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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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7	REPORTED BY: Eliza Spikes, Notary Public
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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

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

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

to get up for any reason, please feel free to do so.

Room if you need space either during the meeting or at

There are smaller rooms available around the Great

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

If you decide not to pre-order, you may purchase snacks, sandwiches, and food items a la carte. The kiosk outside the conference room will be open from 00 until 00 to obtain food and drinks. For media inquiries, our press officer,

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

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

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

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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 and on the web to ask questions and provide 8 perspectives. For those in the room, please raise 9 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.

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

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For those on the webcast, please type

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

4 After the last panel in the afternoon, 5 we will have an open public comment period. The open public comment period will provide anyone in the 6 7 audience the opportunity to make a comment. То 8 participate in that, you would have needed to sign up prior to the meeting or sign up today at the 9 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 public comment period at the end of our afternoon 14 15 break around 2:00 PM or when the sign-up is full. Speakers will each have three minutes to speak. 16 Ιf 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 remaining time. After the open public comment period, 20 21 I will provide closing remarks.

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Now we will briefly cover a few rules

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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 ag	ppreciate
5	the opportunity to hear your perspectives.	The views
б	expressed today are personal opinions. Ple	ase be
7	respectful of others and allow participants	to finish
8	sharing their experiences without interrupt	ing.
9	Participants in the room should use microph	ones 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 interac	t with FDA.
15	The Patient Affairs Staff and the Office of	Orphan
16	Products Development are here and want to s	tay in
17	contact with you, whether it's helping you	stay
18	connected with other activities at FDA or a	ddressing
19	any future questions you might have.	
20	This slide contains our cont	act
21	information. Also, if you choose to tweet	about
22	today's meeting, please use #FDARare2020.	

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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

Page 11 University, where she did her internal medicine 1 2 residency, served as chief resident, and completed her 3 hematology-oncology fellowship. 4 She received her PhD from Flinders University, her BA from University of Pennsylvania, 5 and is boarded in palliative medicine. Welcome to Dr. 6 7 Abernethy. Thank you. 8 DR. AMY ABERNETHY: Thank you very 9 I think somebody's calling us with beeps. much. 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, I reflect on the fact that the combination of 14 15 government incentives -- maybe we should check. Anything you need from me? I sort of feel like E.T. 16 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 Act in 1983, the number of orphan indications approved 21 2.2 in the U.S. has risen dramatically.

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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

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

Patients living with rare diseases and 3 4 their families can provide invaluable insights that directly impact medical product development and 5 improve day-to-day care in the clinic for people today 6 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 that can be tracked over time and allow us to better 14 15 understand disease progression in the real world. Participation in clinical trials facilitates getting 16 17 safe and effective therapeutic options to the market. 18 Understanding the natural history of 19 rare disorders is critical to developing appropriate clinical trial endpoints for rare diseases, because 20

otherwise these diseases are poorly understood.

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also helps us understand how the disease course can be

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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

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1	provide meaningful insights as to how patients fare
2	Dit eh 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

Page 17 support and satisfy post-approval study requirements. 1 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. With these exciting opportunities for 6 7 the use of data, it's important that FDA modernize our 8 technology platforms so that we can support the advances coming to make a difference in your lives and 9 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 technical infrastructure in ways that allow us to 14 15 receive, analyze, and use data in ways to support our regulatory mission. 16 17 One way we are working to meet this goal is by designing technical interfaces and tools to 18 19 enable to streamline submission and review of data. Creating standard, digital safety reports is an 20 21 important step towards more sophisticated data and 2.2 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 modernization efforts. This effort will streamline 6 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 electronically. This effort is another example of 11 12 FDA's commitment to broader efforts in overall 13 technology modernization and orphan diseases. Importantly, the foundation of these 14 15 technical enhancements are supporting the development of safe and effective products for rare diseases for 16

17 patients and families.

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

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It's essential that we work with	h you,
all of us, those who are directly impacted by	
diseases. And this informs our efforts as we w	move
forward. We are here to listen and work toget	her with
you.	
Thank you for the opportunity, a	and we
want to make sure you know we're listening. The second sec	hank
you.	
DR. JANET MAYNARD: Thank you se	o much
to Dr. Abernethy. And now I am pleased to inv	ite our
first panel up on the stage. So as they come,	
everyone can take a little bit of a stretch.	I know
it's a long day, and we're so excited to have	you
here.	

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

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

I just wanted to introduce myself. My

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,

what role they fulfill in the agency, and also provide 1 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. Caños, and then next we have Dr. Bryan. 6 So I'll have 7 you start, Dr. Stein, first, providing your fiveminute introduction. 8 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 together to develop drugs for rare diseases. 14 15 I am the Director of the Office of New Drugs, which is the office that regulates drugs that 16 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 appropriate continued benefit-risk of those drugs. 20 21 And I say new drugs, but as Dr. 2.2 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.

So, much of the work that we do across 6 7 my organizations is involved in supporting companies 8 during their development phase, during the IND development phase for rare diseases, and then 9 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 deficiencies and related conditions. But across all 14 15 of the different divisions -- neuroscience and endocrine and many other divisions -- we see 16 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 these important diseases. 20

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
-	a fait amount more erme boen on ents panet and in ene
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	a national	evaluation	system	for	health
2	tech	nologies.				

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 through promoting implementation of unique device 6 7 identifiers, also increasing the use of regulatory decision-making that utilizes and leverages clinical 8 9 It's supported over 50 regulatory decisions evidence. 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.

So with this system, the National 15 Evaluation System for Health Technologies Coordinating 16 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 records. And this is just the start of the system. 20 21 In the coming months they're going to establish and 2.2 release a quality framework document as well as a

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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 from respiratory failure. 16

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

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

4 Where we get into trouble is when natural history data don't give -- don't seem 5 reliable, don't give reliable endpoints. 6 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. Ι 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 Many of them very rare, many of them very diseases. 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 to get that therapy for every patient who has those 20 21 rare disease. And we at CBER are very committed to 2.2 working with other stakeholders like the NIH to figure

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

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.

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

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

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 it be collected in a way that provides detailed 9 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 comparable patients, doesn't necessarily have a 14 15 comprehensive data collection or similar data collection, data quality issues may occur. 16

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

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 predicable 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 at diagnostic criteria from 10 or 15 years ago, we may 20 21 be looking at different patients than the current 2.2 study that we're trying to compare those patients to.

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

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.

So that all provides substantial 14 15 challenges when we get a comparison group submitted compared to a single arm trial, can we really compare 16 17 it. And I really would push to say that what's really critical as we go forward and are working 18 19 collaboratively together with patient groups and with other stakeholder groups as we think about the 20 21 development of registries' prospective collection of 2.2 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

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
there, as well as the definitions, you know, 1 consistent definitions and how those outcomes are 2 ascertained really are challenges that we are seeing 3 with evidence from clinical experience. 4 And I'd like to speak to some of the 5 work items that we have at CDRH and are working to 6 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 these meetings or on the calls as well as industry 11 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 registries to address regulatory questions. 20 And 21 within that same effort, we are also working on 2.2 increasing the quality from these registries so that

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1	there	can	be	а	fair	appraisal	of	these	evidence
2	syster	ns.							

3 And in my introductory comments, I 4 mentioned this National Evaluation System for Health Technologies Coordinating Center, housed within the 5 Medical Device Innovation Consortium, the MDIC. 6 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 quesswork 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 areas that we can, frankly, improve. 20

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

infrastructure and collaborating with the stakeholder
community.

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, it can be utilized at times when appropriate for 6 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 representative. And so it could lend some support or 11 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,

the analytics side, the partnership side for 1 2 developing the infrastructure, as well as the methodologies to really maximize the use of evidence 3 4 from the clinical experience for regulatory decision-5 making. DR. ERIKA TORJUSEN: Excellent. 6 Thank 7 you. And Dr. Bryan, do you have anything you'd like 8 to add from the CBER perspective? I know you touched on some of this in your introductory comments. 9 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 They are very important for designing 16 more than that. 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 endpoint in that population. 20 21 Too often we have scientists, 2.2 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
б	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

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using a natural history study, designing a r	natural
history study or registry? Do you have any	advice or
recommendations in that regard?	
DR. PETER STEIN: Well, I thi	nk the
answer is early. And we are very much open	to have
these kinds of discussions with stakeholder	groups to
provide direction, to engage with them. And	l we are
working on a rare disease accelerator, which	nis
intended to be a new infrastructure for regi	stries so
that we can support and work with patient gr	roups to
develop these. This is a collaboration with	n NORD and
with the C-Path Institute to try to provide	this for
patient groups as a resource.	
But I would say early. You k	now, come
to the division early. If there's a program	n going on,
if there's development in this area, talk to	o us about
what we think might be needed. We are here	to try to
be collaborative and to be part of the solut	tion.
DR. ERIKA TORJUSEN: Exceller	nt. Thank
you. And do you both agree with that recomm	nendation?
DR. WILSON BRYAN: Yeah. It'	s a

22 challenge, because we know that there are thousands of

Page 45 rare diseases. And we would like to see natural 1 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 want to do what we can. 6 7 But I think more of us need to develop 8 expertise in how to do these natural history studies so that they meet regulatory requirements, you know, 9 10 formative for a drug development. DR. ERIKA TORJUSEN: Excellent. 11 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

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

the way down in the corner there in the white shirt.

20

with the MD Foundation. Just a couple of comments 1 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. Engaging early with the FDA is really 6 7 They're always willing to converse. important. And the same thing with any pharma or academic research 8 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 even be thought of, much less emerge. 16 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. And if you don't know what that point is, which might 20 21 be a clinical trial endpoint, if you don't know what 2.2 that is, that doesn't mean you shouldn't start with

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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

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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

Page 50 registries, what can be collected, and different 1 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 quidance out that talks about --DR. ANNETTE BAKKER: I saw that. 6 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 tart 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. DR. ANNETTE BAKKER: Or like those that 14 15 will be used, as you said, for clinical trial design and for really to understand the course of a disease. 16 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 to move this ahead. Doing these natural history 20 21 studies is not easy. 2.2 DR. ANNETTE BAKKER: Exactly.

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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	tramework 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
12 13	We certainly don't want to discourage you getting started, because getting started is
12 13 14	We certainly don't want to discourage you getting started, because getting started is critical. Downstream we can think about additional
12 13 14 15	We certainly don't want to discourage you getting started, because getting started is critical. Downstream we can think about additional ways that natural history study or registry can
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12 13 14 15 16 17 18	We certainly don't want to discourage you getting started, because getting started is critical. Downstream we can think about additional ways that natural history study or registry can evolve. DR. ERIKA TORJUSEN: So I would also now like to just make sure that we acknowledge we have
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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

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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. Т 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. And I said I can't review five natural history 14 15 studies. Send me two. Send me two protocols for natural history studies. And I enlisted some 16 statisticians to help me look at them, but they were 17 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

they often just don't get around to working with 1 2 someone to get the natural history studies done. But I expected most of us here at the FDA would love to 3 4 see a protocol for natural history study. And they'll probably do what I did, which is dig around to try to 5 find somebody to take a look at it. Now, hopefully 6 7 we'll get better than that. 8 DR. PETER STEIN: And just as a quick 9

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.

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

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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-subs 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.

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1	DR. PETER STEIN: Just as another
2	opportunity, is we have a biomarker qualification
3	program both for CO8 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

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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
б	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

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	Meeting February 24, 20
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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.

MAN: And very quickly. Gooey
morning, everyone. As a patient suffering from
myositis, interstitial lung disease, and pulmonary
arterial hypertension, one of the things when you're
talking about looking at the patient in your studies,
natural or otherwise, the gentleman said at the first
statement about I can't remember exactly, but it
had to do with looking at the patient in its entirety.
One of the reasons why my treatment has
taken so long is because I was exposed to secondhand
smoke. And I would like to ask if at any point in any
of your research I know I'm looking at the National
Institute of Health environmental factors are taken
into consideration. But I haven't seen anything
that's dealing with the patient and indoor air
quality. So that's either a question or a comment
about how you're approaching that from your
perspective. So I'd like to know if any of your
research that you're doing addresses that factor.
DR. PETER STEIN: You know, I can't
I don't have the answer to that question. I'll try to
find out, but I don't have the answer. But I do want

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

Page 66 to be able to ask questions during the break, which 1 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 now. And, again, I wish you a very nice morning, and 9 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 the issues for us. And we're going to discuss them 16 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 Drugs and at FDA. 20 21 So I'm going to -- with me we have a 2.2 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.	KAT	THLEEN	DONOHU	JE:	Sur	e.	Good
com	e.	I'm e>	cited	to b	be w	ith	you
on	deve	eloping	g treat	cment	s f	or 1	patients

2 morning and welcome. I'm excited t 3 today. I work on developing treatme 4 with rare diseases, inborn errors of metabolism. And 5 so this is sort of the front lines. And I'm really appreciative for the questions we've had from patients 6 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 you want to come back and talk more about. 16 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 launched a Cures Accelerator Initiative that Theresa 20 21 Mullin is actually leading and Klaus Romero is also

2.2 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 development of both our patient registry and our 14 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 that registry was so valuable for us in really 20 21 identifying where patients are, establishing better 2.2 prevalence of the disease. And we were able to use

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that registry for the next 15 years to help enroll				
research studies and clinical trials.				
At the same time, several of our				
clinician researchers also started studies and				
clinical outcome measures. And FARA worked closely				
with those clinicians to parlay that into a natural				
history study. And so we've had a prospective natural				
history study with clinician-entered data going for				
almost 18 years now. Yeah.				
And so, you know, as much as I can				
share with everyone what our experience has been with				
both a patient registry from my perspective that's				
patient-entered information as well as natural				
history prospective studies and sort of the role of				
the advocacy group in facilitating that, I'd like to				
be able to share those experiences with everyone				
today. And thank you for having me.				
DR. THERESA MULLIN: Thank you.				
DR. PETRA KAUFMANN: Good morning. My				
name is Petra Kaufmann. I am a neurologist. And for				
most of my career, I've been taking care of patients				
with rare neuromuscular diseases. So having taken				

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,
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into this difficulty of justifying that choice over 1 2 another. So I think that emphasizes the point of, (A), we have to look at this as a platform and make it 3 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 development and for trial planning, that's not really 14 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

research networks that we have at NIH, but also I 1 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 It's called RaDaR, which stands for 5 that we have. 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 Thank you. DR. KLAUS ROMERO: 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 panel. And essentially what that platform is intended 16 17 to do is provide a home for the standardization and 18 the integration of patient-level data across rare 19 And this stems from the experience that diseases. we've gathered at the Critical Path Institute with the 20 21 support of the FDA and being able to integrate data 2.2 from registries, observational studies, and clinical

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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

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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

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

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 could or should play in supporting drug development? 16 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

21 experience of the disease. It can be sort of

20

based on seeing patients and patients' direct

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 cardiac aspects of this disease and the endocrine 16 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 expand the focus of the natural history to be beyond 20 21 one system into multiple systems.

22

And so sort of going to your point

Page 80 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?

1

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 each rare disease to do a natural history study and 16 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 different groups that maybe started them. 20 Sometimes 21 registries are started patient groups, and they are a 2.2 very grassroots, maybe low-resource endeavor. Natural

history studies sometimes are started by academic 1 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 about that purpose. So I don't really know that that 6 7 distinction in the long run will hold. I think the goals are important, and they are shared. And like 8 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 development. 14 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 observational data. So there can be many different 18 19 types of registries. 20 A natural history study, the intention 21 of the natural history study is to really define the 2.2 disease, define the entire scope and spectrum of the

1	disease.
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2 So I think someone was mention this in the last session, but a registry could be for example 3 4 a communication registry. This could be the first effort to try to organize the community, and you could 5 be collecting some very simple data, people's emails 6 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 to the total opposite end of the spectrum and be 9 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 start to go in a different direction or broaden out 14 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

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starting to generating the answers as to, okay, what 1 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 set up the inter criteria for a clinical trial, which 6 7 again, relates to the source of variability of disease 8 progression and drug effects. The placebo effect, especially in certain neurological conditions, that is 9 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. So I just want to echo some something 14 15 that was mentioned in the previous panel. Sure, using and optimizing control arms using quantitation and 16 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

diseases themselves, because that's what gives you understanding of all the aspects that really matter when you want to design a clinical trial. Because

what's the name of the game here? If we want to 1 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 much uncertainty, that gets up the chain of command in 6 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 like you now to talk about best practices that you've 16 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 2.2 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

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

7 And so it's things like how are 8 patients coming to attention. Right? That's changing So it used to be you had to present with, 9 over time. 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 so different. We have to be able to understand that. 16 17 So how are patients coming to medical 18 What were the results of those genetic attention? 19 Do we have other biomarker tests that are tests? 20 getting done, and can we capture the results of that? 21 It's so boring. But if units are different, Units.

22 this creates such a headache. Like, thinking about

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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

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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 your point of getting proper consent and data sharing 6 7 up front, when we started our clinical outcome measure 8 study in 2004, our consent was not broad enough for the data sharing that we eventually needed. 9 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 2.2 would handle queries to make sure that the data was

being captured correctly and in a very standardized 1 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 know, I did not appreciate all of those things when we 6 7 got started, but I'm very grateful for them because we 8 were able to then use those standard operating procedures and case report forms in future clinical 9 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 sites for FA clinical trials. And that was also one 14 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 like in a clinical trial. We couldn't ask people to 20 21 come back, you know, once a month or every few weeks. 2.2 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.

But what we don't have is really what 8 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.

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

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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

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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

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

5 I'll give you one example we had for a GI disease many years ago. We were using the medical 6 7 term dysphasia. And to some people that meant pain 8 with swallowing, to some people that meant I couldn't swallow, some people meant choking, some people meant 9 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 from the beginning, and especially the patient groups, 16 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

some of these just really can burn out your community. 1 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 to be able to stick with this over time so that we can 6 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 in a way that doesn't inhibit and stifle innovation 14 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 heard loud and clear, not just in rare diseases. 20 21 Think about how to set up the structure 2.2 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

Page 100 1 single piece of data. So that's another important 2 point. And we're here to help. If you want to 3 4 talk to us on how to annotate your case report forms and think about how to set up a structure of a 5 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 standards? 11 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 mentioned? 14 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 checklists, we have spreadsheets, we have referrals to 20 21 things like fair data practices and some more of these 2.2 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

and rules. And therefore I think when patient groups 1 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. Try not to go it alone. There are many groups out 7 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 geographical locations. And understanding the 16 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 I see we have a number of people. And I wasn't 21 much. 2.2 looking, so I don't know who was up first. So I will

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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 to have a data manual, publish it, and put it up on 6 7 the web and just be extremely transparent. But we've 8 also seen people put video clips and things on their 9 I think most of information sharing now is website. 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 what interest there is in tackling that specific 14 15 aspect of the disease. Because that's going to help you understand what information you want to prioritize 16 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 applications. And that's where connecting with 20 21 industry -- and patient groups have that unique 2.2 ability to have that bride with industry.

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Page 107 DR. THERESA MULLIN: Thank you. Yes? MEGAN O'BOYLE: Thank you. My name is Megan O'Boyle. I ma the PI for the Phelan-McDermid International Registry. But first and foremost, I'm Shannon's mother. And Shannon has Phelan-McDermid syndrome. I did what most groups do when you start a registry; I started from scratch, I asked questions. We asked stakeholders for help, researchers. Even Dr. Pariser was at FDA when we started our registry. And we tried to do everything right, and we did a lot of things wrong. I have whole presentations on what we did wrong. And I'm watching other brand-new genetically-found diseases do the same thing over and over again. So I just want to put in a plug for RaDaR and also NCATS has the toolkit for drug development, which takes you from the registries to post-market. Had we had RaDaR, I would not have a presentation on all the mistakes we made. The overburdening, the too many questions. We had the knowledge to have IRB and things like that that other

1 groups did not. I just want to make a plea. You all 2 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 the word investment. I understand that. It's taken a 6 7 huge investment, half a million dollars for our organization over the years, for very little return in 8 many ways. And I really believe that rare diseases in 9 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 I don't mind if somebody makes millions of 20 data. 21 dollars, but one, be transparent with me, and two, 2.2 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.

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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

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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

tied to the fact that the acceleration of drug 1 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. And there's another part that I forgot, 6 7 but I think we're out of time. 8 DR. THERESA MULLIN: All right. I want to thank our panel very much, and thank you all. 9 And 10 so with this we'll close for lunch I guess. 11 (Break) 12 DR. NINA HUNTER: I am Nina Hunter. Т 13 am Director in the Office of Clinical Policy and Programs. And I am delighted to introduce Dr. Stephen 14 15 M. Hahn, who was sworn in as the 24th Commissioner of Food and Drugs on December 17th, 2019. 16 17 Dr. Hahn is a dedicated clinician, 18 having trained in both medical oncology and radiation 19 In his previous leadership roles, he has oncology. always carefully balanced executive management with 20 21 clinical time to continue to serve oncology patients, 2.2 his true passion.

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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
б	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.

So thank you very much for joining us 6 7 I hear we have a great turnout, both in this today. room and online. 8 So thank you very much. And of course this coincides with the commemoration of Rare 9 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 listening to each other -- and that's FDA's number-one 16 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 of new and better treatments for rare diseases. 20 21 I spent a good portion of my career, as

22 Nina mentioned, researching and treating cancer, and

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

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

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

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

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.

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

22 patients with cystic fibrosis, the first treatment for

approved the first triple combination therapy to treat

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1110	$\sim un$	5

Page 120 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 atrophy. And of course we've all seen how that has 5 affected children with this. And it's just a 6 7 remarkable event, something that I hope we'll see more 8 of in the near future. Last year we approved also 76 rare 9 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 approved 77 medical devices, including the last three 16 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 2.2 rapidly advancing science, that is really I think

unprecedented around the world. And it isn't just 1 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 world with researchers and innovators in developing 6 7 these products. But it also means, as I said, that we have much work to do, and we cannot step back from 8 these efforts. 9 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 guite a bit 21 to lower regulatory burdens for innovators. And I 2.2 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.

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

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

disorders. Another one of our priorities, as I said, 1 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 of medical products, both for themselves and for their 6 7 family. 8 To effectively support the development of treatments and to inform our understanding of any 9

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.

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

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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.

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

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

studies, and patient registries. And we have to have 1 2 a better and more robust way of integrating all of 3 these data sources into our regulatory decision making 4 process. Terrific work is being done at this 5 Agency to modernize our approach to data. Much more 6 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. I want to emphasize one other point. 14 15 And that is that we will use the data that exists to make the absolute best decisions for the American 16 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 later need to revisit because additional data are 20 21 available. This is the sign of a learning 2.2 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	product development. Together, we can and will find the answer and overcome these challenges.
18 19	product development. Together, we can and will find the answer and overcome these challenges. I want to thank you for your
18 19 20	product development. Together, we can and will find the answer and overcome these challenges. I want to thank you for your participation today. It is so meaningful for the
18 19 20 21	<pre>product development. Together, we can and will find the answer and overcome these challenges.</pre>
18 19 20 21 22	<pre>product development. Together, we can and will find the answer and overcome these challenges.</pre>

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.

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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

Page 130 Shuren, Director of the Center for Devices and 1 2 Radiological Health. And we oversee gizmos. 3 DR. JANET MAYNARD: I like that, 4 gizmos. So the theme of today's meeting is 5 supporting the future of rare disease product 6 7 development. What are some of the opportunities and 8 challenges you are each seeing in your centers in terms of those considerations? 9 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 2.2 progress fast, and some progress slow. And, you know,

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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
б	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

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

8 And I see Chris Austin is here. Т 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 area of expertise. And it's critically important that 14 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.

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

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

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what we call Ship, a System of Hospitals for
Innovation in Pediatrics. Because the challenge here
is you have sort of wide you have these very tiny
pediatric populations spread out across the country.
We need to link them together so we can get the
patients, we get the top expertise, and we get the
kind of good monitoring on them to get that evidence
on the clinical side, on the non-clinical side. It is
critical. And if we can combine that with very
important regulatory reform and hopefully we can
talk about this, some call it progressive approval
we can have a very refined engine to drive the
development of new technologies for patients with rare
diseases, and in particular for our children.
DR. PETER MARKS: And I think from our
perspective in terms of gene therapies, it's
increasingly clear that there are going to be any
number of individualized gene therapies that are going
to come along. And we have to put together
essentially a pathway that those can follow in this
area. And even there's rare diseases and there are
diseases that are diseases that are very rare,

1 diseases that are not so rare. Even in the not so 2 rare diseases, they become rare once you break them up into all the different genetic mutations. 3 And so 4 having pathways to deal with how one can think about the individual genetic mutations that might be 5 addressed even within one of the more common rare 6 7 diseases is really necessary. 8 So we're really thinking about how we can address that by leveraging what information we 9 10 So the idea is that as we put together things have. 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 made using one manufacturing technique and only a 16 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 manufacturer to leverage the application of the 20 21 original product as they have this modified product. 2.2 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.

And so next Tuesday we'll be having 6 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.

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

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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 about leveraging and how can we do the best that we 6 7 can possibly do for patients and families for rare 8 diseases. And I know many patients and patient advocates frequently ask how can I get involved, what 9 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?

Well, I'm going to 14 DR. PETER MARKS: 15 let Janet continue on. But I think one of the things that I would say is that one of the key things we need 16 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 develop that gene therapy, in the meantime while 20 21 they're developing that gene therapy, getting baseline 2.2 information on the course of disease, how fast people

decline, is really -- or how something changes over 1 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 be able to have some clinical measure in addition to 5 6 the ability to measure the product that's being 7 replaced by a gene therapy. 8 DR. JANET WOODCOCK: Yeah, I agree. And practical ways to do that. Of course people with 9 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 And the NORD IAMRARE and the to-be accelerator 16 data. would be two mechanics, but by no means not the only 17 18 ones in which to do that. 19 Further down the pathway, like I said, working with or sponsoring preference studies, like 20 21 has done by CDRH in certain areas, or developing PROs 2.2 or working with the professional societies and medical

experts on biomarkers, raising money for that. 1 All 2 those things are really important, every single one of 3 And they come at different stages. them. But 4 unfortunately once somebody has a candidate product in hand, they wanted to have all that information a while 5 It's kind of too late. And that's one of the 6 ago. 7 reasons it takes so long often, even after a discovery 8 is made in the lab. People can't figure out why -you know, I only heard of one patient that's ever had 9 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. DR. JEFFREY SHUREN: And to build off 20 21 of that, if you think about it, pretty much everybody 2.2 is or has been or will be a patient. So we kind of

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Page 144 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 development and evaluation. Today there are patient 5 communities, they are do-it-yourself technology being 6 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 was in college when he first developed a life-14 15 threatening illness. He almost died. And then he had relapses when he was in med school. Almost died. 16 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 had different hypotheses about what caused it and all 20 21 this stuff. He had a variant that didn't respond to 2.2 what people usually started with. People had no idea
what to do next. So they decided to treat him with
 chemotherapy. Okay? Which they did for a while. But
 then he continued to have relapses.

4 And now he had a leg-up because he was a med student. But still he wasn't like some advanced 5 6 expert. And he went ahead and -- but he found the 7 experts. They hadn't gotten together. And this --Chris is, you know, something should be done about 8 They hadn't gotten together and figured 9 this, right? 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 he was able to find a treatment, an existing treatment 16 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 I really think patients have much more 20 scientists. 21 than they think as far as knowledge of their own 2.2 disease and ability to contribute if we can only help

Meeting Page 146 provide those pathways. DR. JANET MAYNARD: And speaking about sort of forward-looking, we've seen additional interest in sort of the development for ultra-rare or small populations. And we have a panel this afternoon that's going to talk about perspectives on individualized therapies. But I was interested from your perspectives kind of what are you seeing in this space and how are you helping to address the regulatory considerations? DR. PETER MARKS: So there's a tremendous amount of interest in this space, whether it's for antisense oligonucleotides, cell therapies that are specifically designed for one person's cancer or gene therapies that are developed for very small populations of patients, because they might be for one individual's mutation that might turn out to be either unique or only in a few patients. So we clearly have to find a way to get from where we are to being able

20 to have treatments that get to patients.

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21 So there are two pieces to that. There 2.2 is the piece of how you go about getting the

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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

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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 development. Like Peter said, we're wrestling with 6 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 So we are on top of this I think is the best them. 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 over and over again in different countries. 20 Right? 21 If you have something that affects only five people in 2.2 the United States, we don't want to have to have this

reinvented in Asia, in Africa, in Europe over and over
 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 break down barriers. Because sometimes we do have 6 7 different regulatory structures and different regulatory frameworks that might inhibit the ability 8 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 So we get involved in DR. PETER MARKS: these very small populations in a variety of ways. 16 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 databases and kind of that pooling of information on 20 21 genetic variance. Because a lot of these, they are 2.2 one-offs or few-offs, and you have to be able to

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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

following. Let's not make the limit 8,000. You can 1 keep HDE. But let's keep the standard of HDE in a 2 small population. It could be 9,000, 10,000, 20,000. 3 4 But then you have to get the rest of the data within a 5 certain amount of time. So within three years you show reasonable assurance of safety and effectiveness. 6 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 might restrict distribution to those centers that 16 17 actually have good oversight, good monitoring. And 18 that bring us back to (inaudible) 19 So if on the pediatrics side we have progressive approval and (inaudible), we could have a 20 21 very powerful engine for driving development 2.2 technologies. But not only that, driving the evidence

to then better understand the use of technologies when
 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.

DR. PETER MARKS: I would say that one 6 7 of the wonderful things about genomic medicine is that 8 we are lucky that in some cases if we do things right, if we have the right baseline data, if we have the 9 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 a given timepoint, it doesn't take that many patients 16 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.

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

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 purposes normal. And that's truly remarkable. 16 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 I think it's wonderful to all share in this success. 20 21 And we want to try to bring that to a greater number 2.2 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 and really develop a study that has validity? 5 And the other question is not only 6 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 the Facebook group would be willing to participate. 14 15 It's just that they cannot physically come here. So that's my question. 16 Thank you. This is an 17 DR. PETER MARKS: 18 interesting place where I think what you're saying is 19 there are examples of collaborations which have been effective. And I guess this is where in the rare 20 21 diseases space I think there might be an opportunity 2.2 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 sure that I see people in the room who have helped 9 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 taking place, especially for sample collection where 14 15 it doesn't even require global regulatory approvals. But even on the space where there have been 16 interventional trials, clearly multinational trials in 17 18 this space are quite possible.

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

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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.

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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. Ι 8 think there are a variety of things we've encourage people to do, which is, (A), try not to have very 9 10 restrictive registry criteria to the extent that one 11 Unfortunately, sometimes the fastest way to get can. 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 FDA level with expanded access and access outside of 16 trials, it's that -- and this goes back to something I 17 18 keep harping on manufacturing -- it's that they cost 19 so much and are so complex to make that, for instance, in the gene therapy space, oftentimes manufacturers, 20 21 particularly small ones, can't afford to make 2.2 additional doses of their therapies.

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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

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behind in this situation.
DR. JANET WOODCOCK: Yeah. And we've
talked before. FDA I think is becoming more aware of
this situation. It used to be we would hear people
who were studied in a trial, and then we'd say who it
was reasonable to also be included in the indication.
And we would often have some special study saying
renal failure or whatever so we can include those
people and the right dosing.
But now that isn't the case. And we
are having some work to raise awareness amongst the
staff. Seminars are being held and everything about
how the label effects coverage and access to treatment
and reimbursement for treatment.
As Peter said, on the trial side, if
there is enough material, then it's very reasonable to
include other people, not maybe in the main trial if
you're worried, or you can have an arm in that trial
that isn't the randomized comparison arm, but it's
actually to provide safety and additional types of
people beyond the people, you know, that you have
otherwise enrolled.

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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

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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.

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I think it does have to be done very
carefully, because I think we want it's patient
autonomy. You should be able to participate if you'd
like and opt-out if you don't want to. But we're a
little ways from getting there.
DR. JEFFREY SHUREN: And I think also
there is the use of those technologies for going
through information to developing better tools for
identifying patients who have particular rare diseases
as well.
DR. JANET MAYNARD: Good point. And
I'll look over to see if there's questions from the
web.
DR. NINA HUNTER: Yeah, sure. So this

10 as well. 11 DF 12 I'll look over to 13 web.

14 DF is 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 registration? 20 21

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

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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

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probably slowing things down a bit. But the dialogue
is going on.
DR. JANET WOODCOCK: As far as small
molecules, we do have a lot of harmonized standards.
But it's clear that between the EU and FDA in U.S. an
many other countries, we may not have the same
approval decisions. And that is a matter of sort of
national sovereignty. Usually we're working off the
exact same data set.
And if things are approved in Europe,
often the European folks will have more difficulty
obtaining reimbursement even than in the United
States. And we've already discussed some of the
difficulties here. So a lot of this gets into how th
healthcare systems are set up and what their standard
are and so forth.
But we do work very closely with them.
We are aware of all these things. We talk neurologis
to neurologist and infectious disease doc to
infectious disease doc and everything. But the
approval decisions overall are taken up at a somewhat
higher level.

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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

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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

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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,

where somebody was removed from his opioids, and he
eventually lost his job because he couldn't get to
work anymore, and then he got arrested because he was
trying to get some pain medicine on the street. And
these examples show that we really have to keep the
patient in mind. It should be about the patient and
what they need.
And of course these opioids are
addictive. We know that. And we know some people can
abuse them. But we know other people have their pain
controlled very well by them and don't develop these
problems. So it's really a matter of
individualization again.
DR. JANET MAYNARD: Thank you. And
I'll look to the web again to see if we have a web
question. No web questions? Great. In the room?
SHEILA MIKHAIL: Hi. My name is Sheila
Mikhail. I am the CEO and co-founder of AskBio.
AskBio is a AAV gene therapy company that was founded
back in 2001, way before it was popular to be in gene
therapy. We were founded by researchers and parents
who have children with devastating diseases. WE also

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.
б	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. Well, I think there 9 DR. PETER MARKS: 10 are a couple different things that can be done. Ι 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 new licensing process, one doesn't have to look at a 20 21 different manufacturing process. 2.2 On the other hand, I think turning to

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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
	to happen. And so we re working towards that. And r
15	hope we're not too far off. Thanks.
15 16	hope we're not too far off. Thanks. DR. JANET MAYNARD: Thank you. Any
15 16 17	hope we're not too far off. Thanks. DR. JANET MAYNARD: Thank you. Any other questions from the audience in the room?
15 16 17 18	hope we're not too far off. Thanks. DR. JANET MAYNARD: Thank you. Any other questions from the audience in the room? WOMAN: (inaudible) Foundation.
15 16 17 18 19	hope we're not too far off. Thanks. DR. JANET MAYNARD: Thank you. Any other questions from the audience in the room? WOMAN: (inaudible) Foundation. Excellent panel. Thank you so much.
15 16 17 18 19 20	<pre>hope we're not too far off. Thanks. DR. JANET MAYNARD: Thank you. Any other questions from the audience in the room? WOMAN: (inaudible) Foundation. Excellent panel. Thank you so much. One quick thing I wanted to throw out</pre>
15 16 17 18 19 20 21	hope we're not too far off. Thanks. DR. JANET MAYNARD: Thank you. Any other questions from the audience in the room? WOMAN: (inaudible) Foundation. Excellent panel. Thank you so much. One quick thing I wanted to throw out there when this discussion was happening about our
15 16 17 18 19 20 21 22	<pre>hope we're not too far off. Thanks. DR. JANET MAYNARD: Thank you. Any other questions from the audience in the room? WOMAN: (inaudible) Foundation. Excellent panel. Thank you so much. One quick thing I wanted to throw out there when this discussion was happening about our platform trials. So we are in fact now collaborating</pre>

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.

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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 neurogenetive 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

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

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 a real second shot at life. Mila was seven years old 14 15 when she was diagnosed -- I'm sorry, when she was treated and obviously, had lost quite a lot, so she, 16 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.

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

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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
б	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.

DR. TIMOTHY YU: Thank you, Maarika. 6 7 And first of all, I want to thank all of you for the chance to come and participate in this Rare Disease 8 Day here at the FDA. I'm sitting on this stage as an 9 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 development that are available to us, built off of 14 15 many people's decades of hard work.

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

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

4 I want to fill in some of the details as to how we came to develop what folks are saying is 5 one of the first examples of a truly individualized 6 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.

It's an interesting time. It used to 14 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 way -- the reason I say that is that now, being able 20 21 to pinpoint the mutation, as in Mila's case, sometimes 2.2 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 instance of your daughter that she had an unusual type 8 of mutation that's a type of splicing mutation that 9 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 for her modeled after a drug that you've already heard 14 15 about called SPINRAZA for spinal muscular atrophy and customize it quickly for her, based on studies of her 16 17 own tissue samples. 18 And with a lot of support from many 19 people in academia and industry and from the regulatory space with the FDA, the Division of 20 21 Gastroenterology and Inborn Errors, we have been 2.2 treating her with this for the last few years, and to

what we believe is meaningful impact on her course of 1 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 creative -- to develop creative different ways of 6 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.

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

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 disease is characterized by bacterial infections in 14 15 the lungs, predominantly. And over time, these bacterial infections lead to lung damage, lung 16 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 November of 2018 and I saw a documentary of a patient 5 with CF who was treated by Yale -- Yale University 6 7 Researchers -- and I contacted these researchers and I 8 was very interested in having this therapy. And I communicated directly with them and they were very 9 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 confident in understanding this therapy and making the 14 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 it, right, it was an experimental therapy. 20 It's not 21 FDA approved. But I decided to go through with the 2.2 therapy. So by January of 2019, I was very ill. Ι

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

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

13 And so, you know, it was kind of where I was in a dire situation and that was certainly a 14 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.

So I traveled up to Yale and it was --3 4 it was difficult, because I wasn't sure if I was even going to be able to physically make the trip; I was 5 that ill. But, long story short, I received the 6 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 things from this morning. One is clearly being a 16 patient scientist yourself, and the other was Dr. 17 18 Marks' earlier mention of this being a good example of 19 what is often thought of as a more common condition as -- once broken up become something rare, and in this 20 21 case, truly individualized. So thank you.

22

So now, let's turn to hear some

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

DR. CELIA WITTEN: Yes, thank you. 3 I'm I'm the deputy director of the Center 4 Celia Witten. 5 for Biologics and FDA and as Dr. Marks said at the previous session, that's the center at FDA that 6 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 we really need to try to pay attention to how we can 16 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 patient and some may be customized for a patient, but 20 21 either way, they're really made for an individual 2.2 patient or a small group of patients.

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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

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development of these products and availability to 1 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 different models of collaboration right now and some 5 amazing individuals and organizations who are leading 6 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 needed, too, that include different stakeholders from 14 15 who has traditionally been included. I mean, I'm struck not just at this meeting, other meetings I've 16 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 don't -- I think we'd like to think, eventually, that 20 21 there could be a system where you don't have to go to 2.2 these heroic efforts to have a treatment available.

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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.

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

13 DR. PATROULA SMPOKOU: Hi. My name is I'm a clinical team leader in 14 Patroula Smpokou. 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 before joining the agency and so I think from my 21 22 perspective, the case of individualized or targeted

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

3 So I was fortunate enough to be 4 involved along with, you know, collaborate with team on the application for Milasen. This was a tremendous 5 opportunity for both myself and the team to learn from 6 7 both team members, group, from the family, from -- you 8 know, we all were very invested in trying to figure out how can we best fill the gaps and truly pave a new 9 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 can be, keeping in mind the end goal and also the end 16 result, right. So I guess first of all, I know the 17 panel previously talked about natural history studies 18 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

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

There was kind of a clear path of where 3 4 this would lead and so the question, at least from our 5 perspective and the team's perspective is what do we need at a minimum to make sure that we satisfy the 6 7 regulatory requirements the way that FDA interprets the regulatory requirements, and of course place those 8 in the context of this individualized therapy and the 9 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 like I was just so excited to be involved with this, 16 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 read it and, you know, try to figure out and email 20 21 people and say, okay, here's what we have now, what 2.2 should we do next.

And so it was great of course, very
satisfying because for myself, I've seen those
children, I've diagnosed those children and so I very
well know how the patients and the families think. So
I mean, from a regulatory perspective, you know, it
can be very difficult. This is novel. We're not used
to it. FDA is not used to it. (inaudible) it's a
normal paradigm and the question becomes, do you fit
this into your traditional paradigm or do you created
a brand new paradigm, right, for those individualized
therapies.
And the question is, we probably do a
little bit of both, which is what our team also did.
You know, you really have to understand the
regulations deeply to really know why was it a
regulatory climate. It's not only, okay, well, you
make two studies or in two different species for
toxicology, but why is that and what could we do, you
know, to get the minimum amount of, let's say,
toxicology data, right, to have some assurance of
safety so that the patient can get treatment.
So I feel like our team really did a
So I feel like our team really did a

fantastic job really coming together and thinking 1 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 continue to learn as we, and of course, Tim and Julia 6 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 listening to the five of you, I've got two questions 16 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 these areas, and what that brought to mind for me was 20 21 considerations of benefit and risk when you have

2.2 previously uncharted waters in a treatment.

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And so could each of you sort of
reflect on how you experiences with individualized
therapies have brought how you've considered
benefit and risk and how it might be different from
other areas or may be similar, and from your various
perspectives as patients, as parents, as regulators,
and as physicians?
ELLA BALASA: Well, when I received the
therapy, as I mentioned, I was in a dire need where I
my life was at risk, and so I think that's an
important consideration when deciding what is the
appropriate time to do an individualized therapy or if
at all, and weighing that benefit and risk analysis.
For phage therapy, personally, it's something this
is not it is a new therapy, but it's been around
for a while and it had been tested in patients before,
so I wasn't the first.

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

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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
б	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 pursued, and
21	also what dose to use, how to escalate the dose, but

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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

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the dose or making changes to the frequency or 1 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 mean to them. Because, of course, patients with rare 6 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 the patients and the families are truly the ones who 20 21 can make that decision, so -- but just to point out 2.2 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

should start Milasen or not. There was no other 1 2 There was no other treatment and Mila was option. 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 Taking five steps, one step, couldn't step at 6 month. 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 understanding what Milasen entailed and believing that 20 21 there was some reason to have hope that Mila could 2.2 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
б	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 we 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

accumulate trash, so to speak, and what we found was 1 2 that treatment of her cells with those -- with that drug was sufficient to allow recycling to happen again 3 4 and so they actually got healthier in front of our eyes. We could see this and you could -- we could 5 build up a scientific rationale. This was not a shot 6 7 in the dark. This was something that looked 8 scientifically plausible. All that being said, there were still 9 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, very clear and we could talk about them with Julia and 16 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. I think that's the interesting part of this. Now, if 20 21 we take an agency which holds great institutional 2.2 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,

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

So one of -- Celia, I think it was you, 3 4 talked about these situations often being successful when there's somebody heroic in the mix gluing 5 everything together or I tend to think of it as sort 6 7 of the stars aligning in a particular situation, and I 8 think our aim is that this shouldn't only be successful when the stars align perfectly or when we 9 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 ensure that these treatments are available to the less 14 15 than amazingly heroic among us and then also what -in that vein, what were your reflections on working 16 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 efficient process? 20 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.

And I really applaud Patroula and her 6 7 team for shifting to a really different mentality that 8 they were not used to and really thinking about Mila. And as we moved forward, now, this has opened up a 9 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 require working off of this new entirety and thinking 20 21 how do we face risk/benefit analysis when there's one 2.2 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

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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 these wonderfully advancing tools to develop 6 7 individualized treatments and then figure out how to 8 scale it? And the true measure of success, I think, in this space, if we do this right, is that these 9 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. Т 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, you -- one patient, you can get amazing things done, 16 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. Ι think that that's a really critical piece that I see 20 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?

So and the diagnosis is many of the 6 7 rare diseases and in the inborn errors metabolism which is the area that I work in is sometime actually 8 quite challenging, even in this era of this, you know, 9 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.

What we see sometimes is that there's 14 15 no specific guidelines of how the diagnosing of those patients or how to treat them, now to follow them over 16 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, you know, progress with a disease over time. 20 21 So I think what we were discussing 2.2 today about Mila's case and other cases, is actually a

great example of all the fundamental concepts that I 1 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 have access to some of those technologies through some 6 7 infrastructure and networks, but also a very delineated trajectory of disease. 8 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 other piece of that is really the collaboration, the 16 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 when I myself try to attempt meetings and really learn 20 21 from the outside and so I think at least for me that 2.2 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.

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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

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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 interesting. As soon as we got the momentum going, 5 that people are very interested in getting engaged 6 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 It's like one in a million, so it's -- we found 11 rare. 12 maybe about 20-some-odd patients around the world so 13 far.

14 But being able to get someone interested in funding something like, if we got 15 positive results from the liver gene therapy, you 16 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 is a challenging area, which is why I think we're --20 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 <mark>Olise</mark>
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	therap	ies.						

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 expensive, so finding ways to really make this work 6 7 will require thinking about ways where we can leverage 8 results from one experiment to another experiment of a close -- involving a closely related drug and another 9 10 experiment involving another closely related drug.

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

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

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 Γ

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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.				
б	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				

extreme, young extreme for me and it's always an
opportunity for me to think about how to move some of
these therapies forward in the neonatology space.
And as I was talking to Janet, it's
nice that I was going to help to focus some of the
discussion today on pediatrics, but I don't need to
because we've actually had a lot of really good
discussion about pediatrics throughout the day in all
of the panels.
So I know that we will continue to do
that here as well, but I don't think we have to
highlight it as much as I thought we were going to.
So with that, we're going to talk about the ecosystem
of rare disease product development, especially
related to a lot of collaborations and we kind of
talked about that sort of through the course of today.
I'm going to let all of my august panel members kind
of introduce themselves and as you're introducing
of introduce themselves and as you're introducing yourself, tell us kind of a little bit about high
of introduce themselves and as you're introducing yourself, tell us kind of a little bit about high level, what you think in terms of where we are in
of introduce themselves and as you're introducing yourself, tell us kind of a little bit about high level, what you think in terms of where we are in terms of the ecosystem and collaborations for rare

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

Page 236 what separates us. We may have different disease 1 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 do with each other that gets together to work on a 6 7 common problem. That's when magic happens, and I think 8 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're 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 Hi, good DR. MARTHA DONOGHUE: 17 afternoon. Is this working? 18 DR. SUSAN MCCUNE: Mm hmm. 19 Excellent. DR. MARTHA DONOGHUE: Μv name is Martha Donohue. I am a pediatric oncologist 20 21 and clinical team lead for the team that oversees the 2.2 regulation of new cancer drugs to be developed for

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qastrointestinal cancers and I also do quite a bit of 1 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 quess to summarize sort of where I think the ecosystem is for development of rare -- of 6 7 drugs to treat rare cancers, I think the ecosystems is 8 alive and well. It's evolving and changing and is extraordinarily complex and it's exciting to be a part 9 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, actually, of drugs to treat a variety of diseases that 16 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 of the very first time, we were able to approve a drub 20 21 not based upon sort of the histology of the tumor or 2.2 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 we were able to give a relatively broad indication for 6 7 these two drugs based upon a biomarker and tumor, at 8 the same time these biomarkers were extraordinarily rare for almost every cancer, so less than 0.1 percent 9 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 paradigm for -- those particular drugs highlighted a 16 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 cases like that, it kind of helps us to kind of 5 innovate and drive collaboration and communication 6 7 with one another and be flexible and creative and all 8 those other attributes that I'm hearing a lot of other people speak about on this panel. And it's, you know, 9 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.

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

from these drugs, and so that adds a degree of -- an 1 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, working together becomes even more imperative that it 6 7 It's always been important, but as we're once was. seeing more and more things become rare diseases, it's 8 forcing us in many good ways to work together. And so 9 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 Excellence forum in the Office of the Commissioner, 15 and the reason for the Oncology Center of Excellence 16 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 Center for Biologics, the Center for Devices and 20 21 Radiologic Health, and the Center for Drug Evaluation 2.2 and Research so we can work together to streamline

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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

to different investor conferences with all the Wall
 Street crowd and they would just walk away from me.
 It was almost like I had the Coronavirus written on my
 forehead.

5 Today, it's a different era, but again, I think the number one thing that I want to say is you 6 7 really have to collaborate with patients because 8 that's what makes your effort sustainable. They can't walk away, in many instances, from their endeavors and 9 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.

We also developed treatments for giant axonal neuropathy, and in that case, we had parents who had Relay for Life races and bake sales, but on the basis of those grass roots fundraising efforts, we actually have treated several patients and with the collaboration of NIH and the support of NIH.

We have also advanced treatments for

2.2

hemophilia which are now being advanced by Takeda.
We're in the clinic right now for a Pompe and heart
failure -- late stage heart failure. We'll be in the
clinic hopefully by the end of the year for MMA and
limb-girdle 2i. We're also working on Huntington's
which we hope to be in the clinic next year. Gene
therapy is exciting.

8 It has a lot of potential and it's giving a lot of hope to patients, and I'm very 9 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.

We had parents who literally put in their own money, did bake sales, did a lot of things to advance a therapeutic. GSK, this is another example of a collaboration, gave us access to a capsid that they just had sitting on the shelf and that allowed us to use what we thought was going to be the

Page 245 1 best capsid available. 2 We collaborated with academics who had the dog models, the Golden Retriever dog models and 3 4 didn't have a lot of money, so people are just -- are kicking into this effort. We went into the clinic 5 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 little boys the size of an eraser. Not -- knew it 14 15 wasn't going to have therapeutic effect, but we had to demonstrate that it was safe, baseline safety. 16 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 correct the dog model. Could not get funding. 20 21 Everybody said, it would not work. (inaudible) 2.2 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 we're very happy because we have met many of the boys 6 7 in that clinical trial and they should be in 8 wheelchairs today but instead, they're playing Little League baseball and they're enjoying swimming lessons, 9 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 our foundation, because it's equally important to me 16 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 rare indications that can be treated by gene therapy. 20 21 We do this through a nonprofit structure. These are 2.2 indications with 100 or so or fewer patients.

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We don't have a hard stop, but we know
that those are not commercially viable indications,
and so we donate our technology, our manufacturing
capacity, our (inaudible), our regulatory, our legal
support to the advancement of these drugs. Today,
we're working on AADC, amino acid decarboxylase
deficiency. That's a mouthful. And we have treated
20 patients free of charge. I think we're one of the
few groups that has done that.
We're also have in our pipeline for
the foundation (inaudible). So those are the diseases
we're working on. Thank you.
DR. SUSAN MCCUNE: Vasum?
DR. VASUM PEIRIS: Thank you. Mic's
on. Perfect. First of all, thank you very much for
everybody for continuing to stay here. This is a very
important cause and it's wonderful that as we've
talked about before, that the meeting is happening. I
just want to thank Janet and the entire OOPD team that
has put this together and all of the people that have
worked to get this to happen, so it's wonderful to see
so much registration and so much interest across the

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. Shuren, the center director mentioned. For the 5 purposes of this panel, I am the gizmo guy, so I'm the 6 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, but22 I'll try to focus on that you brought us towards, as,

you know, what is the ecosystem, what is the state of the ecosystem and where are we going, really. I think it is wonderful that we are coming together and that there again, there's so much interest. There is a great deal of work that's being done, I think, in the biologics and drug space.

7 There continues to be great potential in the device space and I think as we move forward, we 8 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 If you really think about it, when you go encounters. 13 to a doctor and you have a doctor visit, there's a higher likelihood that you actually might engage with 14 15 a medical device -- you know, a thermometer, a 16 dipstick, a blood pressure cuff -- than you might with 17 a druq.

That that's something to be cognizant of as we think about how technologies are affecting lives and especially with respect to small populations and rare diseases. We -- a couple of the earlier panels alluded to this a little bit, but I think

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.

And from where we are right now, when you think about how do we optimize the potential of the ecosystem, we've got to bring together issues not

just in the regulatory space, not just in the clinical space, but in the economic space as well because we recognize that there are a great deal of efforts that could be considered perhaps one-offs, a great deal of philanthropic investment in certain area, either certain aspects of Milasen or a specific disease or a specific drug or a specific medical product.

8 What we want to get towards is a platform that allows anybody with great ideas, great 9 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 together to really consider what is the next step in 16 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
Initiative to help bring awareness to those rare
 diseases and the causes.

ICAN and being part of the Hope for 3 4 Henry patient and team board collaboration is a really 5 important step to bring more awareness to these diseases and to start a communication and 6 7 collaboration with patients and the environment and 8 the community around and to better educate more people about the things that are going on with those 9 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, academia, industry, and government entities. 16 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 undertaken and I'm thrilled today that every panel had 20 21 talked -- has been talking about public-private 2.2 partnerships and consortia efforts and I'm going to go

back to Rhiannon to start the conversation. 1 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 pediatric patients. And so my question to the folks 6 7 on the panel is, all of us have been involved in 8 consortia efforts. Clearly, we not have -- we're now getting an experience that's in -- upwards of years, 9 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, what are done well, and then where are -- where do we 17 18 have some challenges. 19 RHIANNON PERRY: So like I said before, I work with Hope for Henry and so we have a patient 20 21 advisory council and then we also have a teen board 2.2 where teens in the community can come take part of

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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 we go into Children's National Medical Center and we 9 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 at these programs that are implemented to help them 16 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 to spread awareness about these diseases and illnesses 20 21 that really need to be brought up. And one thing that 2.2 we can definitely work more on is our outreach in

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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

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absolutely makes a difference for the types of
initiatives that are necessary to really move forward
in the field of rare diseases. I know that there have
been a number of different consortia efforts that have
some together in an attempt, in their own spheres to
break down silos.

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 think, that we're trying to do right now with the 14 15 consortia that we're developing for around SHIP.

We wanted to ensure that stakeholders across the ecosystem are involved, patients included, but that also includes, again, not just that regulatory world like I mentioned before. It also brings into play the individuals that invest in the development of these medical products, like (inaudible) Funds, Angel Funds, all of that, because

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 I find that people are SHEILA MIKHAIL: usually more cooperative in collaborations when they 16 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 2.2 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

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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,

they've been increasing involving in the -- with the U.S. as well with the help of an advocacy group called (inaudible). We had our first meeting in the United States this fall and this particular one was on development of a particular class of drugs called epigenetic modifying agents for patients with cancer, for pediatric patients with cancer.

And because of the ability to have this 8 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 any definitive decisions, I think we all came away 14 15 with increased understanding of one another and better -- to make the best decisions that we could for 16 patients. 17

So I think that's one excellent example of sort of a new way to collaborate in a pretty competitive way. We're all sort of having the same goals, but I think also respecting the competition piece of it as well. And I think we still have a lot

of challenges. I think we need to bring in other
 regulators into this conversation, not just Europe and
 U.S.

4 I think at this particular meeting, we had representative from Australia as well, but I think 5 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 complexities can be really tested when we're thinking 9 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. Everything we do is a collaboration, but I decided, 20 21 like a lot of scientists, you learn the most from the 2.2 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, European Commission, Japan, Canada, Australia, China, 6 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 They come from the entire spectrum of languages. 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 quy 17 who's there enemy. 18 And so the common enemy here is the 19 enormity of the rare disease problem. Those of you who've heard me talk will know that I am fond of 20 21 saying where -- unfortunate truth, that at the current

rate of progress, which is really quite remarkable,

2.2

but at the current state of progress it will be 2,000
 years before there is a treatment for all rare
 diseases.

4 So we have to do things differently. 5 That is just not an acceptable answer. And it doesn't have to be, but all of these folks were brought 6 7 together by this common desire to say, well, if we 8 coordinate what we do internationally and so the NIH knows what the European Commission is doing, would 9 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 It was actually an enormous pleasure, but what 16 years? I learned was that first of all, it is critical that 17 leadership -- leadership's really important in this 18 19 case -- keep articulating what the goal is, what -why are we all here. And it -- that sounds sort of 20 21 obvious, but it's easy to lose track in the nitty-2.2 gritty of individual projects, why we're doing this.

	5
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.

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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

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that. So that's one of the efforts that we're really
trying to take now.
DR. EPPS: Are you guys using a lot in
terms of social media to reach out to other folks?
RHIANNON PERRY: Definitely.
DR. CHRISTOPHER AUSTIN: I guess the
only thing I would say is if you think about a sports
team, so I was in Boston for 20 years and the Red Sox
would be pathetic to being really good. When they
were pathetic, I was like one of, like, four people at
the ballpark. And when they started winning, all of a
sudden everybody was a Red Sox fan. So having some
people love to be part of the winning team. And so I
think all of us have experienced this, that we all
have long-term goals but you've got to start winning
individual baseball games, and that will bring in more
people so there's this adage that we all have.
You know, got to have some short-term
confidence building measures. That's really
important. And it's and all of us say, well, gosh,
you know, that's just it's such a small step and it
doesn't really matter because it's not it's

infinitesimal the way we want to go. It really
 matters because it will bring other people in who will
 make your team bigger and stronger.

4 SHEILA MIKHAIL: Just to build on that, 5 sometimes, too, it's -- the team maybe isn't your company or your organization, but it's a field. I 6 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. AveXis uses our technology and that's a major --9 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 still very vulnerable and we need to have some more 14 15 So when the SMA drug was approved, that was wins. really good and now, hopefully, the DMD drug will be 16 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 the main pathway diseases. 20

With Medtronic's help, we're not in
heart failure and that's a pretty big step. At least

with monogenetic diseases, you know what the drug is. 1 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 get the right one. So, anyway, for us, I agree with 6 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.

For the Red Sox, it was probably the four people that knew plus my entire pediatric EPT. They were always there. That's all we talked about during rounds. But on the team concept, there's a big team that can do a great deal of great work. You know what that team is? HHS, the government. Right.

That team is doing a lot of work. What if -- again, to Susie's question -- what if there is better collaboration, NIH, CMS, FDA, and others that came together to try to begin to truly address this across the spectrum? How do we begin to develop more of a collaborative environment within those teams?

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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,
б	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.

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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 But we could envision a world where a 11 with the FDA. 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 there was a master file filed at the FDA that 14 15 investigators could refer to, it might accelerate drug 16 development.

The capsids have a certain tropism, right. They're always going to have a certain tropism. The thing that's changing is the drug that you're putting and essentially it's the gene that you want to express. And so it could simplify and accelerate getting I&Ds filed. Г

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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.
б	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

last five years that we've really had this big
 collaborative consortia is that there's two elements,
 I think, to successful collaborations.

4 One, is an incentive. Try to 5 understand why people don't want to collaborate and try to pull them over to the side where you want them 6 7 to be. But the second thing, and this is a request, I 8 think there is also something where we really need help from federal agencies and that's around policies. 9 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 taxpayer dollars and that these animals are not 16 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. 2.2 WOMAN 1: But I see -- I think we need

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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 they're going to be activists against their treating 6 7 clinicians, which is really not a good thing to do. 8 So we need policies. So this is my request. So my hope is it works and Chris helped. My request is, 9 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 to overcome a number of different issues in the system 16 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, geographically disbursed heterogenous populations that 20 21 we just can't get all the information for. Well, 2.2 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

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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

NORD'S pretty good, but then we had a patient
 organization from Botswana that was significantly
 smaller and had significantly less experience and so
 what this allowed was this sort of big brother/big
 sister relationship.

But you're absolutely right. 6 That's 7 what these countries needed. But what we discovered was that U.S. and Europe, we lose track of how far the 8 culture has come to take the patient seriously. 9 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 cultural barriers? And so we do a lot of work and 16 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 absolutely essential. The other thing that the --20 21 each of the countries has to do which the United 2.2 States hasn't done yet, of course, but we managed to

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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.

And the reason why and the only way 5 that you will get a consortium is if John Q. Public 6 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 excited to be here. I'm so happy that we get the 9 10 opportunity to come and share our experiences with 11 But from a patient, from a parent, and from John vou. 12 Q. Public just sitting out there, I have no idea what 13 you're talking about.

And if I don't have an idea of what 14 15 you're talking about, I can't advocate on Capitol Hill the way I am with Be The Match to bring some of the 16 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, John Q. Government, this is what we, the American 20 21 public, want. We want you to bring down the walls and 2.2 the barriers that prevent us from working together,

country to country, community to community to community.

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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 consortium. So I applaud each and every one of you 9 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.

If there is additional time after, we 6 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.

As you are speaking, you'll notice you 14 15 have a timing light to guide you. The green light will indicate when you can begin speaking. It will 16 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 If you have not concluded your remarks by the end. end of your allotted time, I will ask you to do so 20 21 kindly.

22

As a reminder, you also have the option

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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 challenges across many chronic rare diseases. 3 These 4 include diagnosis, clinical trial participation, unique needs of women, and underserved populations, 5 and the important of support systems. 6 7 Delay to diagnosis is a great concern. Those living with artery diseases see on average eight 8 doctors and take five to seven years to receive the 9 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 complex treatments, some with harsh side effects, to 17 18 address the damages done. 19 Additionally, repeated misdiagnosis creates a mistrust of the medical community. Finally, 20 21 delay to diagnosis means that the time patients 2.2 receive their diagnosis complications they have

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incurred may make them ineligible for clinical trials.
Clinical trials are the beacon of hope
for patients and their loved ones. We need to do
better to ensure that clinical trials are for all
individuals. Women make up 80 percent of all
autoimmune diseases; yet it has been shown that women
participate in clinical trials at a lower rate than
met, something the FDA has already been working on to
address through policy changes and the Women in
Clinical Trials campaign.
In considering trial design and patient
engagement, it behooves us to hear the unique
challenges that women with rare diseases face,
including future fertility, balancing family, job, and
the increased likelihood of being caregivers for
others with health problem. These issues are
compounded by the complexities of their own rare
disease. For women with myositis seeking to have
children, concerns about participation in clinical
trials are multiplied by the knowledge that increased
flares can make it more challenging for them to care
for their children and the stress of a regimen of an
1

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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 living with rare diseases like myositis is virtually 6 7 important to improve opportunities for clinical trial 8 participation for women, in order to ensure that all treatment options meet the differing biological needs 9 10 of both genders.

Similarly, we must consider the unique 11 12 challenges for those in underserved and diverse 13 populations living with a rare disease like myositis. Women of color have the highest prevalence of 14 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 2.2 do not meet eligibility criteria for many clinical

Page 290 1 Additionally, most individuals from trials. 2 underserved populations are distrusting of 3 experimental treatments and clinical trials due to historic breaches of trust. The population --4 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 extraordinary work. Appreciate it. 9 10 CATHERINE PARK: Thank you. Next we have Matt Buck. 11 12 MATT BUCK: Thank you. I'm Matt Buck. 13 I'm vice president of regulatory affairs at Ionis Pharmaceuticals. I'm here today representing the n-14 15 Lorem Foundation which is a nonprofit, so I have both 16 industry in here, representing nonprofit. I quess 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, antisense oligonucleotides to treat patients with 21 22 ultra rare disease which affect about one to 10

patients. The foundation was established at the end of 2019 and our mission, of course -- sorry, our goal and who we work with is Ionis Pharmaceuticals and the Undiagnosed Disease Network, the UDN, to provide these individual therapeutics.

We were just established at the end of 6 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. One of those is that, ideally, CDER would have a sole 20 21 division within the FDA that would manage individual 2.2 therapeutic INDs. And that is so that a single

philosophy or standard can be uniformly applied to all
 of the evidentiary requirements.

Second, with respect to evidentiary 3 4 requirements, when it comes to ASOs that are well characterized, that we would be able to utilize what 5 we know about that platform to establish more minimal 6 7 data standards which we believe would be -- examples 8 are a single-species tox study such as single-species rodent tox package and of course an abbreviated 9 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.

2.2

MICHELLE ADAMS: Hi, I'm Michelle

Adams. I'm with the National Organization of Rare
 Disorders and I don't have any disclosures. Thank
 you. On behalf of the 25 to 30 million Americans with
 one of the over 7,000 rare disease, would like to
 thank the FDA for holding this meeting today to
 commemorate and celebrate rare disease week.

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.

Rare Disease Day is observed in community settings, governmental legislative offices, school classrooms, college campuses, and hospitals, all to make the voices of rare disease patients heard. It is truly inspiring to know that people around the country are coming together at events like this one with the shared goal to promote awareness and improves

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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. Nest we
20	have Tisha Wang.
21	TISHA WANG: Hi. My name is Tisha
22	Wang. I'm a pulmonary physician and clinician at

UCLA. I thank you for the opportunity to speak today.
 As the clinical director and vice president of the
 Pulmonary Alveolar Proteinosis or PAP Foundation. My
 travel was funded, but I have no financial interest
 here.

PAP is a rare disease without any 6 7 approved therapy in which patients drown in their own surfactant proteins and develop shortness of breath 8 and respiratory failure. In 2005, I was a trainee and 9 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 of this disease. 14

15 Based on what we knew about the cause of PAP which is that her cells and her lung were 16 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, we were both so young, but we trusted each other. 20 We 21 took a chance together and I gave her the protein and 2.2 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 on GM-CSF and stopped, only to have their disease 6 7 recur off therapy. Fortunately, the research has 8 progressed in the last decade. We have a Phase 1 trial in the U.S., two recently completed randomized 9 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, the amount of abnormal surfactant present, and the 14 15 quality of life of these patients.

We at the foundation find these results encouraging and consistent with the experience of our patient community. So we at the PAP Foundation remain steadfast around a mission to become one of the few rare diseases to have an FDA approved therapy for our patients. We're committed to working very closely with the FDA to achieve this and applaud the FDA for

granting breakthrough therapy designation for
 Molgradex, which is a formulation of inhaled GM-CSF.
 What is striking about this meeting and being her all
 day today is that everybody in this room is on a
 mission.

The missing is slightly different for 6 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 statement to the FDA probably mirrors the sentiment in 9 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 conjunction with the FDA. 14 15 Thank you again for the opportunity to speak on behalf of the PAP Foundation, the PAP patient 16

17 community today.

18 CATHERINE PARK: Thank you. Next, we 19 have Jen McNary.

JEN MCNARY: Hi, thank you. I'm Jen McNary, a rare disease advocate, mom of three sons with rare disease. I'm the founder of One Rare, a

board member of various organizations, and a 1 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 incredibly important to me and it's been discussed at 6 7 other venues this year, such as JPMorgan, in thinking about this concept a little broader throughout the 8 day, as we realize the benefits of precision genetic 9 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

to continue to ensure that this trickles down
 throughout the entire agency to allow a visible path
 forward for good science.

4 Switching gears, in the spirit of being wholly supportive of faster FDA approvals, I would be 5 remiss in not also mentioning a troubling situation in 6 7 the access and reimbursement landscape that's going to 8 affect us all. I'm aware that in order for innovation to best serve patients in this room, two things need 9 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 They found sufficient evidence of the 17 Disabilities. 18 discriminatory nature of qualities to warrant concern, 19 including concerns raised by bioethicists, patient rights groups, and disability rights advocates about 20 21 limiting access to life-saving medications.

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In a recent article, the Pink Sheet,

ICR calls itself an expert to help the FDA understand 1 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 FDA is doing an amazing job of incorporating the 6 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 organization in favor of working with foundations, 14 15 some of which are in this room: EveryLife Foundation, ARM, IGT, (inaudible). They all have a proven track 16 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. 2.2 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 access to treatments by helping develop potential 5 treatments, identify patients for clinical trials, and 6 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	
20	percent of overdose fatalities were caused by patients
21	taking their own prescribed opioids, so 98.7 percent
21 22	taking their own prescribed opioids, so 98.7 percent are due to illicit or illegal activities. Pounding

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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

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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 dogs 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 ciprofloxacin could destroy my qut. 14 Indeed, I was 15 never informed that I should even take a probiotic. 16 I didn't know that amitriptyline would result in orthostatic intolerance. I didn't know that 17 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.

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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.

This concludes the open public comment period. We
 really appreciate everyone participating today. I
 will now transition to Janet Maynard to provide
 closing remarks. Thank you.

5 DR. JANET MAYNARD: So we're going to transition to closing remarks, because unfortunately 6 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.

This has been a very important meeting 14 15 to all the participants including FDA, patients, researchers, and the industry representatives. 16 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 There are exciting opportunities in rare disease 20 do. 21 product development, and great unmet needs of patients 2.2 and families living with rare diseases. In the

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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

patient affairs staff can help. You can send them an email at PatientAffairs@FDA.gov. They can help you stay connected with other activities at FDA or address future questions.

You can also connect with the Office of 5 6 Orphan Products Development at Orphan@FDA.gov. As 7 mentioned earlier today, we strongly encourage you to submit comments to the docket which will be open until 8 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 staff working at this meeting, and those are the folks 16 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 am closing this public meeting. Thank you. 20 Safe 21 travels and have a wonderful evening.

22

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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
6	proceedings were recorded by me and thereafter reduced
7	to typewriting by a qualified transcriptionist; that
8	said digital audio recording of said proceedings are a
9	true and accurate record to the best of my knowledge,
10	skills, and ability; that I am neither counsel for,
11	related to, nor employed by any of the parties to the
12	action in which this was taken; and, further, that I
13	am not a relative or employee of any counsel or
14	attorney employed by the parties hereto, nor
15	financially or otherwise interested in the outcome of
16	this action.
17	
18	
19	Plia Shihon!
20	
	3854897
21	Notary Public in and for the
	State of Maryland
22	

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	Page 316
1	CERTIFICATE OF TRANSCRIBER
2	I, Sonya Ledanski Hyde, do hereby certify
3	that this transcript was prepared from the digital
4	audio recording of the foregoing proceeding, that said
5	transcript is a true and accurate record of the
6	proceedings to the best of my knowledge, skills, and
7	ability; that I am neither counsel for, related to,
8	nor employed by any of the parties to the action in
9	which this was taken; and, further, that I am not a
10	relative or employee of any counsel or attorney
11	employed by the parties hereto, nor financially or
12	otherwise interested in the outcome of this action.
13	
14	Sonya M. destandi Hyde
15	Sonya Ledanski Hyde
16	
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21	
22	

[0.1 - able]

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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.

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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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