations on opiates.

2 The U.S. government needs to get out of
3 the doctor's office and leave it 100 percent up to the
4 FDA to regulate and approve what medicines are on the
5 market. The FDA's full prescribing information
6 already contains limits and conditions and guidelines
7 tailored to all drugs, and that is all that is needed.
8 All other parties need to, frankly, get out because
9 not only are the misinformed of the facts, their
10 politicalize guidelines have cause as much death and
11 misery for chronic pain patients while not helping
12 addicts whatsoever.

13 Sheriffs, which in the report, they are
14 not seeing prescription drugs found on deceased
15 overdose victims, but instead see illicit fentanyl,
16 heroin, and other illegal drugs such as
17 methamphetamines, for at least the last eight years
18 now. Can't CDC and others outside the FDA see their
19 own data doesn't add up? A recent study said 1.3
20 percent of overdose fatalities were caused by patients
21 taking their own prescribed opioids, so 98.7 percent
22 are due to illicit or illegal activities. Pounding

1 that 1.3 percent down to zero percent is more likely
2 to kill hundreds or thousands of times more as
3 disabled and elderly patients are suddenly on the
4 street buying heroin for pain relief and getting God
5 knows what in their cartel-provided medicine.

6 How about we do something right for a
7 change instead of driving good people to end their
8 lives via suicide or become criminals? If that is
9 what our society has decided to become, perhaps our
10 nation needs to dissolve and let each state become
11 independent, because our federal system is not helping
12 people who need help the most. It is, in fact,
13 crucifying, torturing, and driving people who've
14 worked their entire lives to support this nation into
15 --

16 CATHERINE PARK: Kelly --

17 KELLY THORNTON: -- a state of insanity
18 because --

19 CATHERINE PARK: Thank you so much.

20 KELLY THORNTON: -- regulation.

21 CATHERINE PARK: Thank you.

22 KELLY THORNTON: Please stop their

1 perpetrating going into circles. Please. Thank you.
2 I didn't get to finish it.

3 CATHERINE PARK: Next, we have Amanda
4 Proctor. Okay. Then next, we have Bonita Talotti.

5 BONITA TALOTTI: Good job.

6 CATHERINE PARK: Thank you.

7 BONITA TALOTTI: Hello. Good
8 afternoon. Thank you so much for having all of us
9 here. My name is Bonita Talotti. I'm a patient
10 living with Ehlers-Danlos syndrome. I'm here today on
11 my own representing our organization as one of the
12 volunteers local EDS -- Metro EDS and HSD support
13 group. No one's funded my travel. I'm just coming
14 from Virginia.

15 I'm here today to talk about access,
16 one of the few things that was not talked about
17 throughout the day. I heard a lot today about patient
18 focused, patient centered, individualized treatment,
19 but very little to no discussion on access. I found
20 out about Ehlers-Danlos syndrome four years ago, after
21 I'd been taking ciprofloxacin for three years and
22 finally connected the dots and recognized cipro did

1 something to me. It turns out, cipro is actually a
2 fluroquinolone antibiotic that is contraindicated for
3 patients with Ehlers-Danlos syndrome and unfortunately
4 for me, FDA did not connect the dots and come up with
5 the black box warning until 2018 about two years after
6 I was diagnosed.

7 I'm here today to point out that we, as
8 patients, deserve and need to have the full facts of
9 the drugs that are being prescribed to us. I didn't
10 know at the time that I was given cipro that it can
11 lead to tendinitis or tendinosis. My shoulder, which
12 has been hurting throughout the day, is a result of
13 EDS as well as ciprofloxacin. I didn't know that
14 ciprofloxacin could destroy my gut. Indeed, I was
15 never informed that I should even take a probiotic.

16 I didn't know that amitriptyline would
17 result in orthostatic intolerance. I didn't know that
18 naproxen which is what's been prescribed for me for my
19 shoulder could result in GI risks of bleeding. None
20 of this was ever informed to me or disclosed to me,
21 rather. I had to find that out from various other
22 sources.

1 As patients, we need to know exactly
2 what it is that we're taking. We need to know the
3 benefits as well as the risks. We also have another
4 access issue that's really never talked about in any
5 public meeting I've ever gone to, at FDA or at any
6 other event, and that's financial. We as patients
7 don't have access financially to all the latest
8 technologies or treatments, the new drugs, the new
9 devices, CRISPR, gene editing, gene therapies.

10 What good does all the innovations do
11 if we as patients can't even afford them? I would
12 urge industry, FDA, and other stakeholders to
13 recognize that we have a serious financial access
14 issue. If our payors aren't covering these things, we
15 can't access them, plain and simple. I won't get into
16 the opioid debate, but I will say this. We as
17 patients don't have access to alternatives to opioids
18 as well. What good does anything do if we don't have
19 access to anything?

20 We as patients need access, first and
21 foremost. Thank you.

22 CATHERINE PARK: Thank you so much.

1 This concludes the open public comment period. We
2 really appreciate everyone participating today. I
3 will now transition to Janet Maynard to provide
4 closing remarks. Thank you.

5 DR. JANET MAYNARD: So we're going to
6 transition to closing remarks, because unfortunately
7 we're out of time for the open public comment period.
8 So on behalf of FDA, I'd like to thank all of the
9 panel participants, speakers, and everyone in the
10 audience here in the Great Room and also on the
11 webcast for participating in today's meeting. We
12 greatly appreciate your attention and your interest in
13 these topics.

14 This has been a very important meeting
15 to all the participants including FDA, patients,
16 researchers, and the industry representatives. We
17 greatly appreciate perspectives and personal
18 experiences that were shared with us today. Today, we
19 heard that patients are at the heart of all that we
20 do. There are exciting opportunities in rare disease
21 product development, and great unmet needs of patients
22 and families living with rare diseases. In the

1 morning, we heard about natural history and registry
2 studies. Key points included the importance of
3 patients and patient advocates in these studies and
4 the need to think globally and evolve over time.

5 In the afternoon, we heard about the
6 importance of collaboration, leveraging data, and
7 learning from each other. This was a very informative
8 meeting for us here at FDA. Rare diseases have
9 enormous impacts on patients and families and the need
10 to develop new therapies for rare diseases is immense.
11 We look forward to incorporating what we have learned
12 today into the agency's thinking on rare disease
13 product development. Your perspectives and voices
14 were heard today.

15 Working together, we can support
16 optimal development of safe and effective products for
17 patients with rare diseases. I want to let you know
18 that just because the meeting is over, it doesn't mean
19 that this is the last or only opportunity to interact
20 with FDA. Today you heard from FDA's staff and the
21 agency who want to hear from you and learn about your
22 experiences. If you don't know where to start, the

1 patient affairs staff can help. You can send them an
2 email at PatientAffairs@FDA.gov. They can help you
3 stay connected with other activities at FDA or address
4 future questions.

5 You can also connect with the Office of
6 Orphan Products Development at Orphan@FDA.gov. As
7 mentioned earlier today, we strongly encourage you to
8 submit comments to the docket which will be open until
9 March 29th, 2020. Details on how to submit comments
10 to the docket can be found on the Federal Register
11 Notice for the meeting. On your chair, we have placed
12 a short survey that we hope you will complete so that
13 we can continue to improve our public meetings.

14 When you are done with the survey, you
15 can give it to the registration desk or to the FDA
16 staff working at this meeting, and those are the folks
17 who are wearing the nametags. For those on the web,
18 we will be sending you the same survey via the email
19 address that you registered with. And on that note, I
20 am closing this public meeting. Thank you. Safe
21 travels and have a wonderful evening.

22

1 CERTIFICATE OF NOTARY PUBLIC

2 I, 3854897, the officer before whom the
3 foregoing proceedings were taken, do hereby certify
4 that any witness(es) in the foregoing proceedings,
5 prior to testifying, were duly sworn; that the
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I, Sonya Ledanski Hyde, do hereby certify that this transcript was prepared from the digital audio recording of the foregoing proceeding, that said transcript is a true and accurate record of the proceedings to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.



Sonya Ledanski Hyde

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Federal Rules of Civil Procedure

Rule 30

(e) Review By the Witness; Changes.

(1) Review; Statement of Changes. On request by the deponent or a party before the deposition is completed, the deponent must be allowed 30 days after being notified by the officer that the transcript or recording is available in which:

(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.

(2) Changes Indicated in the Officer's Certificate. The officer must note in the certificate prescribed by Rule 30(f)(1) whether a review was requested and, if so, must attach any changes the deponent makes during the 30-day period.

DISCLAIMER: THE FOREGOING FEDERAL PROCEDURE RULES ARE PROVIDED FOR INFORMATIONAL PURPOSES ONLY.

THE ABOVE RULES ARE CURRENT AS OF APRIL 1, 2019. PLEASE REFER TO THE APPLICABLE FEDERAL RULES OF CIVIL PROCEDURE FOR UP-TO-DATE INFORMATION.

VERITEXT LEGAL SOLUTIONS
COMPANY CERTIFICATE AND DISCLOSURE STATEMENT

Veritext Legal Solutions represents that the foregoing transcript is a true, correct and complete transcript of the colloquies, questions and answers as submitted by the court reporter. Veritext Legal Solutions further represents that the attached exhibits, if any, are true, correct and complete documents as submitted by the court reporter and/or attorneys in relation to this deposition and that the documents were processed in accordance with our litigation support and production standards.

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