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PATIENT-FOCUSED DRUG DEVELOPMENT

METHODS TO IDENTIFY WHAT IS IMPORTANT TO PATIENTS AND  
SELECT, DEVELOP OR MODIFY FIT-FOR-PURPOSE CLINICAL  
OUTCOME ASSESSMENTS

October 16, 2018

10903 New Hampshire Ave, Building 31,  
Room 1503 (Great Room)  
Silver Spring, MD 20993

Reported by: Michael Farkas

Capital Reporting Company  
1250 Eye Street, NW, Suite 350  
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C O N T E N T S

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Elektra Papadopoulos

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1 P R O C E E D I N G S

2 WELCOME

3 MS. CHALASANI: Good morning, everyone. I see  
4 a lot of folks still getting settled in so I'll give  
5 another minute or two and then we'll get started.

6 Okay. Okay. Good morning, everyone. Let's  
7 get started. Thank you all for being here today. My  
8 name is Meghana Chalasani from the Office of the Center  
9 Director within the Center for Drug Evaluation and  
10 Research at FDA. I would like to welcome all of you in  
11 the room and on the webcast to day 2 of FDA's patient-  
12 focused drug development workshop on methods to  
13 identify what is important to patients and select,  
14 develop or modify fit-for-purpose clinical outcome  
15 assessments.

16 This meeting is a second workshop in a series  
17 of workshops we are conducting as we work towards  
18 developing a series of patient-focused drug development  
19 guidance documents. Dr. Michelle Tarver will provide  
20 opening remarks in a few minutes during which she will  
21 recap on what we presented and discussed yesterday.  
22 But first, let me provide a high-level overview of the

1 agenda for today.

2           After Michelle's opening remarks we will  
3 continue our discussion on the Guidance 3 discussion  
4 document. In the morning we will have two panel  
5 sessions, the first focusing on considerations for the  
6 selection and use of clinical outcome assessments in  
7 special populations followed by a panel on methods for  
8 determining and interpreting within-patient meaningful  
9 score changes in clinical outcome assessments. We will  
10 then break for lunch.

11           And in the afternoon we will reconvene for a  
12 panel session on emerging technologies to support fit-  
13 for-purpose clinical outcome assessment. We will wrap  
14 up our 2-day workshop with a final session on  
15 identifying key themes and next steps. Similar to  
16 yesterday, throughout the day the audience will have  
17 several opportunities to ask questions and provide  
18 their views.

19           After our panel sessions this afternoon we  
20 also have time set aside for open public comment. To  
21 participate in that you will need to sign up at the  
22 registration table. Participation is on a first come

1 first served basis. As folks who were here yesterday  
2 very well know, we have a public docket for the  
3 workshop that will remain open until December 14, 2018.  
4 Through this docket the public may submit general or  
5 detailed comments or examples regarding specific  
6 aspects of the discussion documents or topics raised  
7 during the workshop.

8           You will see a slide that provides information  
9 on how to access this public docket several times  
10 throughout the day. With our large number of webcast  
11 attendees we will not be able to take comments or  
12 questions from the webcast during the workshop. We  
13 will however take back all of the comments that we  
14 received via the webcast and review them. We also  
15 encourage our webcast participants to submit comments  
16 to the public docket.

17           A few brief housekeeping items. There are  
18 food and beverages available for purchase at the kiosk  
19 outside the room in the lobby. It gets pretty crowded  
20 at lunch, so we do encourage everyone to preorder your  
21 lunch. Bathrooms are down the hallway in the lobby  
22 behind the kiosk and on the left. The WiFi password

1 for this room can be found at the front desk in the  
2 lobby. And finally, this workshop is being transcribed  
3 and a live webcast is being recorded both of which will  
4 be archived on our website. And so with that I'll turn  
5 it over to Michelle for opening remarks.

6 OPENING REMARKS

7 DR. TARVER: Good morning, and welcome to Day  
8 2. I've been tasked with recapping what happened  
9 yesterday and to give you a little teaser about what  
10 we're going to talk about today. Before I start  
11 though, I want to take the bird's eye view.

12 We're all here together because we are  
13 committed to promoting public health by helping to  
14 ensure that safe and effective medical products are on  
15 the U.S. market. In order to do that, we are focused  
16 on making sure that the outcomes we're assessing in the  
17 studies really are capturing what's most important to  
18 patients and can help inform the provider-patient  
19 conversation.

20 That means that the outcomes have to be  
21 relevant, they have to be understandable, they have to  
22 be validly assessed and that the change in those



1 outcomes has to be meaningful to patients. So while we  
2 are working on developing tools that help inform that  
3 conversation I want to talk about how we're just one  
4 part of this ecosystem in the health care system.

5           When we develop clinical outcome assessments  
6 those assessments are often incorporated into provider  
7 guidelines, preferred practices and integrated into  
8 healthcare systems through their electronic health  
9 records. We've seen a number of EHRs now have PRO  
10 measures that they are asking their providers to  
11 collect at every visit. This information is  
12 influencing payers and other health care insurance  
13 providers and making decisions about what they're going  
14 to cover and enforcing in some cases that there is this  
15 assessment prior to determining whether or not a  
16 patient and provider can utilize a particular  
17 diagnostic or particular therapeutic.

18           Not only are we seeing it at that level but  
19 we're also seeing it at state levels. Minnesota has  
20 mandated that for many surgical -- orthopedic surgical  
21 procedures patient-reported outcomes must be collected  
22 and publicly reported so that patients can make

1 decisions about healthcare. So what we're talking  
2 about in this room today has rippling effects  
3 throughout the entire healthcare system and has the  
4 ability to transform health and have meaningful impact  
5 in everything that we do.

6           Yesterday Theresa Mullin talked about the four  
7 guidance documents that we have been committed to  
8 generating. And those guidance documents really do  
9 give a reflection of the patient experience through  
10 different lenses. One of the two principles that I'd  
11 like to highlight though is that some of the guidance  
12 documents are reflective of the different medical  
13 product spaces, so the devices, drugs and biologics.  
14 And because of that they're written in a way that is --  
15 takes into consideration our statutory guidelines. So  
16 we all have different rules that govern how we evaluate  
17 medical evidence. And the discussion guides try to  
18 reflect that.

19           Not only do we have different statutory  
20 requirements, we also have different mechanisms by  
21 which our medical products act on patients. And so we  
22 need to take that in consideration too when we're

1 determining how do we measure that, how do we capture  
2 that, what are the study designs that we're required to  
3 do in order to better reflect that information and  
4 transfer that information to the labeling so that  
5 patients and providers can make informed decisions.

6 We're also seeing a greater emergence of  
7 combination products where it may be a device and a  
8 drug or device and a biologic. And those create new  
9 challenges on how we measure outcomes that we need to  
10 consider as we're moving forward in the space. The  
11 second principle that the discussion guidances really  
12 do allude to is the principle that it is helping to  
13 empower everyone in this space, all the stakeholders,  
14 patients included to create tools that can better  
15 measure that lived experience that we heard about  
16 yesterday.

17 So what that in mind I'm going to hit the  
18 highlight reel. One of the recurrent themes we heard  
19 yesterday is that the patients' voices need to be  
20 captured and they need to be captured appropriately.  
21 So both Selena Daniels and Ebony Dashiell spent a lot  
22 of time and wonderful discussion comments talking about

1 Guidance 2. And I'm -- and their panelists gave  
2 wonderful feedback. They did a great job summarizing  
3 it but I'm going to just touch on a couple of points.  
4 The first thing is that we talked about methods to  
5 identify what is important to patients, how do we ask  
6 those right questions and what are the best practices  
7 for how to do qualitative and quantitative research,  
8 how do we operationalize it from the study design phase  
9 all the way to how we communicate those results.

10 What themes we heard from the panelists and  
11 from the audience, I'm going to highlight just a couple  
12 of them. The first is that we don't do a checklist and  
13 instead provide a strategy and approach to how do we  
14 use the tools to generate the information that we're  
15 seeking. We also heard from you all that you wanted to  
16 clarify the evidentiary expectations.

17 And the last theme that we heard was  
18 flexibility. While you are committed to doing rigorous  
19 and transparent work you do want flexibility and so we  
20 will take those comments under consideration as we  
21 revise the guidance document. Elektra Papadopoulos  
22 then moved us to Guidance 3 where we talked about how

1 do you develop and identify appropriate clinical  
2 outcomes assessments. She and the FDA panel emphasize  
3 four general principles. The first is that clinical  
4 outcome assessments should be fit for purpose. And  
5 I'll touch on this a little bit more in the subsequent  
6 slides.

7 She also mentioned that like any other tool  
8 that measures an outcome it should be well developed  
9 and it should be -- this is relevant to all of the  
10 clinical outcomes assessment types. We are open to  
11 alternative methods and approaches to assess these  
12 tools. And I think you heard resoundingly from every  
13 panel member from every product center that we're  
14 interested in leveraging existing clinical outcome  
15 assessments where it's appropriate.

16 So fit for purpose, it's one of those things  
17 that as we talked about yesterday, it requires that we  
18 look at what are we really trying to answer and who are  
19 we trying to answer it and what patient population is  
20 it going to be relevant for because what we're really  
21 looking for at the end of the day is that the tool is  
22 designed for who it's intended to be designed for and

1 it's measuring the concept that we're really interested  
2 in, it should be doing that in a valid way and it  
3 should be reliable and that it should be clinically  
4 relevant and important to patients. Our hope is that  
5 this information can be communicated in the labeling in  
6 a way that is accurate, interpretable and not  
7 misleading to patients or providers.

8 She highlighted two tools, one of them is the  
9 roadmap to patient-focused outcome measurement in  
10 clinical trials. This tool starts with one theme, and  
11 it's that -- it's important to engage the FDA early and  
12 often. Now all of our centers have different  
13 mechanisms via which you can interact with us. At the  
14 Center for Devices and Radiological Health we have a  
15 presubmission process, but we encourage whatever  
16 mechanism it is for the relevant center that you  
17 utilize and then get the feedback you need early on so  
18 that you can target your development plan  
19 appropriately.

20 On the roadmap the first step is understanding  
21 the disease or the condition and this includes the  
22 natural history of the disease, the patient

1 subpopulations, the spectrum of the severity of the  
2 disease and how it's being cared for in the current  
3 clinical paradigm. It also requires that the patient,  
4 the caregivers are having input to that phase of this  
5 development. Then it's necessary to move on to the  
6 second step which is identifying the concept of  
7 interest that's meaningful. That also requires that  
8 you define the context of use, how do you want to  
9 operationalize it in your trial.

10           So you've defined the what, you've defined the  
11 who and now you're defining the how, and that's step  
12 three, selecting and developing or modifying the  
13 outcome measure. And we spent some time talking about  
14 that. Elektra showed you the new, refined wheel and  
15 spoke that has now become a decision tree and how we  
16 have concretely laid out that there are many options  
17 that development is not the only option, that use as is  
18 as well as modification are also on the table.

19           Another theme we heard is flexibility. And  
20 flexibility is really important. We are looking for  
21 creative, efficient and appropriate ways to develop  
22 clinical outcome assessments. There are many ways in

1 some cases to address the challenges that we face.  
2 Sometimes it's the patient population that presents the  
3 challenge, sometimes it's the disease condition,  
4 sometimes it's the therapeutic that we're actually  
5 talking about. Regardless of the challenge, we  
6 encourage you to come talk to us early because we can't  
7 exercise the flexibility option if we're not  
8 approached.

9           The other thing we heard is it's important to  
10 not reinvent the wheel. When one exists, take that  
11 Michelin tire off the shelf and put it into your  
12 clinical trial. If you need to start with a metal  
13 frame and put your own rubber on, that's fine, modify  
14 it. And every now and then we may run into situations  
15 where you may need to reinvent it so -- or start over  
16 because there's nothing there that you can potentially  
17 use, therefore you have to get your chisel out and some  
18 stone and we're willing to help in that process.

19           The last question we asked, is there something  
20 missing, are there any suggestions, any comments, any  
21 examples that you all think that we should incorporate  
22 into these documents to make them more usable and more



1 relevant to what you're doing. You've already heard  
2 about the docket number, and in case you missed it,  
3 it's December 14 is the time that it closes. So we  
4 really do welcome your feedback. One of the themes  
5 that we did hear a couple of times yesterday that was  
6 suggested was missing was patient preference, and so I  
7 thought I'd just mention it here very quickly.

8           Patient preference is the qualitative or  
9 quantitative assessments of the relative desirability  
10 or acceptability to patients of specified choices among  
11 outcomes or other attributes that differ among  
12 alternative health interventions. We find this  
13 information to be useful when there is multiple  
14 treatments but there is no superior one, there is  
15 equipoise.

16           When the patient views about the most  
17 important benefits an acceptable risk may vary within  
18 the population or differ significantly from that of  
19 health care providers or when the evidence supporting  
20 one option over others is uncertain or variable. We do  
21 have a guidance document that's been issued in August  
22 of 2016 by the Center for Devices and Center for

1     Biologics that talks about the methodology that can be  
2     employed to measure patient preference information and  
3     how to do a quality patient preference study. So with  
4     the upcoming World Search series I figured I'd use some  
5     sports metaphors and continue with the theme of  
6     highlights. We'll do previews.

7             So first in our lineup today is Vasum Peiris.  
8     He will be talking about moderating the session on  
9     special patient population considerations. And you've  
10    already heard about some of the challenges that exist  
11    with certain populations, particularly children, where  
12    there may be changes over the lifespan of that child as  
13    they go from one age to another within the time of,  
14    course of the trial there may be different outcomes  
15    that are important and meaningful to capture.

16            Another challenge is linguistic challenges.  
17    Children's language development exponentially increases  
18    from year to year. But linguistic challenges also  
19    extend to areas such as in rare disease where you have  
20    very few patients and they may be scattered  
21    geographically.

22            The other concept that will probably come up

1 in this session is the cognitive changes over time,  
2 particularly for some diseases and how do you do a  
3 clinical outcome assessment when that is the case.

4 Next in the lineup biz Michelle Campbell,  
5 she'll be moderating a session on interpret meaningful  
6 within-patient change and that will be talking about  
7 some of the topics that we mentioned yesterday which is  
8 create -- including anchors in the clinical study but  
9 also considerations of statistical methodologies that  
10 can compliment that information.

11 Digital health technologies to support fit-  
12 for-purpose will be led by Sarrit Kovacs. She will be  
13 moderating that session. And one of the terms I think  
14 that Elektra alluded to is that this terminology,  
15 digital health technologies is one that's a term in  
16 evolution. As you all may or may not know, the Center  
17 for devices regulates many of the products that are  
18 under this heading of digital health technologies and  
19 these include things that are sensors. They may be  
20 mobile or wearables or activity trackers but they also  
21 may be fixed and they may not be mobile but they all  
22 are measuring something passively from the patient in

1 most cases. And so we'll talk about how that  
2 information can complement what we get from clinical  
3 outcomes assessments. And last up, to bring us home,  
4 will be Meghana Chalasani, she'll be talking about our  
5 key themes and our next steps.

6 Now I would be remiss if I didn't do some  
7 shameless promotion, so I'm going to talk about our  
8 coming attraction which is the patient engagement  
9 advisory committee meeting. This meeting is the second  
10 one we've had and our committee is comprised of  
11 patients, caregivers and patient advocates. This  
12 meeting will be held on November 15 from 8:00 to 5:00  
13 p.m. at the Hilton Gaithersburg and we're going to  
14 focus on patient-generated data and how we can use that  
15 information in post-market medical device evaluation.

16 We're going to talk about digital help  
17 technology integration, patient-driven registries and  
18 social meeting and listening. We hope that you'll  
19 attend. On the bottom of the slide shows the link  
20 where you can find more information and we do have a  
21 webcast that you can attend as well as in person. And  
22 that's the end. I'll welcome Vasum Peiris to the

1 podium.

2 (Applause)

3 CONSIDERATIONS FOR THE SELECTION AND USE OF CLINICAL  
4 OUTCOME ASSESSMENTS IN SPECIAL POPULATIONS

5 DR. PEIRIS: So while I'm getting situated up  
6 here, I'll invite our panelists to go ahead and take a  
7 seat and then we can hopefully get the process started  
8 as soon as we finish. I'm hoping everyone has had a  
9 great morning. And I'm looking forward to a very  
10 interesting conversation today.

11 We fortunately, and I thank Michelle for  
12 highlighting my name, but the reality is it's everyone  
13 that's up here that really is going to give you the key  
14 information. And I think that is going to be where the  
15 brilliance of this conversation comes.

16 We have a very simple task today. So all of  
17 this conversation that's been happening about how we  
18 clarify patient perspectives and patient interests and  
19 what's really significant to the patient experience in  
20 all the work that we do in developing medical products  
21 today for our panel we just have to do it for the  
22 special populations, easy enough, right, not too hard.

1 So let me ask all of you, when you think about special  
2 populations I -- and really we want to create this  
3 panel in a very engaging audience engaged manner, shout  
4 out what you think a special population is. I'll start  
5 with the easy one, children.

6 SPEAKER: (Off mike).

7 DR. PEIRIS: Child, okay, got another second  
8 for children, good. Sorry?

9 SPEAKER: (Off mike).

10 DR. PEIRIS: Rare diseases, great, and  
11 everybody speak up.

12 SPEAKER: Minority population.

13 DR. PEIRIS: Minority populations. I heard  
14 orphans.

15 SPEAKER: Women of childbearing age.

16 DR. PEIRIS: Women of childbearing age, great.

17 SPEAKER: Elderly.

18 DR. PEIRIS: The elderly, perfect.

19 SPEAKER: Organ impairment.

20 DR. PEIRIS: Organ impairment.

21 SPEAKER: Mobility impaired.

22 DR. PEIRIS: Mobility impaired. This is good.

1 So I think we're done. No, I also want to ask all of  
2 you. How many of you knew that this conversation has  
3 been happening for decades in health care? Right.  
4 Even before I went to medical school and before I  
5 started training, this conversation's been going on.  
6 How many have heard of the population health dynamic in  
7 the practice of medicine? Great. A few people.

8 How many people recognize that in medical  
9 practice on a regular basis in hospitals that we do  
10 patient-centered or family-centered rounds almost every  
11 single day with our residents and nursing staff,  
12 medical students and the patients and their families?  
13 Great. So these are the things that have really been  
14 evolving in medicine for decades. And when I say  
15 decades, even back as the 1960s and 1970s when managed  
16 care was really beginning to take hold.

17 The concept of managed care really was, I  
18 think as Michelle alluded to, to bring in to create  
19 more value in the healthcare system, reduce costs,  
20 improve outcomes and truly create a healthcare system  
21 that helps patients and where patients are placed  
22 first. The managed care concepts have evolved quite a

1 bit from an economic standpoint but have also evolved  
2 from a social standpoint within medicine. And that --  
3 the social standpoint really has been training in terms  
4 of residents and young doctors about how to engage the  
5 patient voice first and foremost within the care that  
6 they provide.

7 Patient-centered round, when we do those, and  
8 family-centered around, especially in pediatrics and  
9 the elderly are a way of ensuring that the patient and  
10 family and caregiver voice is brought into the  
11 conversation regarding what's really important to  
12 helping that patient and that family unit get the best  
13 that they can out of the health care that they're being  
14 provided.

15 And as we have evolved, this entire concept of  
16 population health has come to be -- has really taken  
17 off and that -- the concert of population health really  
18 is one where we're beginning to take a look at how do  
19 we both combine the economic aspects of medicine,  
20 creating better value for -- within the health care  
21 system and adding the interests of the patients in an  
22 integrated manner, in an integrated whole. And I feel



1 that all the conversations that we're having now really  
2 are beginning to bring those concepts together in a  
3 more meaningful way. So without further ado, I'm going  
4 to ask each of our panelists to provide a brief  
5 introduction to their background and their interests in  
6 special populations and perhaps we can have an engaging  
7 conversation after that. So maybe we can start at this  
8 end.

9 MS. CRUZ: I was afraid I'd be first. Good  
10 morning everybody. My name is Rosangel Cruz and I am a  
11 Director of Research and Clinical Affairs at Cure SMA,  
12 spinal muscular atrophy, which is a rare disease,  
13 neuromuscular disorder that affects brain, lower motor  
14 neuron and muscles, and therefore a child's or an  
15 individual's ability to essentially live, breathe,  
16 move, function.

17 My role at Cure SMA, I work very closely with  
18 pharmaceutical companies in the SMA drug development  
19 space and other nonprofit organizations essentially to  
20 ensure that we do bring the voice of the patient to the  
21 regulatory process, that we very clearly understand the  
22 need of the patient, that it is incorporated in

1 clinical trials as well as the way that the regulatory  
2 authorities understand the disease, that spectrum of  
3 the disease, the way it manifests at different ages and  
4 stages. And last year had the pleasure to organize and  
5 bring together a patient-focused drug development  
6 meeting for this community.

7           Again it was a privilege for me as I had the  
8 opportunity to work with these families in clinical  
9 trials for years managing what was the first  
10 exploratory trial and what resulted in what is now a  
11 treatment that's available for these patients. So I'm  
12 very committed to representing the voices of these  
13 patients, I understand the pain and the -- the  
14 trajectory of the disease. And everything I do stems  
15 from that. So it is my pleasure to be here and thank  
16 you for allowing me to speak on their behalf.

17           MS. DONAHUE: Good morning. My name is Katie  
18 Donahue and I'm a medical officer in the Office of New  
19 Drugs and my work focuses on rare pediatric diseases,  
20 specifically inborn errors of metabolism. I'm  
21 interested in sort of the role of cognitive impairment  
22 and the ability to respond to patient reported

1 outcomes. It's a feature of many of the diseases that  
2 I work with and it presents some unique challenges and  
3 thinking about PROs. Thanks.

4 DR. GREEN: Good morning. My name is Dionna  
5 Green and I'm the deputy director of the Office of  
6 Pediatric Therapeutics at FDA in the Office of the  
7 Commissioner. And prior to being in the Office of the  
8 Commissioner I worked for many years in CDER, the  
9 Center for Drug Evaluation and Research and the Office  
10 of Clinical Pharmacology with the pediatric clinical  
11 pharmacology staff and the guidance and policy team.  
12 And my passion is focused on improving clinical trials  
13 for children.

14 I'm really excited about how far we've come  
15 already in the short span of 20 years or so in terms of  
16 encouraging studies in children as well as encouraging  
17 thoughtful designs of clinical trials in children so  
18 that we have the best chance of success. And so my  
19 interest is to identify tools and aspects and features  
20 of design that can help improve success for clinical  
21 trials in children.

22 DR. LAPTEVA: Good morning. My name is

1 Larissa Lapteva, and I am the associate director in the  
2 Division of Clinical Evaluation Pharmacology and  
3 Toxicology in the Office of Tissues and Advanced  
4 Therapies in the Center for Biologics.

5 I work with clinical development programs  
6 across different therapeutic areas. And most of the  
7 products that we see in the Center for Biologics,  
8 particularly in the Office of Tissues and Advanced  
9 Therapies that are developed for the treatment of rare  
10 diseases or programs that pediatric populations and  
11 other special populations may be enrolled in. So in my  
12 longstanding interest throughout my FDA tenure is to  
13 help successful development programs with more products  
14 on the market.

15 DR. NELSEN: I'm Linda Nelsen. I lead the  
16 patient-centered outcomes team at GlaxoSmithKline. And  
17 my interest is that across my career I have wrestled  
18 with development of pediatric measure as well as COA  
19 for rare disease with very heterogeneous expressions,  
20 sometimes wrestled with it successfully, sometimes  
21 less, so I'm interested in understanding better  
22 approaches so we can make sure we bring clear

1 statements of treatment benefit as well as risk and  
2 understanding of patient experience to our drug  
3 development.

4 DR. TUCKER: Good morning. So I'm Carol  
5 Tucker, I am actually a physical therapist, so I've  
6 practiced clinically for about 40 years. My interest  
7 is primarily in those kids that have mobility disorders  
8 particularly from the child onset condition. I also  
9 have training within some of the big data and analytics  
10 and had the honor to work with several people here  
11 within the Promise (ph) and within the Pepper Project  
12 (ph) which are as focused on developing PROs. And  
13 methodologies to capture both adult but in my case  
14 particularly child health.

15 DR. PEIRIS: Thank you very much. I just want  
16 to say thank you to all of you for actually taking the  
17 time to come here and help us today.

18 (Applause)

19 DR. PEIRIS: I know a lot of you have had some  
20 very exciting mornings, so glad everybody made it.  
21 What I'm going to do right now is help engage all of  
22 you. This isn't intended to be maybe the regular types

1 of panels that we have where go through question by  
2 question unless we need to do that. I'd like to ensure  
3 that there is audience participation. And please feel  
4 free to come to the mic at any time during the  
5 conversation if you have a relevant point or question  
6 related to the conversation that's taking place and  
7 we'll try to engage this in a more integrated manner.

8 I do want to highlight maybe some of the  
9 general areas or the framework that we've been charged  
10 with engaging today for this panel and that area really  
11 is to verify, number one, have we actually considered  
12 all the appropriate special populations, do we capture  
13 all the groups in a meaningful manner and do we  
14 understand what those groups are.

15 I'm going to go through a few of the other key  
16 questions that we'll be trying to address. One of them  
17 is how do we determine what's the appropriate age or  
18 the reasonable age at which somebody can self-express  
19 their desires and wants, especially in pediatrics. How  
20 do we understand what is a reasonable level of  
21 cognitive function for somebody when they are -- when  
22 we are considering engaging them in expressions of

1 their desires regarding their health care. How do we  
2 select the right timing in terms of self-reporting  
3 especially for people that are moving through different  
4 cognitive levels as they gauge in their health care  
5 process and experience their health care process.

6           And when we think about special populations,  
7 minority issues were brought up, are we -- how do we  
8 and are we engaging all the right multicultural,  
9 multinational, multilingual populations. And with  
10 respect to those populations how do we appropriately  
11 engage them in the issues that are important to them.  
12 I'm going to leave those questions there for all of you  
13 to be considerate of and we'll start back with that  
14 first question about, and Dionna I'm going to bring  
15 this for you to begin the conversation on what's -- how  
16 do we consider and determine a reasonable minimum age  
17 for self-reporting in a reliable manner.

18           So I think this is a really important  
19 question, and I think it's important to, you know, from  
20 the start recognize that this may vary depending on the  
21 COA of interest and a focus and as well as the disease  
22 or condition that's being studied. So particularly if

1 the disease or condition impacts cognitive functioning.  
2 But in terms of depending on the COA, so for example  
3 it's important to ask questions such as, you know, how  
4 simple is the COA in terms of language because we've  
5 already discussed and you heard yesterday that that's  
6 an important aspect in terms of pediatrics and their  
7 ability to comprehend and understand the context of  
8 what's being asked of them or what's being measured,  
9 what they're being asked to report.

10           And so it's important to think about is the  
11 language age-appropriate, is it simple in a way that  
12 developmentally the child or the age group that's being  
13 focused on can understand and can interpret. It's also  
14 important to think about how complex is the COA. So  
15 for example in a performance outcome is it  
16 developmentally appropriate for all pediatric age  
17 groups and does it require complex maneuvers or  
18 attention for a focused period of time or sustained  
19 physical activity, those are all things to be thinking  
20 about as you think about whether or not it could be  
21 appropriate or what's the minimum age to perform or to  
22 self-report.



1           It's also important to think about what are  
2           the -- what is the recall time and the duration that  
3           you would have the child be able to self-report. So if  
4           you're capturing symptoms perhaps in a diary are those  
5           symptoms being captured adhoc, are they being captured  
6           daily, weekly, monthly. The longer duration in terms  
7           of having to recall their symptoms and their  
8           experience, that can be particularly challenging for  
9           younger patients and so that may not be suitable or  
10          feasible for certain age groups. So that's something  
11          to keep in mind.

12           But as you think about all these factors, it  
13          helps you to hone in on what is appropriate in terms of  
14          that minimum age. So you really have to think about  
15          the COA that you're focused on and you really have to  
16          think about some of those questions that I just  
17          mentioned in terms of whether or not a child as young  
18          as 2, a child as young as 6, a child as young at 8 will  
19          be able to perform or report those factors.

20           And having a blanket statement to say, well,  
21          perhaps a child around 8 years of age can self-report  
22          can be a helpful sort of ballpark to aim for, but at

1 the same time it really does depend on what's being  
2 asked as I mentioned. So I wouldn't get stuck or  
3 limited in terms of a certain age but instead think  
4 about what's being asked of the patient and whether or  
5 not it makes sense developmentally for all age groups.

6 DR. PEIRIS: Thank you. How many people out  
7 there have children? Great. How many people know a  
8 child? How many people know some adults that act like  
9 children? Great. Try to consider myself in that  
10 portion of the population. And the reason I mentioned  
11 that is it's not just for humor but also for its  
12 relevance here to the points that Dionna is making.  
13 When we think about children, do -- does everybody  
14 think that a 5-year-old and a 7-year-old respond the  
15 same way cognitively?

16 I'm getting some semi-nods, perhaps nods,  
17 perhaps yes. How many people believe that girls that  
18 are 5 have better cognitive abilities or emotional  
19 quotients than boys that are 5 or boys that are 7? See  
20 these -- and the reason I bring this up is because not  
21 only to clarify that there are mild -- even within  
22 small age ranges there are mild variations or beliefs

1 of our variation but there at times are true  
2 variations. And it's not necessarily sex or gender-  
3 based. And the -- for instance, if we have patients  
4 that are coming in for cancer therapy in pediatric  
5 hospitals, many of those patients have actually engaged  
6 in the health care system so frequently and so often  
7 that they've actually had -- they have a very different  
8 experience in life than perhaps a childhood that didn't  
9 have to engage in the healthcare system.

10 Those patients tend to have a far more  
11 effective way of communicating their desires and wants,  
12 especially with their doctors and healthcare providers  
13 and nurses and respiratory therapists, all of those  
14 people that take care of them partly because they have  
15 been engaged in that process, a little bit of it is  
16 that they have been trained in that process. We have  
17 phenomenal child life specialists in hospitals that  
18 help children begin to express how they are feeling in  
19 different ways with different types of activities.

20 But again the point is that even a 7-year-old  
21 who has been engaged in the healthcare system for quite  
22 some time may be able to express themselves very

1 differently than perhaps a 8-year-old or 9-year-old who  
2 hasn't been engaged in the healthcare system and those  
3 are issues to be cognizant of and considered of as we  
4 think about the right age and Rosangel, I want to bring  
5 up the issues regards SMA, if you can help the audience  
6 understand a little bit more about what SMA is and may  
7 be just some perspectives on how SMA may affect or a  
8 patient with SMA may have differences across the age  
9 range in terms of they how they might be able to  
10 express themselves.

11 MS. CRUZ: Thank you for that. So as I  
12 mentioned, SMA is a degenerative neuromuscular  
13 disorder. So it affects about 1 in 11,000 children, so  
14 it's quite a rare discussion; however, to me it seems  
15 like everything that I see, so it doesn't seem so rare.  
16 Essentially SMA is a spectrum disorder, so 60 percent  
17 of children born with this disease are born with the  
18 most lethal and severe type, that's called SMA type 1  
19 and those children essentially present symptoms before  
20 the age of 6 months, 2 months, 3 months, hypertonia,  
21 inability to raise their heads, very little movement.  
22 By the time they are about 6 to 7 months, they

1 essentially require supportive equipment to live, from  
2 G tube or gastrointestinal feeding to BiPAP masks or  
3 equipment to help them breath, to help them eat, they  
4 never acquire in the natural history of the disease the  
5 ability to sit. About 75 percent of the children  
6 succumb to the disease before the age of 2. So it's  
7 really life threatening and very -- effects every  
8 aspect of a child's life and therefore the way that the  
9 parent needs to look after this child in order to  
10 ensure he or she survives.

11           There is an intermediate type that about 27  
12 percent of individuals are born with, this is the type  
13 2 and those children are able to sit, they crawl,  
14 present with regression, are never able to walk, but  
15 have a fairly normal life in the grand span of things.  
16 With time the disease progresses and declines very  
17 steeply and then it reaches a level of stability.

18           And then the type 3 are walkers. So about the  
19 age of 3, 4, may be they start stumbling, they fall, so  
20 this is all one disease with very different  
21 presentations and for example, the most severe type,  
22 everything that we know about those children and the

1 reported outcomes comes to the parents. Obviously we  
2 do have a top intend in other physiological outcome  
3 measures to determine improvement in function. But  
4 then in terms of quality of life or anything of that  
5 sort comes through the parent. Even when they are  
6 adults, these children have such little movement or  
7 those that make it to adulthood that are unable to  
8 speak at all, utter anything, produce language even  
9 though they are cognitively very smart and very able  
10 and compared to the sort of the average population  
11 these kids are all like college, three graduate  
12 degrees, incredibly smart.

13           So for kids like type 1, they are there, they  
14 are ready, they are precautions, they are funny and the  
15 parents are their eyes and their mouths and so when we  
16 talk about a PRO or, you know, I think of these  
17 children are -- the type 1s are adults that essentially  
18 they communicate sometimes through eye gaze. So that's  
19 an important thing that I think we should consider.  
20 Also as part of a potential mechanism for catering, how  
21 patient feels or quality of life in this population or  
22 any other population with movement disorder that are

1 unable to express themselves in words or even writing.

2 I don't know if that helps.

3 DR. PEIRIS: That's great. Thank you. Katie,  
4 I'm going to let you know that you are going to be able  
5 to bat next, but when we talk about the issues that you  
6 described with respect to SMA, we bring into the  
7 conversation the relevance of a parent speaking for a  
8 child, right, especially a child, most of the time,  
9 parents speak of children all the time, they should,  
10 there are times when obviously a child cannot express  
11 themselves either due to their developmental levels or  
12 because of the issues that they are dealing with, with  
13 respect to their healthcare. When we consider how the  
14 practice of medicine between adult medicine and  
15 pediatric medicine has evolved, we tend to think or at  
16 least I tend of think of pediatrics as a very evolved  
17 level of medical practice. We are taking care of some  
18 of the most vulnerable of our population, but also the  
19 children that have potentially the most gain from  
20 exceptional healthcare.

21 But when we talk about the paternalistic  
22 aspects of medicine, we start to recognize that perhaps

1 in pediatric medicine, we're not as evolved with  
2 respect to letting go of that paternalism as we might  
3 be in adult medicine and it's not necessarily a  
4 criticism, but perhaps just a critical perspective and  
5 what I mean by that is many times in most cases related  
6 to significant intervention, significant therapies in  
7 the pediatric realms, most families will just take the  
8 word of the doctor, whoever is taking care of them,  
9 that pediatrician, that pediatric subspecialist,  
10 whatever they say usually goes and there isn't as much  
11 of a deliberation about what truly the child may want  
12 or needs and there is a reason for that because again  
13 there is always that inherent paternalism that exists  
14 between that patient, parent patient bond or parent-  
15 child bond and those issues I think need to be  
16 considered when we understand how paternalism affects  
17 what we do and I want to recognize that as we move  
18 through the developmental spectrum, especially in  
19 pediatrics, there are differences obviously as I  
20 mentioned, what a 5-year-old could tell you versus  
21 perhaps what a 15-year-old could tell you and when we  
22 think about changes in cognition, changes in ability to



1 self-report what's important to you, not just in a  
2 progressive advancement, but also in variability in  
3 each, you may actually get to a level where you're  
4 actually able to express yourself very well when you're  
5 in midlife and then move towards a level where you  
6 might not be able to express yourself as much as you'd  
7 like to be able to as you move into elderly levels and  
8 perhaps have issues related to dementia or Alzheimer's.

9           And Katie, I was wondering if you can start  
10 the conversation regarding that transition in terms of  
11 cognition and the variability in cognition that's  
12 important when we are considering COAs.

13           DR. DONOHUE: Thanks. I'm happy to speak to  
14 that. I think working in rare diseases, a central  
15 challenge is separating signal from noise. We need to  
16 get new therapies to patients and to do that we need to  
17 be able to separate signal from noise. And so my  
18 considerations here are really practical and I think  
19 you raised a good example of patients who are  
20 cognitively intact and could contribute very  
21 meaningfully to the clinical investigation, but perhaps  
22 need assistive technologies. And so any time we can

1 remove obstacles, remove barriers and get right to what  
2 patients are experiencing, I think that increases our  
3 ability to separate signal from noise and so I think  
4 that's a really important contribution to the  
5 discussion.

6           And in some ways I don't like this question,  
7 what other factors need to be considered when  
8 determining a reasonable minimum level of cognitive  
9 function. So I think the challenge with diseases that  
10 can impair cognitive function is that signal-to-noise  
11 problem, right. And so if there is a lot of  
12 variability over time for example in cognitive  
13 function, so if it fluctuates during the course of the  
14 clinical trial, we have got to think about that. That  
15 may make it noisier and harder to tell.

16           And then similarly what about patients who  
17 move between a self-report status and an inability to  
18 self-report. So what if that's informative, right, in  
19 rare diseases is we need to use all the data that we  
20 have and so if that's part of the natural history of  
21 your disease and if you think because our trials are so  
22 small, we often have to have them run for a long time,

1 one, sometimes two years and so that's a lot of time  
2 when you're dealing with pediatric patients. But if a  
3 patient goes from, you know, if you have more patients  
4 in your treatment arm who go from being unable to self-  
5 report to being able to self-report, well, may be that  
6 treatment is working, right, like that could be  
7 informative.

8           Similarly if you have a lot of patients in one  
9 trial arm that go from an ability to self-report to an  
10 inability to self-report, well, that -- may be that  
11 data is not missing at random, right, that's telling us  
12 something and we need to pay attention to that. So one  
13 thing would be to think about what's the likelihood  
14 that patients are going to switch status during the  
15 trial and is that informative and how do you want to  
16 treat those data, can you define that as some sort of  
17 responder definition.

18           So that's that piece and for the minimum level  
19 of cognitive functioning, particularly in rare diseases  
20 where the natural history generally is less well  
21 understood. We heavily encourage sponsors to do formal  
22 cognitive testing even if they don't want to do formal

1 cognitive testing as an endpoint, that's a tough  
2 endpoint to hit in clinical trials, even though it's  
3 very important to patients. But even if that's not  
4 going to be the final endpoint, we often encourage them  
5 to do that sort of in the run-up to their trial to help  
6 select endpoints that are going to be feasible for  
7 patients and I think there's a lot of value in really  
8 formally assessing that. Sometimes parents and  
9 clinician's perceptions of what's possible are really  
10 off base and we have seen that play out in a few of our  
11 clinical trials where the conventional wisdom coming in  
12 turned out not to be the reality in terms of what  
13 patients were really able to do and we may be  
14 underestimating our patients and we may be  
15 overestimating their level of ability and either way  
16 that makes it hard for us to show that a new treatment  
17 is working and we have to, you know, our job is to make  
18 sure that we are getting effective treatments to  
19 patients. So we have got to minimize that noise.

20 And formal cognitive testing I think is an  
21 overlooked tool for really evaluating these patient  
22 populations and making sure that we have a solid

1 understanding of at a population level, the cognitive  
2 functioning of patient and then in very rare diseases  
3 where sometimes you know who your patients are going to  
4 be before you start the trial because there's only so  
5 many in the world and they are sort of known to your  
6 community of investigators, it's that much more  
7 important for choosing endpoints and COA instruments  
8 that are going to be suitable for those patients,  
9 right. Age may not be your best predictor, you may  
10 really just need to do individualized cognitive testing  
11 to figure out, okay, is this patient going to be able  
12 to do a patient reported outcome or are we going to  
13 need an ObsRO and what might that look like. Thanks.

14 DR. PEIRIS: Thank you. Any other panelists  
15 that have thoughts on this?

16 UNIDENTIFIED SPEAKER: I just had a quick  
17 reaction to what you said and thank you for that. It's  
18 just when you are talking about the noise and sort of  
19 like what does the change mean in a specific population  
20 and I just kept thinking, well, this is why we need  
21 robust natural history studies, like you can't go into  
22 a trial not knowing what two years of life in this

1 population looks like for you before you start  
2 assessing that patient because then nobody will know  
3 what's drug, what's natural history. So for us, I  
4 think for SMA as a rare disease, one of the things that  
5 really did help our cause and how to essentially find a  
6 treatment, viable treatment for all patients with that.  
7 There were many, many patient groups and academicians  
8 and folks that were very invested in the understanding  
9 because otherwise how do you prove anything. So I just  
10 wanted to say, and also I think COAs need to be driven  
11 by the mechanisms of the drug, like if it doesn't  
12 affect speech as far as we know, even though it is  
13 important to the patient, is it fair that we are  
14 measuring speech when it's actually working on the GI  
15 system. I'm just kind of randomly making something up.  
16 But I think that that's also relevant is the  
17 understanding of the biological, pathophysiology, the  
18 biomarkers, vis-à-vis how that reflects and the  
19 behavior, but I love how you guys call it signs and  
20 symptoms and seeing things in a disease and then what  
21 is the expectation and then the other aspect is  
22 understanding what's important to the patient, how do

1 we target that in a drug. So we go from here to here  
2 to then go back from patient to how do we address that,  
3 it's just what we try to do.

4 UNIDENTIFIED SPEAKER: I think one of the  
5 things we, as we are considering developing or  
6 modifying COAs for children who are cognitively  
7 impaired, it would be important to do concept  
8 elicitation or qualitative research against the most  
9 extreme ends you can consider. You might find that  
10 young children experience the disease in a different  
11 set of symptoms or a different expression, they might  
12 express a concept like shortness of breath or chest  
13 tightness differently than an adult would. You would  
14 be surprised you can -- my favorite was interviewing a  
15 6-year-old child who could describe chest tightness as  
16 the feeling of wearing skinny jeans around her chest.  
17 She clearly knew what chest tightness was, but we  
18 needed -- would need to find a way to create a question  
19 that's appropriate to children. Some diseases have  
20 very different expression, eosinophilic esophagitis is  
21 one that's well known where young children have  
22 vomiting and reflux, adults have dysphagia. So a

1 questionnaire adapted from adults to children simply  
2 won't work.

3           So if you do concept elicitation and push it  
4 to the extremes, you can begin to find ways where it  
5 might be expressed, either the disease itself or the  
6 way children can express that concept in a way that's  
7 friendly to them and then begin to think about  
8 developing measures that relate to their abilities and  
9 from a very practical drug development perspective, we  
10 would want to make sure that those ranges are  
11 overlapping. If I move into a clinical trial and only  
12 have ePRO for age 4 to 8 and from 9 to 15 and my  
13 clinical trial needs to cover a different age range,  
14 it's really difficult. And so if these have  
15 flexibility around them, it will also enhance our  
16 ability to use them.

17           One other thing I wanted to add, one reason to  
18 try to live within ePROs as much and avoid ObsROs as  
19 sort of a quick fallback is there is so much richness  
20 we lose with only an ObsRO. I can get insight into  
21 pain or shortness of breath or sleep or fatigue when  
22 I'm limited to an ObsRO and so as often as we can find



1 ways, bring the patient's own voice in, in ways that  
2 are acceptable to that group, I think the better off we  
3 are and the better sense we have of how the patient is  
4 feeling and functioning.

5 DR. LAPTEVA: I would echo the previous  
6 comment. I think it is absolutely essential to really  
7 weigh into the ages and be able to reformulate  
8 questions according to the age related understanding.  
9 But I also wanted to at that speaking of the first  
10 bullet, maybe make an analogy, in clinical research  
11 adult patients or adolescent patients can give informed  
12 consent and then there is and then do you want me to  
13 speak more about it. There is a pediatric assent and  
14 over the years there've been multiple considerations  
15 for what would be the right age of assent and then  
16 essentially what is currently considered is really not  
17 any specific age of assent, but rather whether a child  
18 could be not just following directions or agreeing to  
19 do something within a clinical study or clinical trial  
20 or even natural history study framework, but whether  
21 they are actively willing to participate and what's  
22 their psychological state at the time and in the

1 nearest future as well as the maturity level. And so  
2 all of these factors are really important I think for  
3 self-report and really for participation in the kinds  
4 of studies that we are talking about today and  
5 yesterday and in finding right clinical outcomes  
6 assessments.

7 MS. NELSON: Also, well, I wanted to speak  
8 about one other special population, but if you like to  
9 continue. Okay. So because that topic I think is  
10 particularly important as we are defining relatively  
11 general, very few types of populations that are  
12 considered special populations in the drug guidance. I  
13 just wanted to perhaps speak about one other  
14 population, which I think qualitatively perhaps  
15 different from all of the, about what we have just  
16 talked about and this would be people with ongoing or  
17 progressive decline in their sensory input and I'm  
18 talking about folks who have visual decline or auditory  
19 or tactile changes because the level of communication  
20 may be again qualitatively different.

21 I would like to give one example, we are at  
22 the stage when products, new therapies for folks who

1 have visual changes, auditory changes, we are at that  
2 stage where these products are not science fiction  
3 anymore, they are actually something that can be  
4 potentially investigated and made. I will give you one  
5 example, we've recently in the Center for Biologics  
6 approved a treatment which was a gene therapy for  
7 patients with rare genetic disorder and that gene  
8 therapy was a product that's called Luxturna voretigene  
9 neparvovec, it is a subretinally administered treatment  
10 that corrects a genetic mutation in the cells inside  
11 the human eye. This is very interesting and the  
12 particular story I think from the perspective of  
13 clinical outcomes assessment development because when  
14 the therapy was just at the initial stages of  
15 development, it was quickly recognized that the  
16 outcomes that were clinical outcomes that were  
17 available at the time were not really adequate to  
18 detect the change in that particular condition and the  
19 rare genetic disorder. And the developers with the  
20 help of patient community as well as the expert  
21 ophthalmologists developed this, again somewhat  
22 different outcomes assessment, it wasn't just a measure

1 of vision, it was a measure of functional vision, it's  
2 called multi-luminance mobility test and it reflected  
3 the ability of a patient to navigate through a course  
4 at different levels of light, which was very meaningful  
5 for patients with this condition and so it ended up  
6 being a success story, but I think because of many  
7 other factors why it became a successful development  
8 program, one of those very important aspects was really  
9 finding the right clinical outcomes assessment  
10 specifically for this very special population. So I  
11 think we should not forget about folks who have decline  
12 in sensory input. That's another special population.

13 DR. TUCKER: Yeah, so a lot of great comments  
14 to start with and as I had mentioned, I work a lot with  
15 kids that have either respiratory or mobility  
16 impairments and the comments that Linda made really  
17 resonate with me. I think we really have to take away  
18 our adult lens of what might be important to these  
19 children and really think about it from the kids'  
20 perspective about how they report. I do a lot of  
21 physical activity and if I were to ask each of you, how  
22 much did you exercise in the last day, you do exercise

1 as kind of a fit part may be of your schedule or  
2 hopefully you do. Kids embedded in play and we found  
3 that they really respond better to asking about  
4 physiological symptoms and those things in terms of  
5 reporting and making it more robust. So we can  
6 repurpose adult measurement or even adult lenses.

7 I think looking at the guidance document to  
8 really emphasize some the qualitative research aspects  
9 in developing measures or readopting them from one  
10 pediatric group to the other. When we look at  
11 impairments and structures and functions and symptoms  
12 which are lot of biologics, there may be other things  
13 other than self-reporting kids that work well, but when  
14 you move up a little bit, it's really participation  
15 that the family is often interested in, what does that  
16 child do, do they walk, do they talk, what is the job  
17 of a 1-year-old. It may not necessarily be at that  
18 biological endpoint and so I would make the case that  
19 for some of these family important or children  
20 important that you look at them from the long  
21 perspective and then the only other comment I'd like to  
22 add is I feel pretty confident being in the field I'm

1 in that whether they; however, if they have the  
2 cognitive capacity to understand health and the younger  
3 you are, health is kind of a mixed thing, it may be  
4 that your arm hurts, but you may be relating it to  
5 other things going on or you have a headache, but it's  
6 your full body that's kind of impacted by it, it's not  
7 adults that tend to have discrete streams, but a lot of  
8 kids with child onset condition, it's part of them.

9 I may have, well, I have gray hair now, but I  
10 may have had light brown hair when I was younger and  
11 blue eyes, but if you talk to a child with cerebral  
12 palsy, that's just part of them and so our adult  
13 perspective of what's important to them to be fixed may  
14 not necessarily be the same thing to them because they  
15 view it and so as I said, I worked and promised and we  
16 had a lovely set of measurements about stigma, but the  
17 question started with does your disease and when we  
18 pivoted it to children or adolescents, with an adult or  
19 with a child onset condition like I don't have the  
20 disease, it part of me. And so really I think for the  
21 guidance I would really recommend that we embed some  
22 flexibility and some really purposeful qualitative

1 assessments to look at it and just also think about the  
2 mode that we are asking those questions and I have  
3 worked at Shriners and within rehabs and if I ask a  
4 child there if they can hop, they may say no, I can't  
5 hop and I look at them because they're hemiplegic and  
6 say, well, hop on your left foot and they're like,  
7 well, I can hop on that, but why didn't you tell me  
8 that or why don't you consider that. Well, when I come  
9 to the hospital, you're always interested in what is  
10 wrong with me and what you can fix, you never really  
11 focus on what I can do.

12           And so as we look at these measures, if we are  
13 really looking at their impact out in the community, it  
14 may be thoughtful about all the problems associated  
15 with web-based or sensors are wearables or things that  
16 are out there, it gets really mucky. But that maybe  
17 actually what we want to change because they will tell  
18 you within some of those clinical settings what they  
19 think your here to say. So I will just stop there. So  
20 I think cognitive I went into a whole bunch of things  
21 beyond cognitive, but I think those things really, it's  
22 more than just cognitive understanding and self-report.

1 DR. PEIRIS: Thank you very much. How many  
2 people have actually ever felt tired after a long week  
3 or a long day? Yeah, a few of you. I have been there  
4 as well. So when you are feeling tired, do you respond  
5 to your world in the same way that you do when you're  
6 feeling happy, excited, exuberant, full of life? Not  
7 necessarily, right? And this is the point that's being  
8 brought up here is that a lot of these children or  
9 really it applies to anybody across the age spectrum.  
10 When you're engaged in a critical situation or  
11 something that is part of your life every single day  
12 and people are asking you about it and trying to fix  
13 you, it really begins to wear on you and how you  
14 respond at that moment especially during that  
15 questioning period may be very different in terms of  
16 how you live your life every single day outside of that  
17 healthcare room.

18 The other point that was brought up about  
19 observer related information versus patient specific  
20 information that's being accessed, I would just want to  
21 reemphasize that point about getting information  
22 straight from the patients and especially if you ask it



1 in the right way for the right population, you will be  
2 able to assess a great deal more about their experience  
3 than you might just from an observer. For instance,  
4 something very fundamental to our health like sleep,  
5 right, you might never really ask an observer about how  
6 their patient is sleeping and even if they think that  
7 they are sleeping and they are in bed for eight hours,  
8 that sleep may not be very good. If you ask that  
9 patient about that experience, it could be far more  
10 meaningful and that information can actually make a  
11 significant difference in both how you manage that  
12 patient and understand what's going on for them every  
13 single day.

14 I will give you a very simple example,  
15 something that all of us I think can relate to just to  
16 get a sense of what, if you just almost exponentially  
17 increase those issues when we are considering what a  
18 person living and experiencing and engaging with the  
19 healthcare system for most of their life is really  
20 going through, so just to be cognizant of that.

21 So maybe we can transition if -- before we  
22 transition to the issues regarding multinational,

1 multilingual and cultural, I just want to make sure,  
2 are there any questions that the audience has regarding  
3 the topics that we've addressed, especially with  
4 respect to development, progressive advancing  
5 development, variable issues when you're actually  
6 engaging with the healthcare system or dealing with  
7 your "disease" or variability in terms of what's going  
8 on with respect to your cognition especially as you're  
9 being given therapies. Any questions, comments?

10           So before we move on, I just want to bring up  
11 one other point that was alluded to and perhaps just to  
12 emphasize that. For many patients when they are  
13 actually coming into a hospital, especially for  
14 patients that are in critical health, they get  
15 medicines, right. Each one of those medications  
16 influences how they're feeling, their cognition, their  
17 ability to really convey information. Let's take the  
18 patient that doesn't get any medicine, let's take for  
19 example the -- let's take a pediatric heart failure  
20 patient, right. My field is in congenital heart  
21 disease and I just wanted to emphasize the point that  
22 was brought up in terms of translating adult related

1 measures to pediatrics. We can't really ask the same  
2 questions as has been pointed out in a pediatric  
3 population that we would ask in an adult population.  
4 Pediatric patients that have actually lived a very  
5 healthy, exuberant, active life and started to have  
6 symptoms of heart failure may experience that in very  
7 unique and subtle ways that would not be the same in  
8 terms of how an adult patient experiences it and we  
9 also think about perhaps gender or sex differences,  
10 that applies in pediatrics as well.

11 I will give you one personal example. I had a  
12 patient that came to me after having had a couple of  
13 years of what they called questionable therapy from a  
14 number of their doctors and one of their doctors  
15 referred them to me saying that you really got to go  
16 figure out whether this is something to do with your  
17 heart. This is a patient that is at the top of her  
18 game with respect to swimming. She conveys the  
19 experience, she used to win all of the time and this  
20 was when she was 12, 13, 14. Now she is considering  
21 applying for scholarships at some of the top  
22 universities across the country and she is recognizing

1 that it's becoming more and more challenging for her to  
2 maintain that status of winning all the time and she's  
3 not really sure what's going on and she's really unable  
4 to, when you just ask her, she tells you, everything's  
5 fine, I'm really just here because my parents are  
6 worried, my doctor is worried and they just want me to  
7 get checked out. She really didn't want to admit that  
8 she's not doing as well as she could especially because  
9 this issue regarding college acceptance is very  
10 important to her and she definitely doesn't want to put  
11 it out there that perhaps she is unable to do as well  
12 as she thought she was, very similar to perhaps a  
13 football player or a professional athlete that doesn't  
14 want to convey the transitions that they're going  
15 through as they age in terms of their performance.

16 But for this patient the subtlety of her  
17 ability in terms of comparing her performance to, let's  
18 say, another child her age, she can outperform me and I  
19 used to be an athlete at some point in my life and I  
20 know that there are other children that are at her age  
21 that she can outperform. We did a treadmill test and  
22 she is far towards the 99th percentile. But how she is

1 feeling about her abilities is very different.  
2 Fortunately she actually didn't have a cardiomyopathy,  
3 but she had more of an undiagnosed or perhaps a  
4 misdiagnosed level of asthma that was exacerbated when  
5 she was in the water especially with respect to the  
6 breathing that it takes to perform at the elite level  
7 that she needs to perform at.

8           So for her, comparing her to another child or  
9 even another exceptional some -- an athlete with a  
10 great ability was not the comparator that was  
11 appropriate. For her it really was something at an  
12 elite level and we have to be cognizant again of those  
13 variations across the board and I think as we have  
14 these conversations, we are not really trying to say  
15 that oh this population is this way and this other  
16 population is always this way. I was told a long time  
17 ago, don't judge a book by its cover, and that's  
18 certainly not what we're trying to get to. But we're  
19 trying to begin to understand the nuances of  
20 variability that happened within a lot of these very  
21 special populations and sometimes elite athletes are  
22 also a special population.

1           So perhaps we can move over to the issues  
2 regarding multicultural, multinational and multilingual  
3 areas. And Linda, I'm going to open this one up for  
4 you, so if you can go ahead and --

5           MS. NELSON: Okay. So as many of you know,  
6 I'm sure, most of the -- probably almost all of the  
7 development programs nowadays include trials that are  
8 multiregional, multinational or at least multicenter  
9 trials and studies. We generally encourage, when a  
10 study enrolls patients from different centers, because  
11 at the end of the day when you look at the primary  
12 evidence of effectiveness of a product, you want to  
13 make sure that the effects are actually generalizable  
14 and they are not attributable to just one center where  
15 certain procedures have been run in a certain way. So  
16 most of these studies, if not all, are multiregional.

17           Now speaking of whether they're done  
18 oftentimes in other countries or in other cultures,  
19 there may be multiple reasons why sponsors of medical  
20 products do that and one end of this spectrum maybe  
21 multinational enterprises that have resources and  
22 capabilities and need fast recruitment and they would

1 go to different countries to recruit patients. On the  
2 other end of the spectrum maybe a small company whose  
3 portfolio includes one to two rare diseases and they  
4 have to go into every corner of the world to find those  
5 patients who, we all know, maybe quite dispersed  
6 geographically.

7           Besides the linguistic and obviously cultural  
8 understanding types of issues, in different cultures,  
9 in different healthcare systems, more so, people may  
10 have a different understanding of what constitutes  
11 improvements in the certain condition and the health  
12 care professionals may have different thresholds on  
13 when to start treatment, so all these factors actually  
14 need to be at least accounted for in contemplating and  
15 designing clinical studies. And when we're talking  
16 about clinical outcome measures and clinical outcomes  
17 assessments development, I would envision -- and this  
18 is from some of the programs that we see, there would  
19 be three more or less common scenarios. So one would  
20 be, is when you have to really start clinical outcomes  
21 assessment from scratch. And you by virtue of what's -  
22 - what would be the patient population in that disease

1 would have to go and include folks who come from  
2 different cultures in different countries.

3           And so, here you have to really do the hard  
4 work in formulating the questions and the items in  
5 reformulating them, adopting them to the cultural  
6 understanding. And the different -- and the devil  
7 there will be in the details as to how questions are  
8 asked, how verbal and nonverbal responses are  
9 interpreted. And so in those situations it's helpful  
10 to have one or more, however many you need, people from  
11 that culture who could actually help with adaptations  
12 of the items and then eventually with making sure that  
13 the domains and the concepts are represented  
14 appropriately. It is also helpful to include a cycle  
15 of nutrition at some point other -- either at this  
16 stage of development of a COA or PRO or at the stage of  
17 the validation, but that's just kind of optional.

18           So the second scenario, which is also  
19 frequently observed, is when you already have an  
20 instrument and you have already defined your concepts  
21 and you know how things are measured and the thresholds  
22 for what is considered improvement in what is



1 considered variation towards one or another answer has  
2 already been determined, but you want to validate it in  
3 an entirely different culture or language. And then --  
4 so that that is helpful to some extent, because things  
5 have already been predetermined and all you need to do  
6 is just to adopt culturally and maybe fine-tune some of  
7 the questions a little bit to ensure that that other  
8 cultural language interprets the same questions in the  
9 same way.

10           And then the third scenario, which is probably  
11 the most frequently seen, and oftentimes considered the  
12 probably the simplest, yet there are slips in that  
13 approach too. And that's when you have an instrument  
14 and you just enroll people from multicultural  
15 environment in a clinical trial, multiregional trial  
16 and you just translate that instrument, make sure that  
17 certain things are appropriately understood by another  
18 language or another culture, study participant. And  
19 you just send it to that other center and they would  
20 administer the instrument to the patients.

21           The slips happen when the instructors who give  
22 the questionnaire or administer the test are not

1 actually bought into the philosophy of the instrument.  
2 And so it's important to really provide training to the  
3 instructors to ensure that even though the instrument  
4 has been translated and culturally adopted, that the  
5 instructors and those who give the tests, the  
6 investigators in the study are properly trained on how  
7 to explain to the patient and what they need to do. So  
8 these are the -- and I think we put a number of  
9 checkpoints in the draft guidances about the assurance  
10 of feasibility, of obtaining data from different  
11 regions and appropriate timing and to ensure that the  
12 format and the content and the context of the questions  
13 and the stimulus that is elicited by a question would  
14 be kept the same across different the cultures when you  
15 are considering a COA development or administration.  
16 So I'll invite everyone else to participate in this.

17 MS. CRUZ: I actually have a question for the  
18 FDA. How do you ensure that the instruments that are  
19 adapted from one, say, disease to another are actually  
20 valid? And let me just elaborate on that. So we were  
21 using for some of the clinical -- I'm not going to say  
22 what clinical -- some clinical trials we were using a

1 PRL that was from one disease to another. When the  
2 children saw some of the questions, for example, how  
3 hard is it for you to walk? Type 2 patient never  
4 walked. Not hard at all. Yet, we're using that as a  
5 secondary endpoint or tertiary endpoint, I don't know.  
6 But we were using it. And the only way I realized it  
7 was really not of the best instrument is because of the  
8 reaction of the patients, right.

9           So this is not something that the doctors  
10 aren't really paying attention to or the sponsors for  
11 sure aren't, you know we're just, okay, we have an  
12 instrument and it's accepted. So how do you go from --  
13 and this is a challenge for all of us -- but from is a  
14 good enough outcome it's validated and for this  
15 disorder, it's good. Like, how do you assess that this  
16 is really representing the patient's voice and the  
17 questions are appropriately asked and measuring what  
18 they're supposed to measure.

19           MS. NELSON: I can respond from a sponsor  
20 perspective. I would be quite horrified to use a  
21 measure like that, because I would be likely having a  
22 nonresponsive endpoint, because you're asking a lot of

1 items and you can't possibly move in these children.  
2 You're not going to get them there. And it always  
3 starts with content validity. So even if you want to  
4 throw an existing measure in, you need to start with  
5 concept elicitation and interviews to make sure that  
6 the concepts that are important to patients actually  
7 exist in that questionnaire and cognitive debriefing to  
8 make sure those items are relevant to the patients and  
9 that the measure is comprehensive to their disease  
10 experience. So it starts always with talking to the  
11 patients at some level.

12 MS. CRUZ: What if you don't -- I'm playing  
13 devil's advocate here. What if you don't have anything  
14 else? This is what you have. You have a drug that you  
15 know works. You have your primary endpoint. You'll  
16 have three, five years to develop a new thing from  
17 scratch.

18 MS. NELSON: You can still do qualitative  
19 research in that patient population with an instrument  
20 in mind. So it will be a much shorter process. You  
21 may need to delete some items. You may need to then  
22 develop the second metric properties at risk during the

1 trial. So you're doing things at risk, but you're  
2 living in a rare disease population where if you plan  
3 ahead and anticipate the need, it's not going to be  
4 three to five years. But if you start without that  
5 evidence, you may have a trial that fails, because your  
6 measure is bad, not because your drug is bad.

7 DR. TUCKER: So yeah. And I think just to add  
8 onto that, that's where some of the -- in the past  
9 years, we've seen a little bit more item banking. And  
10 so in your case if you're talking about, you want to  
11 get rid of the walking items or maybe some of the other  
12 inappropriate ones, there may be banks of items where  
13 you can take out those and still managed to capture  
14 some of the range of the function, not always but  
15 sometimes.

16 But I also want to just bring up, which is why  
17 I raise my hand. That we also, I think, need to look  
18 at the responsiveness of these. So it is whether the  
19 items are appropriate or the concept is appropriate  
20 within the different cultures or regions. But I think  
21 we also need to look at the impact that change may have  
22 when we ask. So I do a lot of medical service down in

1 Guatemala. And here in the United States if I ask can  
2 you now do X, Y and Z, the answer may be yes. But  
3 within some cultures, where the dynamics of society and  
4 the opportunities for be it any of those, once human  
5 move kind of beyond this symptom level, and you're  
6 really looking at what they do in their day-to-day  
7 life, a measure that's responsive in the U.S. or a very  
8 rich environment where there are opportunities as your  
9 health improves to do more may not be available in  
10 other ones. And I think that comes back again, as  
11 Linda said, to really some deep testing and is it  
12 appropriate, but also to look at the fit of the  
13 individual and their environment for responsiveness and  
14 longitudinal measurement.

15 MS. NELSON: I would say it's sort of the same  
16 principle when you're adapting to multinational,  
17 multicultural. You want -- we often think of it as a  
18 frill to go out to a few other countries. So it's  
19 going to add time, it's going to add expense. In the  
20 end, you have a much better understanding. As Carol  
21 said, the symptoms are probably consistent, but the way  
22 it impacts may be very different across countries,

1 because the health care setting -- system is very  
2 different, because the experience of having caregiver  
3 support may be very different in different cultures.  
4 And therefore the impact of having limitations may  
5 differ. And so I think we need to at least cognitively  
6 debrief instruments across cultures to make sure they  
7 still fit and acknowledge that, yes, it will be more  
8 expensive and take more time. And yet, in the end, we  
9 should end up with a richer set of measures. And I  
10 think it speaks to the idea of being collaborative in  
11 precompetitive spaces and building on each other's  
12 knowledge, rather than think we always need to start  
13 from the beginning.

14 DR. GREEN: And I would just say that, I  
15 think, throughout this whole panel, basically the theme  
16 we're hearing is that conceptions or assumptions  
17 regarding what's important or what's relevant, coming  
18 from a lens that's fixed, may ultimately lead to  
19 something that's not relevant. And so whether it's  
20 cultures, whether it's age, whether it's cognitive  
21 impairment, I think, we have to move beyond thinking  
22 that we know what's important for the patient. And

1 instead, think about their unique scenario, think about  
2 their activities of their life, think about -- as was  
3 mentioned what would a one-year-old be doing what would  
4 a person who had this set cognitive impairment be  
5 doing, what's their role and function. Like, what is a  
6 baseline for whatever that particular scenario is. And  
7 I think that, as a starting point, will help us to  
8 think about special considerations when developing  
9 these assessments and tools.

10 DR. PEIRIS: Please go ahead.

11 MS. SPEARS: Yes, I'm Patty Spears, Patient  
12 Advocate and I really like your cadendrum there. And I  
13 volunteer a lot as a patient advocate in clinical trial  
14 development. And one of the things that I required to  
15 do -- I like to do in all the studies that get started,  
16 I volunteer at the Alliance for Clinical Trials in  
17 Oncology, is really look at the assessments that  
18 they're going to do and see how appropriate or not they  
19 are. And I've actually sent some of the fact be -- the  
20 one for breast cancer, I send it out to my group of  
21 breast cancer patients to kind of review this whole  
22 packet of instruments, questionnaires. And the male



1 breast cancer survivor did not like the question -- do  
2 you feel like a woman? And I think we really need to  
3 think about our audience and really vet it through the  
4 appropriate people and get more patients involved in  
5 clinical trial development upfront.

6 DR. PEIRIS: Thank you very much. And just on  
7 that topic on -- this is not going to be an answer, but  
8 merely bringing up a question on issues related to sex  
9 and gender and the LGBTQ community. Because this is an  
10 area where, even in medicine, we have to develop  
11 special programs at medical schools to help all of our  
12 young physicians and perhaps even some of our  
13 practicing and senior physicians begin to recognize  
14 what these unique nuances are amongst communities that  
15 they perhaps don't -- have not engaged with on a  
16 regular basis.

17 And I'll bring in the -- and want to open the  
18 conversation up to the audience. But as we're as  
19 people are thinking about the questions and topics, I'd  
20 like to continue to discuss further. I'll bring in the  
21 issue, when we can think about multicultural, we tend  
22 to think about different countries and I think that

1 absolutely applies. There's no doubt about that.  
2 There are differences in how people are brought up. I  
3 was born in Sri Lanka. My family grew up in Sri Lanka.  
4 My parents had a very different perspective coming to  
5 the U.S. and raising their children, my brother and I,  
6 than perhaps a lot of my other friends' parents, so  
7 that that applies.

8 But I also want to bring in the issue of  
9 differences in culture just inside the United States.  
10 I grew up in California, did all of my education and  
11 training out in the northeast. And I was faculty out  
12 in Texas. I got to tell you, those are very unique  
13 places in the world and I'll bring a very interesting  
14 aspect. This gets into a little bit of maybe things  
15 that we're not always comfortable speaking about, but  
16 the differences in practice and maybe culture between  
17 the Northeast and the area that I worked in in Texas.

18 There is a number of, say, religions in the  
19 state that operate truly on a relationship between the  
20 man's role in the family and the women's role in the  
21 family. And the reason that I bring that up is,  
22 because when there are patients that I'm counseling,

1 especially if it's one of the women that I'm  
2 counseling, the answer many times is, "Let me figure  
3 out what my husband thinks. Let me understand what he  
4 would like to do." And it was very it was very  
5 different for me having come and taking care of so many  
6 patients at the Northeast began to hear that. And I  
7 want to bring that up again. These were not posing the  
8 answers, but again bringing out the questions so that  
9 we can begin to clarify the answers as we move forward  
10 in these topics.

11 But understanding the distinctions in culture  
12 just within the United States is important. I'll give  
13 another example, there's a there's a later adolescent  
14 woman. She was about 17 at the time that I was  
15 speaking to. She came into the clinic with her  
16 grandmother who speaks Spanish only. And what was  
17 interesting for me is I was not only -- she also had a  
18 2 year old baby. I was not only her baby's doctor, but  
19 her doctor and her grandmother spoke Spanish only. So  
20 she would always interpret everything to her  
21 grandmother after I would say it. And I would always  
22 try to have very concise sentences, she would interpret

1 to a grandmother and then she would answer to me in  
2 English. I mean then she would tell her grandmother  
3 what she said.

4 So she was very articulate, very intelligent.  
5 And considering how young she was I did bring up the  
6 issue regarding contraception, and especially as she  
7 moves forward family planning, because this is going to  
8 be important because of her congenital heart disease.  
9 She's at a higher risk for certain types of  
10 contraception. And when we brought that conversation  
11 up, especially regarding whether she would like to  
12 consider contraception or not, she stopped translating.  
13 And she no longer told her grandmother anything. She  
14 just continued speaking to me and it was very kind of  
15 her to be as open as she was. But she did tell me that  
16 one of the reasons that she had a child so young at her  
17 age, because she recognizes that this has completely  
18 changed her life. She wanted to go to college. She  
19 doesn't feel like she can right now. She has to defer,  
20 do work and also help her family.

21 But the point that you brought up was that,  
22 when she -- just a couple of years ago -- remember her

1 daughter is 2 years old - she had asked her doctor  
2 about getting contraception. And this brings into the  
3 issue of cultural practice in terms of medicine around  
4 those areas. The doctor didn't feel that it was okay  
5 for her to consider contraception at such a young age.  
6 In addition to that, the conversation that she had had  
7 with her family was one of, if you use contraception,  
8 well, you're going to be considered a slut and it's  
9 going to be shaming the family. And all of those types  
10 of issues come into play when we understand culture  
11 just inside of our country.

12           And so I think those types of issues are  
13 things that many physicians deal with on a regular  
14 basis. You might think that they're relevant only  
15 again to general practice situations. But this is an  
16 example where it's absolutely relevant to the health  
17 and well-being of a patient with congenital heart  
18 disease that has significant risks with respect to  
19 anticoagulation and issues related to contraception.  
20 So these conversations help elucidate that even within  
21 certain regions, certain areas, there are multicultural  
22 perspectives and just different perspectives in terms

1 of how people are leading their lives and why they're  
2 making the decisions that they are and we just need to  
3 be cognizant about them.

4 I'll open up the panel as well if they have  
5 any thoughts about this.

6 DR. TUCKER: You know, I think, when you talk  
7 about multicultural and you gave a good example of  
8 roles of that 17 year old within that society. But  
9 again I think that's going to come back to when the  
10 people are asking those questions. We know that for  
11 kids that filled out surveys in school, we got very  
12 different responses than those that filled it out at  
13 home with the mother, may be watching over their  
14 shoulder as they answer questions about family  
15 relationships.

16 And, again, I don't know how to build that  
17 into the guidance, but I do think it comes back to that  
18 very thoughtful, not just what are the questions, but  
19 where they be asked and who and what is the role of  
20 that person as well as those people that are  
21 surrounding them when they are answering them. And we  
22 all know that a 13 year old will probably give a very

1 different response with the mom sitting in the room  
2 than maybe the dad sitting in the room, depending on  
3 gender. And so again, I think the development of COAs  
4 goes more than just the questions. It's the whole wrap  
5 around about the environment in which they're asked  
6 that we need to be sensitive to.

7 DR. PEIRIS: Yes, I think the point was  
8 brought up earlier about training the people that are  
9 taking -- that are administering these measures to  
10 ensure that they recognize those issues as well. I  
11 think you bring up a very good point. Depending on  
12 where you ask that question, who is in that room, the  
13 answers likely may be different.

14 MS. CRUZ: Yes. I was just going to add to  
15 what you just said, essentially. With the SMA  
16 population and this is where I have the most experience  
17 in, a lot of the parents tend to be very, very  
18 involved. And so when you have a teenager entering a  
19 patient reported outcome or COA, we recognize that the  
20 parents had an incredible influence on the child and  
21 how they responded and they were like covering. So we  
22 just said, you know what, from this point on, you need

1 to leave the room when the child answers this  
2 questionnaire and it's one of those things that you  
3 learn to be more objective in terms of the measures  
4 that you gather gathering, so also understanding the  
5 dynamics -- the family dynamics, the patient dynamics,  
6 as you answer the question and the context and the  
7 environment are all important to consider and make sort  
8 of standardized as part of the outcome measure rather  
9 than just making it like, well if you wish. It should  
10 be sort of like please make sure the parent is not in  
11 the room. If you think that's an issue.

12 DR. PEIRIS: Yes, I think in pediatric  
13 practice many pediatricians, especially as patients  
14 move in towards their early adulthood or even early  
15 adolescence, they have a conversation with the family  
16 members or caregivers in the room and then they also  
17 have a conversation with them out of the room. And I  
18 will tell you, it's very entertaining, the distinctions  
19 and information that you get when you have those  
20 conversations at different times with the patient just  
21 alone.

22 MS. CRUZ: I wanted to circle back to your



1 question about how can we validate a less than perfect,  
2 but existing instrument for a rare disease when you've  
3 got one shot at a clinical trial. And I wanted to put  
4 a plug in for the Complex Innovative Designs Pilot that  
5 the FDA is moving forward. One of the things that we  
6 are pushing for are what are called seamless designs  
7 and we don't want it to take five years to get into a  
8 clinical trial. But sometimes a few months of  
9 foundational work before you go into the pivotal trial  
10 can make all the difference in whether or not that  
11 trial is a success. And so a seamless design means  
12 that you might start out randomizing patients to  
13 multiple different levels of the drug. So inadequate  
14 dose ranging is a real challenge for us in rare  
15 diseases. And if you take the wrong dose, into your  
16 Phase III trial, a successful treatment could  
17 potentially fail. And there are challenges in terms of  
18 pediatric ethics with short term dose ranging trials.  
19 But seamless designs are a good solution to that  
20 problem and a good solution to the problem of PRO  
21 development.

22 So one of the things that we'd like to see is

1 sort of an intensive early foundation period that's  
2 perhaps just a few months long where you could do some  
3 short term dose ranging, perhaps to a pharmacodynamic  
4 biomarker alongside some really qualitative work for  
5 PRO development to really refine the instruments and  
6 make sure that you're asking questions. And you  
7 touched on an important point, which is, can the  
8 patients show benefit on that dimension during the  
9 course of the clinical trial? So they have to have  
10 some degree of symptoms or challenge in that area. I  
11 can think of an example off the top of my head where  
12 for an approval I worked on last year where patients  
13 did an outcome measure. Through the whole trial they  
14 were normal and baseline on that measure and so it just  
15 contributed to their fatigue and the length of their  
16 clinical trial visits, without adding useful  
17 information. And so that was a real missed  
18 opportunity.

19 I think had there been more of this sort of  
20 just foundation work -- and we don't want to keep  
21 patients waiting for years and years, but a couple of  
22 months could make a huge difference for some of these

1 programs. And I think it's something that patients  
2 recognize and want. I'd like to see -- I think  
3 certainly larger pharmaceutical companies really do  
4 understand this and are doing it. There are smaller  
5 companies that have a lot of challenges in getting  
6 therapies to market and are often so eager to move into  
7 the pivotal trial and that's where we're vulnerable,  
8 because it takes some money and some time at the  
9 beginning to do that work. But this complex innovative  
10 designs pilot is designed to allow the agency to sort  
11 of support companies and patient groups willing to do  
12 this.

13           And I wanted to echo something else you said  
14 about the patient groups working on the COA development  
15 and in a precompetitive space. There are huge  
16 advantages this is done within the patient community  
17 and not within the context of one single development  
18 program, because you have more -- you have more time,  
19 more patients, more ability to make sure that that  
20 instrument is representative for the patient population  
21 as a whole as opposed to a company coming in and  
22 saying, "Well, are drug acts in this one specific way.

1 We want to focus just on the symptoms we think are  
2 likely to respond to it." Well that's reasonable.  
3 That's a reasonable scientific strategy and one we  
4 would support. But then you end up with a sort of  
5 single use instrument, right? Another drug that comes  
6 along that may not work and then you have to start all  
7 over, in a rare disease community developing a whole  
8 new instrument.

9           So to the extent that we can come up with  
10 instruments that that really reflect the global nature  
11 of the disease burden, that's going to be a lot more  
12 informative. So I just wanted to tie into a couple of  
13 those things. But seamless designs where we could use  
14 Phase II to do some dose ranging and also some PRO  
15 development and then move that into a Phase III trial  
16 with the right dose and the right instrument, we're  
17 going to have a lot more success.

18           DR. PEIRIS: Thank you. I just want to add as  
19 well in terms of that seamless clinical designs as you  
20 mentioned at CDRH there has been some great work by  
21 Martin Ho and colleagues about beginning to recognize  
22 where the severity of disease burden, how it begins to

1 influence patients in a different way. And just to  
2 bring that down a little bit more clearly is issues  
3 regarding obesity, patients -- or patients that have  
4 few other options with respect to how -- in terms of  
5 managing their disease. Those patients may be willing  
6 to take on perhaps a higher level of risk for maybe a  
7 smaller level of burden or benefit than other patients  
8 would. And so, we have to begin to design the clinical  
9 trials and the evaluations around the -- again, the  
10 perceptions and understanding and the needs of those  
11 specific types of patients.

12 And some may consider, well, those types of  
13 patients at a very severe end of a spectrum of a  
14 specific disease, and very simply put something like  
15 severe morbid obesity maybe a special population to  
16 consider. Are there other questions or comments from  
17 the audience?

18 AUDIENCE QUESTION AND ANSWER

19 MS. ROMANO: Hi, I'm Carla Romano from RTI  
20 Health Solutions. Thanks to the panel and to the  
21 agency for the session. It's really near and dear to  
22 my heart and it's exciting to hear the panel speak that

1 way as well.

2 I just wondered if we could think about  
3 technology as a way to help support younger children,  
4 nonreaders, those with sensory or cognitive deficits,  
5 to be able to self-report in a way that's reliable and  
6 valid and thinking about some of your comments about  
7 parents being over their shoulder allowing also  
8 children to report in a private way. So thinking about  
9 a web based solution or I see two and three year olds  
10 walking around with their parent's iPhone interacting.  
11 So just utilizing technology so that we can really  
12 allow children to self-report and not so quickly move  
13 over to an observer or a rated tool.

14 And also thinking about it's not just an age  
15 related dividing line, when we have kids coming into  
16 clinical trial setting. Utilizing sites staff to help  
17 decide what is the best way for children to self-  
18 report, not being stuck, because this is this is the  
19 measure for five to seven year olds if we need to step  
20 down or step-up. When we interview kids with chronic  
21 illness some miss a lot of school, so they might be  
22 behind in their reading skills. Others, because

1 they're missing a lot of school get way ahead in their  
2 reading skills, so just making sure that we understand  
3 the child on the individual level be able to tailor our  
4 measures and our approach and think about  
5 implementation as part of our evidence base. And  
6 giving that a sense of whether or not this is reliable  
7 information based on training, implementation and  
8 selecting the right tool and the right mode.

9 DR. PEIRIS: Thank you very much. I think you  
10 make an exceptional point with respect to how  
11 technology will continue to influence healthcare  
12 practice. Especially in the pediatric to clinical  
13 area, we want to work towards decreasing toxic  
14 exposures to children, make the entire clinical  
15 experience, whether you're going in for a vaccination  
16 or going in for major surgery, something that is  
17 hopefully less stressful. And part of that  
18 technologies like augmented reality technologies are  
19 being developed that could make a significant  
20 difference in that entire overall experience.

21 So something very much -- very important to  
22 consider. And I do want to commend all the child life

1 specialists out there. I don't think they get enough  
2 recognition and commendation on regular basis, but  
3 there are some phenomenal child life specialists that  
4 are -- that work in hospitals, especially in our  
5 critical care units that truly make the experience of a  
6 child very different and they are trained to begin to  
7 elicit the perceptions of that child in terms of what's  
8 going on for them throughout that clinical experience  
9 in multiple different ways.

10           And they don't do it just based off of age  
11 alone, but they try to understand what's -- how does  
12 that child communicate, how are they expressing  
13 themselves, you know, could they better express  
14 themselves in terms of playing a game on an iPad or  
15 putting in information on an iPad versus talking to  
16 somebody. All of those different potentials are  
17 considered, but again that's something that happens at  
18 the patient level and you know, we need to consider how  
19 we can actually develop tools that may apply across  
20 different populations.

21           DR. TUCKER: Actually can we make a quick  
22 comment? I see Linda wants to say something.



1 DR. PEIRIS: Sure.

2 DR. TUCKER: One of the things that we're  
3 really working on in younger kids, I think if your  
4 comment is also -- and I just want to bring this up  
5 looking at the paradata and so looking at the child's  
6 responses, whether they say it, we actually use social  
7 robots to actually deliver surveys because then there's  
8 not a person there talking to them about some of that  
9 or not, but looking at video responses, the loudness of  
10 it, in terms of looking at some of the reliabilities,  
11 so just when you talk about technology, I think we're  
12 really coming a long way and sometimes it's not just  
13 the answer, but whether, you know, you look at somebody  
14 sometimes answering a survey and you know they're  
15 getting it or not. And so I think we're starting to  
16 see a lot of that technology to come along which may  
17 help with the reliability and validity. But sorry  
18 Linda, jumped in.

19 MS. NELSON: Okay. I was just going to say I  
20 think to widen the scope of technology, this is a place  
21 where we can think about wearables or other digital  
22 technology. If we want to understand sleep quality for

1 example in children, they may not be able to report  
2 that, but we could supplement it with understanding  
3 sleep monitors and come up with endpoints through those  
4 sleep monitors that would give us better insight and  
5 probably better than a parent going in and peeking in  
6 the kid a couple of times a night. So I think this is  
7 the place where you can begin to widen your ideas of  
8 using wearable endpoints as supplements to a lot of  
9 these others.

10 DR. GREEN: And just quickly I just want to  
11 say too that just simplifying it even more in terms of  
12 technology that kids just like technology in general  
13 and so I believe that Larissa brought up the fact about  
14 willingness and if you have a self-report COA as part  
15 of your program and let's say for example it requires  
16 the patient to update or provide, you know, to track  
17 their symptoms over time, writing that out or filling  
18 out a survey may not be as attractive as just using an  
19 app and simply doing that. And so they're using this  
20 in other parts of their lives and so this doesn't feel  
21 very different and so that's just something to think  
22 about in terms of compliance and how that could be

1 favorable for pediatrics.

2 DR. PEIRIS: Perfect. Go ahead.

3 MS. KHAN: Hi. I'm Simi Khan (ph), I'm from  
4 Mitsubishi Tanabe. So I could not agree more with the  
5 panel, so what I'm hearing it in this session is the  
6 variations, you know, so we start with the pediatrics,  
7 so the age variations; cognitive variation; cultural,  
8 linguistic; we haven't talked about socio-economic,  
9 that's another major thing. We're talking about other  
10 countries going to globally, I mean I agree with you  
11 100 percent, I mean I was trained in -- at the East  
12 Coast practice; East, Midwest and California.

13 DR. PEIRIS: It's not just me.

14 MS. KHAN: And the amount of the variation --  
15 amount of the variation within U.S., you cannot imagine  
16 unless you have just been there and you have seen that  
17 on the ground. My question is that we all understand  
18 that there's so much variation within a patient,  
19 patient to patient within a disease condition; culture  
20 to culture where you are in the family and your status.  
21 So we can speak the whole day about the variations,  
22 they are there.

1           When it comes to the sponsor, I'm talking on  
2   behalf of the sponsor and you are talking about a rare  
3   disease, and I understand the seamless design, it sound  
4   like on the papers might be short, when you start doing  
5   it, it's not that easy and straightforward when you're  
6   trying to build up something from the scratch. So what  
7   I'm just asking a question to the panel based on your  
8   experience, what do you think there has to be something  
9   which is unifying, you know, like what we -- as a  
10   sponsor we wanted to see out of this guidance is what  
11   is the unifying characteristics you wanted to see in  
12   your -- those instruments? Some of them has to be some  
13   guidance towards that. Otherwise we'll be back to the  
14   same place where we have been now that in trying to  
15   design right from the scratch.

16           DR. PEIRIS: Now, thank you very much.  
17   Martin, I don't know if you want to try to address this  
18   while you're up here? Is that why you came up knowing  
19   what the question would be? Since this is the thing  
20   you do?

21           MR. HO: No thanks. No thanks. I would defer  
22   to our outstanding panelists. My name is Martin Ho. I

1 am from Center for Devices and Radiological Health. I  
2 was very excited to hear about the enthusiasm towards  
3 the technologies. So I just wanted to remind everybody  
4 that this afternoon we are going to have exciting  
5 sessions on the very specific topic of technologies and  
6 PROs. And I just want to add that people have been  
7 focusing on the potential of the mobile technologies,  
8 but actually things are moving quite a bit ahead, you  
9 know, other than or beyond mobile technologies.

10 Just imagine the Amazon's Alexa will do --  
11 will implement the PRO for you, you know, very nice,  
12 you know, with some soothing music and they ask it at  
13 the right time when they are playful. Or the thing  
14 about, you know, triangulation with our, you know, our  
15 wearable with Alexa, both can provide triangular and  
16 more precision in terms of their student's sleeping  
17 status. Then even they can now -- if -- with enough  
18 samples, they can even distinguish certain types of  
19 perhaps a cough or cold or even I mean looking into the  
20 future, such kind of, you know, combination of sensors  
21 and algorithms would, you know, will provide us with a  
22 much more, you know, wider venue for us to what we do.

1 So just wanted to say that, yes, it's a very promising  
2 future. Thank you.

3 DR. PEIRIS: Thank you Martin. I know we're  
4 at time, but I don't want to -- if this is the -- we'll  
5 take yours as the last question, hopefully we won't go  
6 into break too much.

7 MS. GANGULI: Hi, I'm Rupa Ganguli (ph). I am  
8 an independent consultant with couple of clients in New  
9 Jersey that I advise. And last night I was fascinated.  
10 I read through the guidances again and did a little bit  
11 of independent research. And I think I speak on behalf  
12 of some of my clients here as well; digital health,  
13 when we talk about digital health, the aspect that I  
14 wanted to see a little more clearly stated in the  
15 guidance is the concept of digital medicine because we  
16 now have the first approved digital medicine. And in  
17 that alone lies the possibility that we are  
18 administering digital medicines to potentially kids in  
19 the future.

20 What is the -- what are the ethical constructs  
21 around administering a digital medicine to a pediatric  
22 patient and when you were harnessing that data, what

1 are the, you know, the barriers or the constructs or  
2 the stratification that you might need to build as a  
3 part of administering and what are the assent  
4 requirements, what are the ethics around that? So that  
5 was something that I wanted to see a little more  
6 clarified at the guidance because when we say digital  
7 health, it's a lot of digital therapeutics. It's  
8 capturing digital web-based apps, but we are not really  
9 thinking about the digital medicine which is ingesting  
10 a sensor along with prescriptive medication, so just  
11 something to think about and if the panel has some  
12 ideas? Thank you.

13 DR. PEIRIS: Any thoughts from the panel?  
14 Well, if not, I will say that as Martin mentioned, the  
15 digital health technology section I think is -- will be  
16 happening this afternoon as well and that is definitely  
17 an area where this conversation could be -- can  
18 continue. I'll end this on a -- number 1, a thank you  
19 to all the panelists once again for taking the time out  
20 of their schedules to be here and take the time to  
21 actually contribute in such a meaningful way to this  
22 conversation. I'll provide one other maybe closing

1 comment; how many people have seen that commercial  
2 where there's a robotic monkey that wakes up a sleeping  
3 child and the monkey plays with the child for most of  
4 the day and they play piano and things like that, and  
5 then you recognize that this -- nobody has seen this,  
6 this is very concerning.

7           Maybe it's just me, but the monkey -- thank  
8 you, somebody in the back. And at the end of the  
9 commercial, you recognize that the monkey is actually  
10 being operated by the child's grandmother who lives  
11 somewhere around the world, and the grandmother is able  
12 to play with them. So when you brought up the issue of  
13 robotics and robots administering surveys, what a  
14 wonderful way to be able to engage children in surveys  
15 or other issues, especially when there's psychological  
16 issues going on for those children. So there's great  
17 potential out there and I want to thank all of you for  
18 participating with us as we continue this conversation  
19 as that I mentioned has started decades ago and is  
20 finally evolving over a almost two to three generations  
21 of medical practice. So thank you once again.

22           (Applause)



1 BREAK

2 METHODS FOR DETERMINING AND INTERPRETING WITHIN-PATIENT  
3 MEANINGFUL SCORE CHANGES IN CLINICAL OUTCOME  
4 ASSESSMENTS

5 DR. CAMPBELL: Good morning everyone, and  
6 we're going to go ahead and get started onto our next  
7 panel topic to keep things flowing for today. And  
8 hopefully we'll continue to have an enlightening  
9 conversation during our next panel session. If you  
10 didn't -- were not here yesterday, my name is Michelle  
11 Campbell and I'm a part of the clinical outcome  
12 assessment staff in CDER. And the panel we have today,  
13 we're going to be discussing for the next hour or so is  
14 methods for determining and interpreting within-patient  
15 meaningful score changes in COAs. So I'm going to --  
16 first I'm going to ask our panel to introduce  
17 themselves, and then I'm just going to talk a little  
18 about why this is an important concept and why we're  
19 discussing it today and then we'll get into our panel  
20 discussion. So Adam, can you -- would you like to  
21 start?

22 DR. CARLE: Yeah. All right. So I'm Adam

1 Carle. If you ever jump on a call or a webinar that's  
2 a super-dad, that's always me. Maybe there's another  
3 super-dad out there, I'm not sure, but it's usually me  
4 on the webinars. I'm a psychometrician and a clinical  
5 psychologist. Did my work at Arizona State University.  
6 I worked with Roger Millsap and I do a lot obviously  
7 with patient report outcomes now at Cincinnati  
8 Children's Hospital.

9 DR. CHEN: My name is Wen-Hung Chen. I'm the  
10 team leader at Clinical Assessments Outcome Staff at  
11 the Office of New Drug in CDER and I am psychometrician  
12 by training. And yesterday, today, this is all I do.

13 DR. COON: Hi, I'm Cheryl Coon. I'm the  
14 principal at Outcometrix. I'm also a psychometrician  
15 by training.

16 MS. DEAL: Hi everyone. I'm Linda Deal. I  
17 lead the patient-centered outcomes assessment team at  
18 Pfizer.

19 MS. HOWARD: Hello, I'm Leah Howard, I'm the  
20 chief operating officer for the National Psoriasis  
21 Foundation. And the National Psoriasis Foundation had  
22 an opportunity to do a 2016 patient-focused drug

1 development meeting, so I'll talk about that a little  
2 bit more.

3 DR. REEVE: Good morning everyone. My name is  
4 Bryce Reeve and I'm a professor in population health  
5 sciences as well as professor in pediatrics at the Duke  
6 University School of Medicine, as well as I direct the  
7 Center for Health Measurement there. My background  
8 training is in psychometrics and measurement theory and  
9 my work looks at the impact of disease and treatment on  
10 patient life from pediatric to geriatric.

11 DR. WIRTH: Hi, I'm R.J. Wirth. I'm president  
12 and managing partner of Vector Psychometric Group and I  
13 feel like I should add a lot more after going after  
14 Bryce, but I'm also a quantitative psychologist,  
15 psychometrician by training.

16 DR. CAMPBELL: Thank you guys. And I just  
17 want to say that while the word psychometrics was used  
18 a lot by our panelists, I am not a psychometrician by  
19 training at all which should make this friendly because  
20 we'll keep it going and it will not be necessarily a  
21 numbers-heavy session. But why are we even talking  
22 about what meaningful within-patient change? I believe

1 a lot of our audience members will say this is a  
2 comment they hear often from us. And it's important is  
3 that when we have a -- and when we're looking at  
4 efficacy in the clinical trial and we have a small  
5 effect-size, we have something small that we see and  
6 it's statistically significant, what you need to know  
7 is that meaningful to a patient and particularly to the  
8 individual, not necessarily between groups and looking  
9 at group means, but is it clinically meaningful to a  
10 patient.

11           And this is really important in our decision-  
12 making when we're looking at a benefit risk and is it  
13 making sense when we look at both the risk and the  
14 benefit, so is this change we're seeing in the COA? Is  
15 it meaningful? So it's actually a really important  
16 question that we deal with every single day here at the  
17 agency. And so we really thought that -- and this is  
18 in the guidance, the draft discussion document -- we  
19 really thought it was important to have this discussion  
20 today.

21           Our panelists today are from a wide variety of  
22 perspectives in what they do and they're going to

1 provide that to us. So everyone a question that we're  
2 going to be kind of thinking about today is does this  
3 discussion document capture the most appropriate and  
4 feasible methods to determine within-patient meaningful  
5 score changes, and are there any other methods to  
6 consider. So we're going to start off with that  
7 discussion. I've asked our panelists -- we've talked a  
8 couple of weeks ago about how we wanted to do this  
9 session.

10 We're going to -- they're going to provide  
11 their perspectives on what they think in and talk about  
12 some of the areas that they've worked in when applying  
13 these methods. So I first want to start off with Wen-  
14 Hung to give some early thoughts on this and a number  
15 of our perspective, and then from there I'm going to go  
16 to Adam and then I'll let everyone else there which  
17 order we're going to be because we're not necessarily  
18 sitting in the order we're going to be speaking in, so.  
19 So Wen-Hung?

20 DR. CHEN: Thank you Michelle. So Michelle  
21 pretty much capture the -- our perspective. Yesterday  
22 we have been talking about the event management, the

1 event adapting use the instrument that is fee-for-  
2 purpose and basically what we talk about is what, we  
3 need to measure what is important methods to the  
4 patients. Now this section we will talk about how  
5 much. We are measuring what is important to the  
6 patient. Next we want to know how much of that change  
7 of that important is really meaningful to the patients.  
8 And the -- whether the changes, the thing that we  
9 measure is matter to the patient, by we not needed to  
10 know how much of that changes really matters to them.

11 In the 2009 PRO guidance we talk a little bit  
12 about score interpretations. We talk about like  
13 meaningfulness and we talk about INCA-based (ph) method  
14 and then this guidance number 3 expand upon that theme  
15 and then talk a little bit more about how you can using  
16 different approach, different method to get to the area  
17 within-patient meaningful score change including the  
18 same as INCA-based method and then actually also this  
19 guidance include the accumulated discretion functions  
20 and the PDF and that has very nice figure to explain,  
21 you know, what they are and then how you might use  
22 them. So -- and that's pretty much essentially here's

1 -- I'll give you a copy of that back, but already over  
2 here actually. Three pages, pretty good informations  
3 there. So -- and I'm here even sitting on the panel,  
4 but actually I'm also at the listening mode like our  
5 FDA colleague. So I will leave that next to Adam's.

6 DR. CARLE: So, you know, we had this  
7 discussion and I thought a little bit in the 2 to 5  
8 minutes I had to talk about all the things I would say  
9 and then lots of really smart and great people here in  
10 the audience asked questions and made comments along  
11 the lines of what I was thinking. So I apologize if  
12 some of this has been said before, but I think it's  
13 worth repeating. And one of the first things --  
14 Michelle asked me to talk about both sort of the  
15 within-person change, but also to think about the  
16 pediatric perspective. And so one of the things that I  
17 really wanted to hammer home and raise again here and  
18 it was great to see people already clearly in alignment  
19 with this is that the child's perspective matters.  
20 There seems to be a long history, not necessarily of  
21 anyone in this room has ever done this, of, you know,  
22 we see disagreement between the parent and the child and

1 we think that means the parent's right and the child's  
2 wrong. The kids can't report on themselves.

3           And that's just, you know, our work has shown  
4 again and again and several of the people and then  
5 Bryce has done work in this field and other people who  
6 are here on this panel that are in the room that I've  
7 worked with have shown this. You know, both  
8 qualitative really and quantitatively we've shown that  
9 kids can report on themselves, and it is reliable and  
10 valid. And they're pretty good at it. It doesn't mean  
11 that there aren't things we need to be aware of maybe  
12 on the modeling end as we think in sort of that  
13 psychometric world to make the responses better. But  
14 it's a really important point I think to take home.

15           And then that leads that sort of at least to  
16 this interesting piece that we get impedes,  
17 particularly through the development of lifespan when  
18 we're looking at change across time where parents and  
19 kids may be reporting different types of changes and  
20 that we need to -- I think it's worth thinking about  
21 both of those things simultaneously for those of you  
22 who are statisticians in the room, that's I do



1 structural equation models that lets us model things  
2 simultaneously. I think we get a lot of information  
3 out of that, but I think from a research perspective,  
4 we are trying to understand change both from the  
5 child's view, the parent's view and both of those at  
6 the same time and how differences in the way those  
7 things change can inform us about what's happening for  
8 the child and for -- the system that the child lives in  
9 is another thing that we need to think about.

10           And I think the last thing I wanted to mention  
11 is, you know -- and I hate to bring it back sort of  
12 statistically, Michelle, you can come over and smack me  
13 if you want -- so in my group some of what we've  
14 thought about is that whether or not a change is  
15 reliable. So when we talk about reliability for  
16 measures a lot, we're often focusing on the sort of  
17 average reliability, but when we're talking about  
18 within an individual, we have a different criteria we  
19 need to think about and really evaluate whether the  
20 changes within a given person from one time to the  
21 next, not necessarily five or six, but from just a two  
22 endpoint thing, we really want to focus on whether

1 that's reliable or not, and as kids one of the things  
2 we get out of some of the models that all of us here  
3 have used, we can understand the extent to which change  
4 is likely to be reliable differently depending on the  
5 amount of the condition -- the symptoms that they're  
6 reporting. And that's something my group has been,  
7 that with Chris (ph) -- I should say with Chris  
8 Forrest's (ph) group which I may -- little guy and --  
9 has been working on. I think those are my two main  
10 things.

11 DR. CAMPBELL: Thank you. Thank you Adam for  
12 that, and it's okay, we can throw in the numbers stuff.  
13 It's all right. Bryce, can you give us some of your  
14 thoughts?

15 DR. REEVE: Thank you Michelle. So first I'd  
16 just like to start and say a huge thank you to the FDA  
17 for putting together this 2-day meeting I think on  
18 every small topic. I'd love to be able to just sit  
19 down with all these great, wonderful, smart people  
20 around the room and have really rich discussions and  
21 unpacked all these incredibly important issues that  
22 we've been thinking about from pediatrics to rare

1 disease and other things like that. In addition, I  
2 want to thank the FDA for putting together this  
3 guidance document. It really reflects, you know,  
4 decades of thinking and thought and research behind how  
5 we try to capture how a patient feels and functions  
6 there, and it's reflected in that guidance that is a  
7 very refreshing document and again I think is a good  
8 basis to help guide us researchers and industry for how  
9 to move forward in this field. So thank you for  
10 bringing that together.

11 So on the topic of meaningful change, and in  
12 particular trying to answer this question are there any  
13 other methods that we need to consider, you know, and I  
14 think the guidance document did a really good job of  
15 outlining, you know, the strains and limitations of  
16 both the anchor and distribution-based approaches and  
17 also open up that there are other methods out there  
18 using both qualitative and quantitative methods to help  
19 us understand how patients perceive and experience  
20 individual change. I was asked to talk on two  
21 particular topics and to sort of move us into this  
22 discussion of these topics there, I wanted to reflect

1 on a really important point that Dagmar admin said  
2 yesterday when looking at the guidance 3 document,  
3 there is -- there's not a lot of discussion in some of  
4 the more modern approaches that we've been using to  
5 help us design really good quality standard reliable,  
6 precise valid measures of patient report outcomes and  
7 other key outcomes overall.

8 In particular we're focused on for this  
9 particular part of my discussion here is on using item  
10 response to remodeling as a way to help us construct  
11 and evaluate how WALE (ph) scales and questionnaires  
12 perform. And what's unique in a benefit of eye  
13 response there and this has been used in such  
14 initiatives like the PROMIS, the Patient-Reported  
15 Outcomes Measurement Information System there, is it  
16 takes a look at the items and questions you use in your  
17 particular scales and let's say for example we're  
18 measuring something like depression and what this  
19 methodology allows you to do is for every item you  
20 decide to include in that scale, it assigns a set of  
21 property-set item that recognize most importantly as  
22 how these types of questions tap into different levels

1 of this concept or outcome or interest. For example,  
2 again keeping to the analogy of depression as an  
3 example there, a question like are you unhappy some of  
4 the times, you know, probably taps into sort of lower-  
5 levels depression. I admit I'm unhappy when I'm not  
6 thinking about psychometric theory or Carolina sports  
7 or barbecue.

8           However, you know, when you think about  
9 questions like are you so down the dumps that nothing  
10 could cheer you up, you know, that's a very depressing  
11 question and that recognizes that people who endorse  
12 those type of questions, they represent may be on the  
13 higher end of that depression continuum there. So  
14 those are two different types of questions and what on  
15 response to is allows you to do is avail it to assign a  
16 sets properties which differentiate what severe  
17 depression that particular items tap into. On the same  
18 type of framework of item response theory, we also know  
19 along that depression continuum from low depression to  
20 high depression there we know how people at different  
21 levels of continuum would answer those different types  
22 of questions. We know people of low depression would

1 be less likely to endorse I'm so down at dumps that  
2 nothing could cheer you up.

3 We know a person of high-level depression  
4 would have a high likelihood for -- or answering the  
5 unhappy some of the times and maybe a moderate  
6 likelihood for answering so down -- they're so down at  
7 dumps that nothing could cheer you up. So all these  
8 properties were how we understand how each item  
9 performs and how people answer these questions is  
10 informed for us with PROMIS metric and other metrics  
11 there to understand this trait continuum, this  
12 depression continuum there, and be able to identify on  
13 what parts of these things there are people answering  
14 different types of depression question. So with that  
15 as a background that puts us in a unique position to  
16 try different methods to help us understand what  
17 represents meaningful change and there are two types of  
18 methodologies that aren't included in this guidance  
19 document I was asked to talk about here.

20 One of these concepts is called bookmarking  
21 exercises and so within this type of exercise, a very  
22 qualitative type of methodology where you think of it

1 like a focus group and what we can do is within these  
2 type of exercises there we can have different expert  
3 stakeholders, this could be a patient population or it  
4 could be a clinician population participating in the  
5 focus group. And what we're able to do is as they come  
6 into this meeting there is we're able to start at  
7 someplace along our depression continuum and for  
8 example a person with low-level depression and what  
9 we're able to do within this focus group there is  
10 present them what people of different levels of --  
11 additional levels of depression, change of depression  
12 on our metric there, maybe like a half a standard  
13 deviation change and then one standard deviation change  
14 there and then have them look at how people with  
15 depression would answer those type of questions.

16           And we know that from what we've done with  
17 item response theory through original calibration with  
18 earlier population, and so that provides these  
19 vignettes or clinical vignettes for people to look at  
20 how people may vary from a starting point where their  
21 depression is getting worse or their depression is  
22 getting better there for them to articulate and provide

1 impact and think about what represents a meaningful  
2 change to them. So I think that's a lot of promise and  
3 think about an alternate method to help us think about  
4 capturing individual change.

5 Another method, I was only given 3 minutes, I  
6 know I'm way beyond that, you know, another methodology  
7 that I want to talk about as well is another -- again  
8 is called scale of judgment. So this more of a  
9 quantitative exercise again using item response theory-  
10 based measurement systems there is individuals can be  
11 presented with people at different changes with your  
12 positive change or negative changes there and on the  
13 individual basis they can -- we can present them of how  
14 people answering these questionnaires and then ask them  
15 what to you represents a meaningful change?

16 And so in this quantitative scale of judgment  
17 method, we're not stuck with maybe eight people  
18 reporting on what they think has changed, but a large  
19 number of people can participate again from a patient  
20 side and a clinician side and again that gives another  
21 opportunity for them to reflect on what represents  
22 meaningful change. So I think there's a lot of unique



1 methodologies we can use at IRT and other modern  
2 methodologies to help answer these questions.

3           The last thing I really want to say is I'm not  
4 suggesting that these are the only ways we can look at  
5 individual change. I think through a balance of both  
6 anchor-based and these -- distribution-based and these  
7 other methodologies is we can start to experiment and  
8 look at how these different methodologies result in  
9 looking at meaningful change and start to triangulate  
10 among these things giving way to different  
11 methodologies that we feel more comfortable about to  
12 help judge and what represents a meaningful change.

13 Thank you.

14           DR. CAMPBELL: Thank you Bryce, and I do know  
15 I have the one panel, well, I think all the panels, but  
16 my panel I know we can talk well and we will not have  
17 to fill time, I know that because there are some really  
18 good thoughts on this panel. Cheryl, do you want to  
19 offer some thoughts and then after show we'll to go RJ?

20           DR. COON: Sure. Thank you. So I think that  
21 these guidances are really an incredible resource for  
22 the field now. It was really exciting to read through

1     them and see that the FDA has been in listening mode  
2     for quite a while, that the feedback that we've been  
3     given and maybe the kind of -- the places where there  
4     was some confusion before or some challenges that  
5     they've really been well articulated in these  
6     guidances. And so I'd like to point out a few things  
7     that I really thought was really great in this section.  
8     One is the very clear distinction between within person  
9     change and between group change or between group  
10    differences.

11           When the 2009 guidance came out there was a  
12    lot of confusion about what happened at MID (ph), it  
13    doesn't say MID or reusing MID, can we say MID, MID is  
14    something different and it's actually distinguished in  
15    here. We can still say it, but it's not the within  
16    person change that we're really trying to focus on for  
17    regulatory review. So I'm hoping that the MID issue  
18    gets put to bed with this guidance document.

19           The second is the emphasis on the threshold  
20    being both possible and measurable and this is  
21    something that Cathy Lirrick (ph) I know has been  
22    talking about for a number of years in terms of state

1 change and can the amount of change that you're saying  
2 is meaningful on the PRO or the COA, is it actually  
3 possible to achieve that amount of change and the QLQ-  
4 C30 is a prime example where a 10-point change is often  
5 used, but it's not actually achievable on any  
6 individual item.

7           So I'm glad that this guidance document  
8 emphasizes that we should really not just crunching  
9 numbers, but also doing a gut check with what comes out  
10 at the other end and making sure that it's actually  
11 possible. And then the third thing is the explanation  
12 of ECDFs (ph) using anchor categories. In the 2009  
13 guidance, the CDFs that were mentioned in there were  
14 talking about treatment groups, the treatment groups  
15 with a different curves and then suddenly we started  
16 getting these requests for anchor groups to be plotted  
17 with CDFs and it took some of the psychometricians in  
18 the field number of years to figure out what on earth  
19 we were supposed to be doing with that. I think we  
20 finally got some clarity around that and it's  
21 articulated in the guidance now.

22           So I really appreciate that those details are

1 incorporated in there. Wen-Hung asked me not to  
2 provide any criticisms, so instead I will give some  
3 room for improvement, so the section on anchor-based  
4 methods discusses the anchors, but it doesn't actually  
5 discuss any methods, and I feel like that was kind of  
6 intentional, it was an intentional omission because the  
7 guidance is obviously not trying to be proscriptive, so  
8 it's not saying do this, don't do that, but the methods  
9 themselves do need to be defined in terms of what are  
10 we trying to achieve with these methods. It's leaving  
11 it open for psychometricians to choose the methods that  
12 work best for them that are easy for them to interpret  
13 and communicate. But what are you supposed to be  
14 achieving with those methods that you're choosing?

15 On that note, the ECDFs actually are an  
16 anchor-based method, but they're in a separate section,  
17 so I would combine those sections together or at least  
18 highlight the fact that ECDFs are an anchor-based  
19 method because you are using the anchors in the  
20 calculation of them. The example plots are great to  
21 finally see what those should look like. I keep  
22 turning to you, I'm sorry. I know you didn't write

1 that section by yourself, Wen-Hung, and you are looking  
2 at it for the first time today, aren't you? Here, take  
3 that. The example plots don't have much interpretation  
4 with them and if that was to be provided in here, this  
5 would become a textbook, so I realize there's not space  
6 for that.

7           Yesterday in several of the sessions people  
8 were asking for more examples, more elaboration in  
9 these sections and I think that can be achieved by  
10 pointing to good examples that are either in print, in  
11 publication, or in review documents. So in another  
12 section of the guidance on exit interviews that points  
13 to several documents that are related to the Xermelo  
14 drug that was approved 2 years ago, or last year maybe,  
15 and so there is a reference that was published and  
16 there is also the review division, the statistical  
17 review that's linked in there. And that is a rich  
18 source of information. I was really happy to hear  
19 Teresa Long (ph) yesterday say that the drug approvals,  
20 those documents are -- they become case law because I  
21 like to go to them and I like to see, well, what have  
22 divisions been saying, how have they been reviewing,

1 what should -- kind of what's happening today, how has  
2 the field evolved and what's being reviewed and on the  
3 level of evidence today.

4           So the more examples that you can actually  
5 point to on better actual drug reviews, that Xermelo  
6 example, it walks through how they reviewed the  
7 evidentiary standards for the interpretation and it  
8 talks about, well, this wasn't quite -- you know, the  
9 correlation wasn't high enough here and these groups  
10 were too close together here, so we're going to look at  
11 this different type of analysis and we're going to  
12 triangulate it with this and all of the evidence  
13 together pointed to pretty clear threshold and some  
14 more examples like that would be really helpful.

15           And then finally this came up a number of  
16 times yesterday, how do we go from COAs to endpoints,  
17 constructing endpoints? What do we do with this  
18 information once we figure it out? And I know that  
19 that's in the next guidance, but somewhere in here we  
20 should be saying why are we even setting these  
21 thresholds, what are we going to do with them, should  
22 we be using responder endpoints where we're doing a

1 categorical analysis of the data or should we be doing  
2 the continuous level analysis and using this as  
3 supplementary where you might put the CDF of the  
4 treatment groups in there, draw a line where the  
5 threshold is and kind of leave the interpretation open  
6 to the person who's reviewing the label.

7           So I think that's particularly important  
8 because I'm a consultant to the sponsors and then the  
9 sponsors then, they need to know what to do with this  
10 information and it's not consistent across review  
11 divisions, what they're looking for, my understanding  
12 that it depends on the review division, they can ask  
13 for responder analysis, they can ask for continuous  
14 level analysis, but I've also seen within review  
15 division mixed feedback and feedback that might change  
16 depending on the IND (ph) or depending on kind of the  
17 weather that day.

18           So some sort of indication of what directions  
19 sponsors should take those information once they have  
20 it to kind of save time as protocols are being  
21 developed and as they're going into end of phase 2  
22 meetings that there is -- this is maybe less of a

1 discussion and more of a, yes, we've gotten this  
2 evidence in place and let's hit the ground running with  
3 our extra clinical trial. I'll end there for now.

4 DR. CAMPBELL: Well, thank you. I think the  
5 weather is great today. I see the sun, and since you  
6 brought up examples, I'll just put a plug in that the  
7 docket closes December the 14th and any examples that  
8 you'd like to submit to the docket we would greatly  
9 appreciate. RJ, do you have some thoughts to add?

10 DR. WIRTH: No.

11 DR. CAMPBELL: That may not be an acceptable  
12 answer today.

13 DR. WIRTH: No, well, I want to reiterate what  
14 Bryce said and just thank you to the FDA and everyone  
15 who worked on the guidance. I had -- well, I have a  
16 lot of thoughts reading through the guidance, but one  
17 thing that really struck me going through this  
18 particular section is that I thought I did a really  
19 nice job of outlining what we do now. I think a lot of  
20 the methods that are in there are things that at least  
21 people on this panel have probably done. But what it  
22 doesn't do, it doesn't provide us a framework or any



1 sort of mechanism to change and sort of understand  
2 what's coming next, you know, and I think that's in  
3 part due that there's -- we're still a bit out of step  
4 with measurement science which I think, you know, it's  
5 already been alluded to previously, not just IRT in  
6 terms of being sort of a more modern -- modern method,  
7 but you know, calls for modeling and other aspects that  
8 are out there.

9           But measurement science is an area of  
10 research, right, it's people who spend their lives just  
11 trying to better understand how to model these types of  
12 data which means things progress and things change and  
13 you know, there's a lot of work in deep learning and  
14 putting those algorithms towards psychometrics. There  
15 is a lot of work in game-based assessments. Now, I  
16 know these things are probably very far off from this  
17 industry and this setting, but we need to -- when we  
18 think of a guidance, I don't think we want to write  
19 something now that's good for today. I think we want  
20 to write something that allows us to grow as a science  
21 and I think one of the ways we can do that is get  
22 better integrated into the field of psychometrics and

1 measurement science as a whole.

2           It does -- I think it will do a lot of things  
3 for us. One, it provides us a common language which I  
4 know Michelle referred to yesterday and so it's not  
5 just having a language within the COA and within this  
6 area, but it allows us to collaborate across different  
7 disciplines. It allows us to more efficiently do  
8 literature searches. So when we have a question, we're  
9 using the same terms other fields use, so lot of times  
10 our problems -- this area is relatively new in terms of  
11 psychometrics, you know. A lot of times the problems  
12 we're facing other people have, if not solved it, at  
13 least laid the groundwork to let us sort of jump ahead  
14 and not spend 5 years, you know, using a term we've  
15 heard a lot, reinventing the wheel.

16           So I think structuring the guidance in a way  
17 that just doesn't provide information on what we do  
18 now, but provides a framework and a connection to what  
19 we're going to do later, you know, where are we going  
20 to be 10 years down the road, maybe, you know, adaptive  
21 testing finally becomes more popular. Twenty years  
22 down the road it might be gain-based assessments,

1 especially in pediatrics or with children and right now  
2 we're just going to end up having to rewrite the  
3 guidance in 10 years to do that and I don't want to see  
4 that.

5           One other thoughts I have about how to  
6 structure a guidance, because I know you asked, is to  
7 think more critically again sort of with measurement  
8 science about validity and sort of how we think about  
9 validity because I think again, you know, sort of  
10 validity theory is an area that people spend their  
11 lives just doing and there is lot of writing, there is  
12 a literature out there about how we should think about  
13 validity. And currently we don't really talk about a  
14 measure being valid, right, we talk about inferences  
15 and we talk about claims, and it seems very much in  
16 line with what the FDA wants out of fit-for-purpose,  
17 right? It's not that depression measure is valid, it's  
18 are the claims you're making, are the inferences you're  
19 making based on that assessment tool within the  
20 population of interest what evidence do you have that I  
21 should believe you? And that's really what it's about,  
22 right, how much evidence can we get together?

1           And I think structuring the guidance in terms  
2 of thinking about it in this more sort of current  
3 validity theory idea allows fit-for-purpose not just to  
4 fit in nicely with a well-established sort of area of  
5 thought, but allows that flexibility, you know, because  
6 it's that idea, it's not method-based, it doesn't  
7 matter if it's IRT or classical test theory or some  
8 sort of causal modeling, it's sort of what evidence do  
9 you have. It's not population-based, it doesn't matter  
10 if it's pediatrics or rare disease, it's what kind of  
11 evidence can you bring to bear given what you're  
12 working with given what you're trying to say. And I  
13 think that general structure to the guidance would give  
14 us the foundation to get to the point where we're  
15 interested in whether or not the change between two  
16 time-points is meaningful. But I think there is still  
17 -- I'm concerned that we're writing something that's  
18 really good for today and what I would like to do is  
19 see us try to structure so it's really good 10 years  
20 from now and we don't have to do this again. Not that  
21 I am not enjoying it, but you know.

22           DR. CAMPBELL: Well, thank you for those

1 thoughts. Let's see, Linda, I think we'll go to you  
2 and then we'll end with Leah on the patient perspective  
3 thoughts. So Linda?

4 MS. DEAL: Sure, thank you. Again everyone's  
5 gratitude for the effort in organizing this meeting and  
6 putting together the guidance documents.

7 DR. CAMPBELL: Linda, you may need to be a  
8 little closer.

9 MS. DEAL: Better? Okay. So I know it was  
10 reiterated yesterday a couple of times, but I don't  
11 think it can be said too many times and that is this  
12 whole notion of meaningful change builds on all of the  
13 sessions before you have to start with ensuring that  
14 you're measuring a meaningful concept, right? And so  
15 it would be really difficult to argue that a concept  
16 that is changed, that's not meaningful, had a  
17 meaningful change, right? In addition you need to make  
18 sure you're measuring that meaningful concept well  
19 correctly. That all starts with a well-developed  
20 reliable measure responsive to change and that sort of  
21 thing, but then when we get to meaningful change, I  
22 think it's important when I speak to my colleagues, you

1 know, back at Pfizer it's important to understand that  
2 it depends where the individual starts from, of course  
3 at baseline, and what their expectations are, what  
4 their prior treatment experiences are, and so, you  
5 know, when we went through the whole roadmap process  
6 yesterday in understanding what's important to patients  
7 and depending upon where they are in their disease  
8 state and what they've experienced, I think it's  
9 important to recognize that we can define  
10 meaningfulness for an outcome for certain patient  
11 population today.

12 But as medical advances evolve, we have to  
13 revisit that patient journey because what's meaningful  
14 today could change based on experiences with advances  
15 in medicine. So I don't think it's a one and done  
16 thing for any instrument. I just want to echo Cheryl  
17 and other colleagues also about going from an  
18 instrument to an endpoint and thinking about that when  
19 defining meaningful change. Most of my experience has  
20 been with the anchor-based approach and one thing that  
21 I appreciate in the guidance, there's a box in the  
22 section D that talks about how the anchor that you

1 would use would be less difficult to complete than the  
2 actual COA and of course be related to it.

3 I wonder if we might go even further that if  
4 we're using an anchor for a COA, the human report for  
5 that COA should also be the same human report for the  
6 anchor. But I do recognize that human reports on the  
7 other hand can give meaning and context to biomarkers  
8 and other objective measures and can contextualize what  
9 a meaningful change in those sort of measurements would  
10 be.

11 The other thing I want to acknowledge is that  
12 we have to recognize that from the neutral point in an  
13 anchor or any meaningful change notion, you can't  
14 expect necessarily that positive and negative changes  
15 from neutral are equidistant. So for example it may  
16 take a greater change to be considered clinically  
17 meaningful improvement than it would be a deterioration  
18 or vice versa of course depending upon the meaningful  
19 concept.

20 The only other point that I would like to make  
21 for the guidance that I -- I don't have an easy answer,  
22 it's challenging, but I think we need to think about it

1 as the whole intention here is patient-focused drug  
2 development is these ECDF curves and these PF curves  
3 when we -- the whole point of meaningfulness from a  
4 patient's perspective is still they can understand the  
5 outcomes of a trial, right, are they going to  
6 understand these graphs and how can we express  
7 meaningfulness in a way that that is something that  
8 they can digest and understand what has happened and  
9 while I totally see the value of these curves, I wonder  
10 -- I think the onus is upon us since they are making  
11 decisions about their healthcare to communicate as  
12 fully and accurately as we can in words that they  
13 understand what this meaningfulness and change means.

14 DR. CAMPBELL: Thank you.

15 MS. DEAL: There's lot of meaning.

16 DR. CAMPBELL: Thank you Linda, and I'm just  
17 going to go ahead and forewarn Adam and Bryce --  
18 particularly Adam about this concept that Linda just  
19 brought up about are patients going to understand the  
20 graphs? I know you've been doing some work in  
21 presenting this data and how we present this data to  
22 patients. So start thinking about that as a response



1 and after Leah talks, maybe we can go in there for a  
2 couple of seconds to discuss. So, Leah?

3 MS. HOWARD: Great, thank you. And I want to  
4 reiterate the thanks to the FDA and thanks in  
5 particular for having a patient perspective on this  
6 panel. I think I understand that the experience of the  
7 psoriatic disease community may not be reflective of  
8 other patient communities, but I will do my best to  
9 represent all of us. You know, as we talk about what's  
10 meaningful to patients, I'd like to share a little bit  
11 about the 2016 patient-focused drug development meeting  
12 on psoriasis because I think it really brings a lot of  
13 clarity to some of what we're grappling with here on  
14 this panel.

15 So 2016 the FDA held a patient-focused drug  
16 development meeting on psoriasis alone. I will say  
17 about half of the patients that participated had both  
18 psoriasis and psoriatic arthritis, but for those that  
19 may not be familiar with our disease base, so psoriasis  
20 is a chronic inflammatory disease. It is systemic, so  
21 the rash that you may see on someone's skin that has  
22 psoriasis is really indicative of what's going on

1 throughout their entire system. It's a disease with  
2 the prevalence of about 2 to 3 percent of the  
3 population, so just over 8 million Americans live with  
4 psoriasis and what came through in the course of this  
5 patient-focused drug development meeting which had  
6 about 70 participants in the room and more than 100  
7 participants online was the diversity and experience of  
8 disease.

9           And so we know it's a spectrum condition mild,  
10 moderate, severe patients, but even within any one of  
11 those subsets of patients there was significant  
12 variation in their disease. Some of that had to do  
13 with the different places the disease presented itself,  
14 so if you have psoriasis on your face, maybe your  
15 hands, the soles of your feet, your genitals, all of  
16 those lead to different patient perspectives, lead to  
17 different comments when it comes to most bothersome  
18 symptoms as well as what patients are looking for in  
19 treatments.

20           And so as we talked through those issues  
21 during the course of the day, in particular this issue  
22 of symptoms versus treatments, there was huge variation

1 in terms of what patients were looking for, what they  
2 were expressing as the challenges with physically  
3 managing the disease on any given day, but also the  
4 impacts of the disease on their emotional health, on  
5 their social life, even on their career. And we heard  
6 really significant impacts that I think were very  
7 surprising, not to the patients in the room, but those  
8 that didn't have the disease about the way in which the  
9 disease really impacted their entire life. And so when  
10 you look at what's meaningful to someone with psoriatic  
11 disease, what you see is that it's really challenging  
12 to capture that in a measure, in a tool and I'll just  
13 say that, you know, there's more than 50 outcomes  
14 measures for psoriasis many of which don't speak at all  
15 to what patients are really most interested in.

16 And even when you drill down to those most  
17 bothersome symptoms, we had significant conversation  
18 about the difference between for example pain versus  
19 burning versus soreness or even other localized pain  
20 versus general pain and even with an itching which is  
21 one of the most bothersome symptoms, itching on the  
22 surface versus subcutaneous itching, and so all of

1 these are really challenging and when it comes to  
2 making treatment choices with your provider wanting to  
3 have as much information as possible is certainly front  
4 of mind for the patient, but really at the end of the  
5 day it comes down to what that particular patient's  
6 experience is with their disease is ultimately what's  
7 going to be most meaningful to them and really drive  
8 their decision-making.

9           One thing that I just want to bring up here at  
10 the outset is really this integration of benefit and  
11 risk is critical to patients, and part of the PFDD  
12 meeting was kind of giving these scenarios, imagine you  
13 are a patient talking to your provider and if the  
14 conversation looks like this, what's important to you?  
15 And I think what you saw in that input from the  
16 patients during the meeting was, you know, fear of side  
17 effects are real, but they also want that conversation  
18 to be balanced by the impact of this treatment on their  
19 psoriasis, the impact of this treatment on other  
20 comorbidities they may experience, as well as their  
21 quality of life and their ability to participate in all  
22 those things that are important and meaningful to them.

1 So I'll stop there.

2 DR. CAMPBELL: So, thank you, Leah, and so  
3 this comment is for Cheryl to be thinking about after  
4 we talk about data presentation is I think, Leah, what  
5 I'm hearing you say is that meaningful changes vary  
6 individual to the patient and so we need to make sure  
7 we explore it fully before we really are trying to  
8 achieve and I think that was a comment that was brought  
9 in of I think Cheryl talked about, you know, what is  
10 actually achievable when we try to set what meaningful  
11 change is, so Cheryl, if you want to think about some  
12 of that and maybe some of the work you've done in exit  
13 interview and things like that and how do we really --  
14 and to the entire panelists, how do we really take  
15 multitudes of different patients concepts and variation  
16 of what is meaningful and how can we finally get to  
17 something that we've got to implement and that we know  
18 that it's so critical.

19 So if you guys want to think about that, I  
20 want to touch back on to Linda's comment about  
21 ultimately how do we -- how are patients going to  
22 understand what is meaningful change if we depict that

1 something is meaningful and I -- certainly (ph) a  
2 conversation that we are all having about how do we  
3 express this information. So Adam, I know you've done  
4 some work in data presentation of scores. Though it  
5 may not be meaningful change, it is how do we present  
6 information to patients that they can understand from  
7 using an instrument I think, you know, that taking what  
8 RJ said, let's learn from what others have done, so I  
9 think that's a good point in some -- perhaps maybe a  
10 work of let's start with how do you even present the  
11 score.

12 So I don't know if you want to talk about some  
13 things about considerations you've thought about with  
14 how do we present this kind of information to patients.

15 DR. WIRTH: Thanks. So we have done -- again  
16 this is work initially led by Chris Forrest --  
17 collected data on -- from a nationally representative  
18 sample, our goal, you know, this idea of what is  
19 meaningful is one of the things that we're all trying  
20 to do is root these scores that in many ways have no  
21 meaning to even those of us that are really familiar  
22 with them into something that we understand. And one

1 of the ways to do that is sort of this relativeness,  
2 where are you relative to other people at least in the  
3 general population is where we started out.

4 So we have data from national representative  
5 sample of kids and their parents reporting on  
6 themselves and we've developed these what my partner  
7 Michelle was alluding to is how do we present and show  
8 people where they are and how do we describe what their  
9 score is. And some of the discussions I've had with  
10 Bryce and others then also adds into that how do we --  
11 how do we incorporate visually or do we our own  
12 uncertainty about what someone's score actually is as  
13 we start to think about measurement there and all these  
14 different things, you have the -- we've really -- in  
15 many ways we had a great discussion about this as part  
16 of the PEPPER (ph) Group and Bryce, I couldn't tell you  
17 what PEPPER stands for because I don't think it stands  
18 for anything. I know that it's pediatric and PROMIS  
19 and all sorts of fun stuff, but it felt like one of  
20 those acronyms they put together so that it could sound  
21 cool and didn't quite match up to the words.  
22 Nevertheless it's the PEPPER Group of which Bryce is

1 one of the PIs.

2           We've had some good conversations around when  
3 -- I was trying -- a man named Mike Cappleman (ph) --  
4 Dr. Cappleman who works in IBD talked about when we're  
5 trying to show how much, so in essence what we are  
6 talking about here are when we look at how much someone  
7 has changed, we start talking about the score itself  
8 and say you've moved from the 90th percentile to the  
9 88th percentile. So now you have, you know, you've  
10 dropped 10, you know, down some or your pain has gone  
11 up some and how do you fit relative to the general  
12 population. And we really struggled with putting these  
13 into groups of just sort of typical, which for much of  
14 the work we're looking at, given the properties, the  
15 instruments themselves and the distribution is probably  
16 about 85 percent of the population and these are all  
17 PROMIS instruments I'm talking about I should clarify.

18           Well, then these last two pieces, since we  
19 haven't yet done the work to look at how these  
20 correspond to other outcomes, right, so just using  
21 distribution-based methods, much like things like BMI,  
22 just saying the 15 percent, so you've got this 10



1 percent that is probably, you know, high and then 5  
2 percent is very high and that we might want to look at  
3 that and Mike Cappleman said, well, I'm -- what if I'm  
4 like a tiger father and my kid has just moved just a  
5 little bit and I want to see them move more and -- but  
6 they're already in the typical range, right? So it  
7 doesn't really matter that they've moved in one  
8 direction or the other from the sort of sense if  
9 they're a healthy person and trying to pull these ideas  
10 together of how do we present scores to patients that  
11 are kind of devoid of meaning in the first place and  
12 where changes on them may not be overly important  
13 because they're still just within the healthy range.  
14 We've been trying to do that a bit again with these  
15 percentiles and then just sort of colors in wide  
16 groups.

17           And we're going to work with -- we're in the  
18 process of doing some work with actual patients and  
19 physicians now, pediatricians now, to try and see how  
20 that works out. But that's what we've been doing is  
21 sort of having these charts with big colors on them.

22           DR. CAMPBELL: So I don't know if anyone else

1 wants to add about potential how would you present  
2 this. I do think this perhaps is a future area of  
3 continuing to work together as this how do you really  
4 are depicting the score and what is change, you know,  
5 what is meaningful change because your example of, you  
6 know, my child may be normal, but I want more, I think  
7 gets down to still this concept of within meaningful  
8 change, but individual person as patient, so perhaps  
9 this is an area where we can maybe all work together to  
10 help explore what are some ways to do this because that  
11 is important. Does anyone else want to add? So Bryce?

12 DR. REEVE: So -- and thank you Michelle.  
13 PEPPER is Pediatric Patient-Reported Outcomes Network.  
14 So the PE part is Pediatric; the PR, PRO measurement.  
15 So I don't know if I have the solution today to provide  
16 for you, but more of a cautionary tale for how we think  
17 about how to present this type of information back to  
18 patient populations. Two key things to know; one is  
19 we're all going to be patients one day and we're all  
20 going to be going through these same type of  
21 experiences overall. So recognizing that when we talk  
22 about patients, we're talking about us, but also, my

1 second point is I think in many ways when we think  
2 about our populations, I think for many of us,  
3 including myself, we sort of sit in sort of a ivory  
4 tower of academic or industry excellence.

5           And so I live in North Carolina. I'm  
6 surrounded in around three incredible universities of  
7 UNC, Duke and N.C. State and know you sort of get  
8 comfortable in that environment where a lot of people  
9 around you have very high degrees and are very  
10 literate. However, we have to recognize in the U.S.  
11 population, I can go 30 miles west, east, north, south  
12 from where I live there and it's a very low -- SES low  
13 literacy populations. And I think we trick ourselves  
14 in trying to think that we can present this information  
15 in a way that a lot of people understand what's going  
16 on with this information.

17           We know that people struggle with numeracy,  
18 just simple numbers and doing with like saying, no, you  
19 know, you or your child is in the 89th percentile, I  
20 don't think a lot of people -- even well-educated  
21 people can understand what that really represents and  
22 means. So I think it's a cautionary note and think of

1 both how we think about designing our questionnaires,  
2 but also how we present this data. And I lose sleep at  
3 night and I worry that we're developing systems that  
4 are only going to benefit the affluent in high literacy  
5 and I think we're missing out on those populations, the  
6 underserved population. You could really benefit from  
7 us providing better ways of assessing this health and  
8 using those to inform healthcare delivery and research  
9 overall.

10           So, you know, earlier your question, Michelle,  
11 was, you know, how to present cumulative distribution  
12 functions to patient populations. I don't think -- I  
13 think I can present that to graduate students or even  
14 people around here, I don't think anybody could  
15 articulate, talk about what a CDF actually means and  
16 represents overall. So with that -- with those two  
17 cautionary notes, there is -- I think, there are ways  
18 we can present and visualize this type of data overall,  
19 I still think we're learning about that and I think  
20 these methods we talk about doing, you know, why don't  
21 do we do cognitive interviewing based on visualization  
22 of data there?

1           So I recommend we -- that's an area that I  
2 think will focus on is how to present what a person is  
3 and how they may change over time. I think we have  
4 good ideas of how to do it, but I don't want to be  
5 prescriptive in how we particularly do that. With that  
6 being a point there is when we want to do these  
7 cognitive interviews, we can't have people that look  
8 like us in that room there. We need to reach out to  
9 those different diverse populations in terms of race,  
10 ethnic, culture, nationality, as well as SES things  
11 there to make sure that they are in that room helping  
12 us to derive what's the best way to present this  
13 information.

14           DR. CAMPBELL: Thank you, Bryce. Linda, did  
15 you want to respond or have anything else to say?

16           MS. DEAL: No, I appreciate the responses. I  
17 just want to just say, you know, one thing I thought  
18 about in terms of the anchor categories, whether using  
19 a change or static anchor, maybe it's as simple as  
20 putting as much effort into creating the anchor and the  
21 anchors to the response get the verbal descriptions of  
22 the categories and the anchor question, maybe it's as

1 simple as developing that item to the rigor we do the  
2 instrument itself in words that means something to  
3 patients. And while we're measuring meaningful  
4 concepts and we can talk about statistical significant  
5 changes, perhaps the meaningfulness of improvement is  
6 more connected to how we construct the anchor and the  
7 verbal descriptors for the rating scale.

8 DR. CAMPBELL: Well, thank you for that. And  
9 I do think that we maybe have identified of course a  
10 new area of research to work together in this. I think  
11 there's potentially some really great lessons learned.  
12 Noting the time and I know I picked on Cheryl about  
13 anything else you wanted to add on the comment that  
14 Leah brought up about, you know, different individual  
15 meaning, you know, everyone has their own idea of  
16 what's meaningful to them. I don't know if you have  
17 anything else you want to add or --

18 DR. COON: Yeah, I just want to kind of  
19 refresh that this guidance is specifically -- I'm  
20 reading from the introduction, it's specifically to  
21 inform and guide the work conducted by medical product  
22 developers, blah, blah, blah, essentially for seeking

1 medical product approval by the FDA. So interpreting  
2 scores on the COA has many, many other contexts of uses  
3 beyond just evaluating a drug for FDA review. So this  
4 idea of individual change and what's important for me  
5 might be different from what's important to Linda and  
6 so on. We're trying to figure out what's  
7 representative of the patient population that's being  
8 evaluated in the clinical trial and pick a number or a  
9 range of numbers that is representative. The way that  
10 that then gets communicated, it sounds like there are  
11 people working on that and I'm excited to see some  
12 plots. I wish we were looking at them today.

13 But when you're actually speaking, so if you  
14 analyze data from psychometrically and you look at the  
15 distribution and I think some of the CDFs and the PDFs  
16 in this guidance document shows there's variability and  
17 you can easily just take a median or some simple  
18 statistic and come up with one number and be done with  
19 it. But when you actually sit down and talk to  
20 patients in a cognitive interview or in an exit  
21 interview, you find out exactly what that variability  
22 means. And you might start to get scared that there's

1 no way we're going to come up with one number. So it's  
2 about finding different source of evidence, qualitative  
3 data, quantitative data, triangulating across all of  
4 them and finding something that's really  
5 representative. Then in the treatment setting, you can  
6 actually work with patients about what their individual  
7 treatment goals are and maybe it's not a 10-point  
8 change.

9           Maybe they want 20 points or maybe 5 points is  
10 sufficient and help them pick the treatment that is  
11 going to be most appropriate for what their treatment  
12 goals are. So the goals of interpreting COA score  
13 change for this discussion or for this guidance  
14 document, it's really for FDA evidentiary review, but  
15 that work needs to be done. The people sitting at this  
16 table and out there still need to be doing that work  
17 for the real world setting.

18           DR. CAMPBELL: Thank you Cheryl. So I'm just  
19 going to let the audience know that we're going to be  
20 starting the public -- the question-and-answer, I'm  
21 sorry in a moment. So if you've got some questions or  
22 are thinking about and we'll put the microphones back



1 up, we took them out so, you know, people won't hear  
2 our conversations during the breaks online. So we'll  
3 put them up, so start thinking about some questions,  
4 but I do want to ask the panel, do they have any other  
5 thoughts you want to add? RJ, do you have anything you  
6 want to add, or Wen-Hung to what's been said? And is  
7 there anything where I've heard some really good  
8 thoughts that I'll summarize in a moment, but is there  
9 any glaring thing that you feel we're missing for  
10 what's there? So RJ, do you have anything? And then  
11 I'll go to Wen-Hung.

12 DR. WIRTH: One, I just want to sort of second  
13 I think what Cheryl just said about and what you  
14 mentioned a moment ago about I think how we present  
15 this information to not just patients, but you know,  
16 even how we present it to the FDA, how we present it to  
17 other stakeholders, how we present it to the patients,  
18 is sort of an area of research that hasn't seen a whole  
19 lot of work. And we actually have done a little bit of  
20 work in this, but it wasn't with patients with -- it  
21 was with financial literacy. But we ended up coming up  
22 with a very similar sort of presentation style.

1           So we might be able to sort of harking back to  
2 this idea of collaborations across disciplines, you  
3 know, we might be able to bring people together and  
4 bring a good team together and move this along because  
5 I do think it's a really important topic and one that I  
6 don't think has gotten much attention as far as I know  
7 in any real discipline about how we present these. So  
8 I'm glad the work is going on, but I think we could do  
9 more.

10           DR. CAMPBELL: Thank you RJ. And Wen-Hung,  
11 did you have anything else?

12           DR. CHEN: Yes, I just want to make comment  
13 about forward-thinking be in tune with the science and  
14 seeing down the road of the thought, the effort that we  
15 put into the guidance is to provide to the sponsors the  
16 patient group to that how best to produce to develop  
17 this instrument and then produce evidence to support  
18 like what shall just read about, you know, drug  
19 development and then get approval in a -- explain that  
20 into the labeling. And so I -- we agree that we should  
21 think ahead and then watch the signs down the row and -  
22 - but by intent of writing the guidance for the future,

1 if we don't know if the thing that work and then we put  
2 that in the guidance and then some drug company use  
3 that and say you tell us to do that, but it failed so -  
4 - so I mean I think we should have a very general  
5 guidance that say, you know, we are open to any new  
6 thought in a new technology, new approach, come to talk  
7 to us, we are -- but something that it hasn't -- we  
8 cannot even imagine at this time I mean writing into  
9 the guidance. So I'm just -- no, I'm not disagree what  
10 you say. I think that's great idea that how to write  
11 out in the guidance, say bring us new stuff, right?  
12 But not saying that oh, use this new stuff. Yeah.  
13 Thank you.

14 DR. WIRTH: Right.

15 DR. CAMPBELL: RJ?

16 DR. WIRTH: Yeah, no, I think -- you know, and  
17 you made an excellent point, I want to clarify it, I  
18 wouldn't write the guidance, you know, with, you know,  
19 how do we incorporate, you know, gain-based assessment  
20 in 10 years? I think what we -- what would be useful  
21 is to think about how can we structure this with a  
22 framework that in 10 years when people are interested

1 in moving in a new direction, that there's sort of a  
2 mechanism or framework in place to kind of say, like  
3 all right, well, according to the guidance, even though  
4 this isn't something we've ever done before, we need to  
5 think about it in these terms and we need to think  
6 about what evidence do I need to show along the way to  
7 get to the point in which any inference or claim I  
8 based on this new technology or this new idea, this new  
9 methodology, people have faith in it. So yeah, I  
10 wouldn't want to ever sort of say like this is how you  
11 use this method because again I think that would just  
12 write us into a corner, which I'm not a fan of.

13 DR. REEVE: And just about -- just of what  
14 it's about --

15 DR. CAMPBELL: Okay, Linda -- oh, Bryce, and  
16 then --

17 DR. REEVE: Oh, go ahead.

18 DR. CAMPBELL: No, go ahead Bryce. And I  
19 think Linda wants to respond.

20 DR. REEVE: Oh, Linda first. No --

21 MS. DEAL: No, no. You go ahead.

22 DR. REEVE: Just to build on what RJ has said

1 there, I think the key thing in writing this guidance  
2 there is in a flavor to be consistent if all the --  
3 rest of the parts of the guidance is to recognize that  
4 there can be a flexible approach to how we think about  
5 assessing a meaningful change overall. And so we don't  
6 want to be prescriptive in this guidance to say that  
7 there is one method that dominates as the best method  
8 overall because it's going to vary depending on the  
9 context of use. So I think what I'd like to see is  
10 guidance there, especially in this area of meaningful  
11 changes, recognize there are different ways we can get  
12 a meaningful change and what is the best way might vary  
13 depending on the context of use.

14 And I think the important part of any sponsor  
15 investigator wanting to put forward their recommended  
16 way to assess it is there's a well-justified model for  
17 why we chose this anchor or this approach to these  
18 things based on what they know about the context of use  
19 of patient population as well as the measure itself.  
20 So I think with that balanced approach of flexibility  
21 and justification is the path forward.

22 DR. CAMPBELL: Thank you Bryce. And Linda,

1 final thought?

2 MS. DEAL: Sure, having followed the special  
3 populations session earlier, I just wanted to kind of  
4 mention it might be worthwhile to acknowledge that no  
5 change at all in the outcome of interest could be  
6 meaningful, especially in a rare disease population.  
7 And I also want to acknowledge even further praise for  
8 this within-patient change notion because in those  
9 sorts of trials in rare disease, they're often single  
10 arm, there is no competitor similarly in some of the  
11 oncology studies. So I just wanted to say -- you know,  
12 acknowledge that that also helps in those scenarios.

13 DR. CAMPBELL: Thank you. And so I see we  
14 have some people ready to ask some questions. I just  
15 ask that you state your name and your affiliation  
16 please. So we'll go and start in the back.

17 AUDIENCE QUESTION AND ANSWER

18 MS. WILSON: Hillary Wilson with Boehringer  
19 Ingelheim. Thanks for the great discussion. I am --  
20 it was really great to hear you guys bring the  
21 conversation back to how do we make sure that  
22 meaningful change is understood in the context of the

1 patient perspective. And I like Linda's comment that,  
2 you know, maybe part of that is just ensuring that  
3 we've selected the right anchor and that we understand,  
4 you know, the context of that anchor. I tried doing  
5 this hypothetically, you know, and giving, you know, a  
6 patient population, you know, well, if you experience  
7 this amount of change, you know what would be  
8 meaningful. And I find this is an incredibly  
9 challenging exercise for patients to do.

10 I want to offer that in my tenure at Evidera,  
11 there was an exit study that I was involved in where  
12 there was actually a qualitative component to that  
13 study. The FDA had actually encouraged the sponsor to  
14 do an exit study because it was a disease condition  
15 where really understanding the clinical benefit from a  
16 patient's perspective and in the amount of change that  
17 would be meaningful, was it really well understood, so  
18 they wanted the sponsor to collect more information on  
19 this.

20 And the exit study had a lot of different  
21 goals and we didn't anticipate using the data in this  
22 way. But we had both a quantitative survey that

1 included an anchor and we did a number of analyses, you  
2 know, quantitatively anchor-based primarily to  
3 understand what would be considered a meaningful  
4 change. But then we also were able to map that  
5 qualitative data back to what was a responder  
6 definition, you know, so we use our triangulation to  
7 find out this is what, you know, numerically would be a  
8 responder and then we could map back, you know,  
9 qualitatively how did patients too had met that  
10 responder definition, how did they describe their  
11 treatment benefit and then compare that relative to the  
12 non-responders.

13 And so I think that, you know, in thinking  
14 about how we might communicate back to patients using  
15 their own words qualitatively of how they described a  
16 treatment benefit versus those that aren't might be one  
17 approach to consider and I'd love to get the panel's  
18 thoughts on that.

19 DR. CAMPBELL: Any quick thoughts on that from  
20 the panel? I will totally pick on Cheryl because I  
21 know she's looked at this. I could pick on Bryce too,  
22 but I want to start with Cheryl.



1 DR. COON: I agree. I mean, I feel like  
2 qualitative evidence to support the data that you get  
3 out of -- get -- that you collect from patients, being  
4 able to put those together can provide a real -- really  
5 robust story that just quantitative data and it's -- I  
6 mean, I'm a psychometrician, I love data, I play with  
7 data for fun, but speaking to patients and actually  
8 hearing in their voice what is important to them and  
9 the nuances with that can really give good context to  
10 that and that example, I don't know if that's  
11 (inaudible), but if it's another one, you should  
12 definitely submit that to the docket because those are  
13 the types of things that we should be looking at, the  
14 success stories and as, you know, going back to the  
15 topic of evolution of methods as methods evolve and  
16 become successful and are used in successful ways, I  
17 hope that there's a resource where the FDA can, you  
18 know, maybe provide a website with links or something,  
19 a living document that shows as the field evolves  
20 here's what's working and here is how people were able  
21 to use this evidence to support drug review.

22 DR. CAMPBELL: So Wen-Hung, you wanted to add

1 some thoughts? And then Leah, do you have something  
2 else to add? We can come to you after Wen-Hung. Okay.  
3 Wen-Hung?

4 DR. CHEN: So I just want to emphasize that  
5 the guidance is a guidance, not a requirement. And  
6 this thing that we talk about in the guidance is what  
7 we think that may work for the sponsors. It doesn't  
8 mean that they will actually work, but you know, and we  
9 actually edit the -- as the interview and then edit  
10 patient quantitative at the survey and then also at the  
11 example and I think what here you said is another  
12 example of that. So I would say that I agree if you  
13 are able to do that, but I won't say you are required  
14 to do that, you know, but basically again back to what  
15 we always said, if you have idea -- if you have some  
16 method or something you want to do, you know, bring it  
17 to us early and talk to us.

18 And then if you can do it and then you can  
19 show, like, you know, let's say provide evidence to  
20 show that, I think that's what Adam say that the whole  
21 evidence or RJ say that the whole evidence of things  
22 and that will be great. But again, you know, truly as

1 a guidance and bring us what you think and then bring  
2 us the new ways and then actually help us as well.

3 DR. CAMPBELL: Leah?

4 MS. HOWARD: Yeah, just to second the comment  
5 that was made about utilizing the language that the  
6 patients use to describe their experience and their  
7 hopes and expectations, I think going back to my  
8 comments earlier about the idea of itch, I think  
9 there's a -- what we heard at the PFDD meeting for  
10 psoriasis was there was a difference between saying  
11 itch and saying constant mind-blowing itch that you can  
12 never scratch. And so I think that the way that  
13 patients were articulating their feeling of itch was  
14 very different than someone that doesn't have  
15 psoriasis, so has never felt an itch like that. And so  
16 it was very important for them to hear other patients  
17 describing that feeling of itch and the comments that  
18 were made by individuals that have that symptom  
19 expressing, yes, that's exactly what I'm talking about,  
20 not this itch that you can, you know, scratch when you  
21 have a bug bite and that goes away 10 minutes later.

22 DR. CAMPBELL: Next comment please.

1 MS. MANSFIELD: Carol Mansfield, RTI Health  
2 Solutions. This is just a comment because patient  
3 preference methods are out of scope for this  
4 discussion. But are there any other methods to  
5 consider? I put forward patient preference studies as  
6 a method to consider. When you design a patient  
7 preference study, the whole point is you have to  
8 describe how the drug is going to benefit them, what  
9 change they're going to experience in patient-friendly  
10 language so that they can tradeoff the benefits and the  
11 risks and to Leah's point that patients want to  
12 consider their benefits in the context of side effect  
13 risks. That's -- you know, that's a strong point for  
14 patient preference methods. So I would -- I feel like  
15 they should be in there at least as an alternative.

16 DR. CAMPBELL: Thank you. I think Wen-Hung  
17 wants to respond, and then Dagmar will be our last  
18 question-and-answer. So Wen-Hung?

19 DR. CHEN: Yes. So patient preference has not  
20 been done in this -- for this purpose, but actually the  
21 scale adjustment method that Bryce talk about is  
22 actually the variation of the preference method by

1 using IRT approach. So is that using IRT to rank the  
2 like it, don't like it, like it, don't like it, like  
3 that. So it's actually similar, okay? But I want to  
4 say is, again just emphasize we cannot include all the  
5 new things in the guidance and either that we don't  
6 know it or it hasn't been tried yet before, but you can  
7 always suggest in a docket or bring it to FDA to talk  
8 to us, say we want to try -- use this method, can we  
9 use that to determine meaningful change? And is open  
10 and we like to know what they are and then we like to  
11 study them. Thank you.

12 DR. CAMPBELL: Thank you. Dagmar?

13 MS. AMTMANN: Good morning, still Dagmar  
14 Amtmann at the University of Washington. Just want to  
15 point out, I didn't say anything in response to the  
16 last session. So I -- sorry.

17 DR. CAMPBELL: It's okay.

18 MS. AMTMANN: I just want to follow up. I  
19 would like to see some recognition on the part of the  
20 FDA and some discussion of what meaningful difference  
21 means in dealing with degenerative diseases. When I --  
22 I often work with people looking at studies and people

1 with multiple sclerosis, we don't have an improvement.  
2 One day we will have drugs that will actually improve  
3 people's functioning, but we don't. And so we're  
4 looking at slowing the progression of the disease. And  
5 so even saying that, you know, if somebody would stay  
6 the same as today, that would be great compared to  
7 which we have, which is continual loss of function.

8           When I worked with the FDA, like with Wen-Hung  
9 on MS-related measures, when you apply the same metric  
10 as you apply in other contexts, it simply does not  
11 work. The companies are asked to provide evidence that  
12 they just have absolutely no way of providing. So I  
13 just appreciate some recognition in the guidance that  
14 maybe in this context, some different methods or  
15 different type of evidence could be considered. Thank  
16 you.

17           DR. CAMPBELL: Thank you Dagmar for that  
18 Comment. So I want to thank everyone and our panelists  
19 for their participation today and their thoughts.  
20 There were some really great thoughts. I think what  
21 we've heard is that it's really nice to see that the  
22 FDA has listened over the last couple of years and take

1 it in and explain where there was confusion in the past  
2 and provided examples of what things look like when  
3 advice is received in the IND process. However, a  
4 framework may be needed, but not a boxed-in framework,  
5 but allows for evolution as the -- of measurement  
6 science in general evolves, how we can make sure we are  
7 still evolving with the methods. It was highlighted  
8 about the inclusion perhaps or how to use the utility  
9 of I guess -- and I'm not using utility in these terms  
10 of patient preference, but the utility of modern  
11 methods, modern psychometric methods of IRT and  
12 (inaudible) and how could that play in and be  
13 supportive.

14           There was a lot of discussion on, well, maybe  
15 the best method may vary based on the context of use  
16 and we should really be exploring that. Adam  
17 highlighted to us in our pediatrics remember that there  
18 can be disagreement between a child and a parent and  
19 that is okay and the child can still be able to self-  
20 report if they're able to and we should really take  
21 that into account that disagreement is okay. And then  
22 we heard some really great -- we had a good discussion

1 about how to present data. We started off with how do  
2 we present meaningful change, but then it ended up  
3 turning into how do we even just present data which is  
4 something that I think everyone would agree that we're  
5 all struggling with and see some opportunities for  
6 collaboration. And then we had some really great  
7 comments from our audience about things to also  
8 consider.

9 So I want to again thank our panel. We are  
10 going to be breaking for lunch. I will put the famous  
11 docket slide, although I got some nice shout-outs  
12 during this session. I know I have to say it. We'll  
13 be breaking for lunch, we'll be returning at 1:15, so  
14 if you can please go right and applause our panelists  
15 and I'll see you back at 1:15.

16 (Applause)

17 DR. CAMPBELL: And remember, you can still  
18 signup for open public comments.

19 (Lunch Recess)

20 LUNCH

21 EMERGING TECHNOLOGIES TO SUPPORT FIT-FOR-PURPOSE

22 CLINICAL OUTCOME ASSESSMENTS



1 DR. KOVACS: Good afternoon. I'm Sarrit  
2 Kovacs and I work within the Office of New Drugs in  
3 CDER. I'm the moderator for this session on Emerging  
4 Technologies to Support Fit-For-Purpose Clinical  
5 Outcome Assessment. We'll be discussing five panel  
6 questions related to digital health technology.

7 In this session when we mention the term  
8 digital health technology, we're referring specifically  
9 to mobile technology tools such as wearable sensors  
10 used within a clinical trial context to capture  
11 clinical outcomes like mobility, sleep and falls.  
12 Terminology related to digital health technology is  
13 still evolving and for the purpose of this session  
14 we'll be using all terms interchangeably.

15 After the panelists respond to the five panel  
16 questions, we'll have some time at the end for audience  
17 question and answer. And please note that you may  
18 submit any comments and feedback that you may have  
19 related to the Guidance 3 discussion document,  
20 appendices, technology, terminology to the public  
21 docket, which is linked on the workshop's website and  
22 is open for the next 2 months, closing on December 14.

1           We're fortunate to have in this session eight  
2 distinguished panelists with a broad range of  
3 backgrounds, perspectives and expertise. I'll now let  
4 each panelist introduce him or herself by stating their  
5 name, affiliation and briefly state the perspective  
6 that they plan to bring to this session.

7           DR. BYROM: Well, you caught me out there I  
8 guess, Sarrit. I didn't know I was going to have to  
9 say a perspective. So let me -- let me try and think  
10 on what I'm speaking.

11           So Bill Byrom, vice president of product  
12 strategy at CRF Bracket. We're an eCOA vendor  
13 supporting clinical trials. And I guess the  
14 perspective I'll bring will be on that technology, eCOA  
15 wearable technology side of things. Over to you, Chad.

16           DR. GWALTNEY: Chad Gwaltney, president,  
17 Gwaltney Consulting. I guess my perspective will be as  
18 a more general COA expert and -- in supporting sponsors  
19 and selecting, developing, implementing and  
20 interpreting clinical outcome assessments. So not  
21 necessarily a specific wearables expert, but more of a  
22 general perspective.

1           MR. HO: Martin Ho. I am associate director  
2 at Center for Devices and Radiological Health. I wear  
3 a couple of different hats. My first hat I wear up  
4 into this session is that I am the methodology lead at  
5 my Center for patient reported outcomes. And my -- the  
6 other -- in another capacity, I am building the real-  
7 world performance component of our Center's Digital  
8 health Technologies' Precertification Program, which  
9 will be -- have an opening by December 1st this year.

10           DR. MORENO: Hi. I am Megan Moreno. I am an  
11 adolescent medicine physician and a researcher. I am  
12 the vice chair of Digital Health at University  
13 Wisconsin-Madison in the Department of Pediatrics. And  
14 in my research hat, I am the PI of the Social Media and  
15 Adolescent Health Research Team. So the perspective  
16 I'll bring is probably more from the research  
17 perspective of looking at how adolescents choose to  
18 interact with technology and share information about  
19 their health.

20           DR. PATEL: Hi. Good afternoon. Kushang  
21 Patel. I am a research associate professor at the  
22 University of Washington. In terms of my perspective,

1 my COA-related research has focused on physical  
2 function assessments using a variety of methods, but  
3 primarily performance-based outcomes. Currently, I am  
4 working with the ACTION public-private partnership  
5 with FDA to qualify an accelerometer-based outcomes  
6 assessment for chronic musculoskeletal pain conditions.

7 MR. REASNER: Hi. I am David Reasner. I work  
8 in a sponsor organization developing and modifying  
9 COAs. I personally have a quantitative bent on that  
10 work, but our study endpoints team works on the  
11 regulatory aspects of COAs, liaising with COA staff  
12 and also as clinical trialists supporting the  
13 operations of clinical trials.

14 MS. SCHRANDT: Hi. Good afternoon. I'm Suz  
15 Schrandt and I am a patient and a patient advocate and  
16 I service as the director of patient engagement for the  
17 Arthritis Foundation. So I suppose I'm representing  
18 all of those facets of my experience. And I spent  
19 several years facilitating patient engagement in  
20 research, QI, R&D, et cetera.

21 DR. SPIEGEL: Good afternoon. My name is  
22 Brennan Spiegel. I am the director of health services

1 research for Cedars-Sinai Medical Center. I'm also a  
2 professor of medicine and public health at Cedars-Sinai  
3 and UCLA.

4 I bring the perspective of being pretty full  
5 from that box lunch.

6 (Laughter)

7 DR. SPIEGEL: And I say that -- actually, I  
8 invented an FDA cleared sensor that can measure how  
9 full you are, which is true. So I am also interested  
10 in wearables, to develop wearables. And I also was one  
11 of the NIH PROMIS investigators. So I've a background  
12 in psychometrics and I bring that background to health  
13 technology and try to understand how we can use these  
14 technologies to measure patient outcomes.

15 DR. KOVACS: Thank you. So we'll move on to  
16 the panel discussion questions now. The first  
17 objective is to discuss recommendations for changes to  
18 definitions included for the categories of clinical  
19 outcome assessments or COAs or any additional  
20 categories of COAs recommended.

21 Specifically, this panel's -- this panel  
22 sessions first question is: Does digital technology

1 that captures clinical outcome data fit within the  
2 established COA categories or should they be considered  
3 a separate fifth COA category? And I'll ask a number  
4 of our panelists to provide their responses to this  
5 question. So, Kushang, do you want to start?

6 DR. PATEL: Sure. So I think there are  
7 several digital health technology-based assessments  
8 that could fit within the current four COA types. For  
9 example, you could use a digital tech outfitted kiosk  
10 to assess the short physical performance battery or  
11 timed up and go test in nonfrail patients, which would  
12 then fall under the PerfO category.

13 However, in my view if you're using  
14 accelerometers to measure sort of discretionary  
15 activity, then this does not conform with the four  
16 measurement type or COA types.

17 And so what FDA could consider is potentially  
18 a fifth category of, you know, a digitally monitored  
19 outcome or a digitally recorded outcome. Or  
20 alternatively FDA could consider expanding the  
21 observer-reported outcome type by including a digitally  
22 monitored subcategory. But I think I'd actually like

1 to hear what other panelists say about this.

2 DR. KOVACS: Brennan, would you like to go on?

3 DR. SPIEGEL: Sure. So I by nature am more of  
4 a lumper than a splitter. So I'd very much like to  
5 find a way to place the type of data that we're talking  
6 about today into this framework. But I'm having  
7 trouble doing that because it's a little hard for me to  
8 see how the data from, let's say, wearable sensors,  
9 ambulation, sleep, steps and so on fits cleanly within  
10 this taxonomy.

11 It's not a patient-reported outcome. It's  
12 certainly a patient-generated data. The patient is  
13 generating this data. It's not being measured by a  
14 trained physician or a healthcare provider. It's not a  
15 standardized task like you would expect for a Perfo.  
16 It's not really an ObsRO, it's not a ClinRO and it's  
17 not a PRO. I've been calling it a PRI, patient-  
18 reported informatics, which doesn't mean anything  
19 really.

20 So I think it's patient-generated data. It's  
21 -- we'll talk about whether it's meaningful or not, and  
22 I believe it is, in the next set of questions. But I

1 believe, unless somebody convinces me otherwise, it  
2 sounds like a separate category in my opinion.

3 DR. KOVACS: David, did you want to comment?

4 MR. REASNER: Sure. Thank you. I would put  
5 forward that from my perspective when you have patients  
6 perform a standardized task with a wearable sensor,  
7 that you could categorize it as a PerfO. The nature of  
8 the validation would be similar to in-clinic equipment,  
9 telemetry. The evidence you'd bring forward to see  
10 that it's fit-for-purpose would be similar, would  
11 follow the same regulatory requirements.

12 And I think we should be indifferent to the  
13 length of the wire. So whether you're in the room or  
14 down the hall or at home, I think as long as the  
15 evidence supports the fit-for-purpose use in the  
16 context of the clinical trial, then I think you can  
17 have a PerfO.

18 So that's maybe the most straightforward  
19 translation. There are some other assessments that are  
20 harder to categorize, but might be ObsROs. As Dr. Dunn  
21 said yesterday, maybe with minor modifications to these  
22 definitions we can include some of these digital health



1 technology measurements.

2           So where you're observing a patient "free  
3 ranging," as some people have mentioned, you know, in a  
4 way it's sort of like an ObsRO. I mean, you can  
5 imagine an observer with a stopwatch and a counter, but  
6 instead you really just have a device, and so if it's  
7 fit-for-purpose for the concept that you're trying to  
8 assess. In a sense the observer is somehow distant,  
9 but, you know, you might stretch the definition there.

10           Some other things that are interesting, I  
11 don't know where they fit in. Maybe they're ObsROs or  
12 things like geo tracking. You know, these kinds of  
13 observations may be are less directly related to what  
14 we've traditionally done as a COA.

15           DR. KOVACS: Thank you. Suz, did you want to  
16 mention something?

17           MR. SCHRANDT: Sure. So I sort of got to my  
18 answer backwards because I couldn't make an argument  
19 for it fitting in the bottom three categories and it's  
20 certainly not a PRO. So I guess where I landed is I  
21 think it could be its own category. But what I would  
22 want to see is almost a dotted line, sort of a

1       bidirectional arrow between PROs and digital tools so  
2       that there would be absolutely no uncertainty that data  
3       generated from a tool needs to be corroborated or  
4       supplemented by the PRO data.

5               And I think that concept of not looking at it  
6       in isolation has come up a couple times already, not  
7       only because we want to make sure the data we're  
8       collecting is accurate and complete, but I think  
9       there's also sort of a -- almost an ethical or a  
10      societal mandate that we validate patients' experience  
11      and we want to be sure we're not supplanting what  
12      you're experiencing with what a tool says.

13              I do think it's always instructive or  
14      sometimes just refreshing to look outside of healthcare  
15      for examples for guidance. And I just happen to have  
16      an experience 2 weeks ago with my smartphone that was  
17      spot on. The battery has clearly gone south, so I took  
18      it to the store and a very nice young gentleman plugged  
19      it up to all his diagnostics and we went through.

20              And I didn't have too many apps and I didn't  
21      have my screen too bright and everything else was  
22      checking out. And so he plugged it into the tool to do

1 the battery diagnostics and it said "battery  
2 functioning at 88 percent" and he said, "Ma'am, battery  
3 is functioning at 88 percent." And I said, "Well, but  
4 my phone is at a 100 percent. I make one call for 5  
5 minutes and then it's down to 50 percent." And he was  
6 completely speechless and he just sort of pointed back  
7 to his tablet and said, "But 88 percent".

8 And I -- you know, outside of healthcare the  
9 way I handled that situation was to say, "Dude, give me  
10 another battery." And now it's working fine. But in  
11 healthcare that could really have some serious  
12 ramifications and I want to be really sure that we --  
13 if we're going to use these tools, which I do think  
14 have a lot of promise, we use them very wisely and  
15 always corroborate with that patient report.

16 DR. KOVACS: Thank you. And, Martin, did you  
17 have something that you wanted to add?

18 MR. HO: I couldn't agree more. In fact I  
19 think all these categories that are listed here are for  
20 human oriented. We are always asking "reported by  
21 whom, interpreted by whom or measured by whom."  
22 However, when a whom is actually a set of algorithms,

1 then all these categories may have a different, you  
2 know, meaning; for example, if some -- or something  
3 that's supposed to measure our activity level at home  
4 and the interpretation of our level is actually  
5 determined by a set of algorithms.

6 And so therefore when I'm at home, I'm not  
7 trying to perform any specific task, but then I -- yet  
8 I can -- through that data collection they can, you  
9 know, capture some of my -- you know, the COA to  
10 reflect my activity level.

11 So I personally don't have -- I'm not very  
12 religious about categorization. As long as the COA  
13 works and useful, then I'm fine with it. But at the  
14 same time I think although some of the digital health  
15 technologies can be categorized under this current  
16 platform, but I think a lot of times these new  
17 technologies may be a bit beyond these categories,  
18 because it's just being beyond the organizing principle  
19 of these definitions.

20 DR. KOVACS: Thank you. So the second  
21 objective of this session is related to the fact that  
22 digital health technology can potentially be used for

1 clinical outcome assessment and to discuss suggested  
2 approaches or methods to provide evidence of fitness-  
3 for-purpose for these tools. For example, walking  
4 speed rather than step count may be most relevant and  
5 meaningful to a particular patient population.

6 Some of the panelists will be responding to  
7 the next two questions on this slide. So the first  
8 question is: Can data obtained using digital health  
9 technology be reflective of clinical benefit and used  
10 to inform regulatory decision-making, and if so, do you  
11 agree that the tools used in this context would be  
12 considered COAs?

13 The second question is: How can data obtained  
14 using these methods supplement and add value to PRO  
15 data or data obtained by -- from other COA types? And  
16 I know that Dr. Brennan Spiegel has a slide to present  
17 in response to these questions, so I'll ask him to  
18 speak first, if that's okay.

19 DR. SPIEGEL: Sure. If you have the slide,  
20 you can bring it up. Great. There it is. So I just  
21 want to show you. This is maybe the equivalent of the  
22 iPhone story we just heard. Although you didn't say it

1 was an iPhone, did you? So the smartphone, not using  
2 brand names here.

3 So what I'm showing you here is a patient who  
4 is enrolled in a trial that I've been conducting with  
5 my research group at Cedars-Sinai validating wearable  
6 data against other anchors, in this case PROMIS. And  
7 this is a patient. She is 64 years old and has  
8 rheumatoid arthritis. And what you're looking at is  
9 the first 30 days of data after she started a biologic  
10 therapy for her RA.

11 And on the left you see the data looking at  
12 her PROMIS pain scores and on the right her step counts  
13 using a wearable sensor. So we're monitoring her and  
14 she had a lot less pain over time. And I'm not showing  
15 you her stiffness -- morning stiffness scores and her  
16 fatigue scores. And they all showed substantial  
17 improvements, meaningful improvements over the course  
18 of this 30-day period.

19 At the same time on the right you can see  
20 what's happening with her step counts. She goes from,  
21 you know, somewhere between 1,000 and 1,500 steps per  
22 day, which isn't a lot, down to almost stopping

1 ambulation completely. And so when we saw this, we  
2 thought, "Oh, she must not be wearing the sensor or  
3 maybe she put it on her dog," which we've actually seen  
4 happen. "Maybe, you know, she's not wearing it all the  
5 time. What's going on here?"

6           So it actually took a phone call. I said,  
7 "Are you wearing the sensor?" "Oh, yeah, I'm wearing  
8 it." "Okay. You know, I noticed that you're not, you  
9 know, walking." Oh, no, I feel great". She said, "I  
10 feel fantastic". I said, "What do you mean?" She  
11 said, "Well" -- she said she's an author and she  
12 writes; that's what she does. So she said, "I finally  
13 have the energy and the enthusiasm and I can" -- "the  
14 stiffness in my knees is better. I can just sit down  
15 and I can write my book finally." "And when you're  
16 hot, you're hot" she said, "for 10 hours I don't stop  
17 writing."

18           So for her success was not walking. Her  
19 success was sitting -- success for her clinically was  
20 sitting there and working. So we were just sort of  
21 mindlessly following her data without putting it into  
22 context about her clinical experience, about her PROs

1 in this case. We would have thought that she wasn't  
2 responding at all, but in fact that was an absolute  
3 success.

4 But I just want to show you that one example;  
5 I'll stop talking. But I will say that though this is  
6 apparent. Most of the time when we look at wearable  
7 data in general versus, let's say, PROMIS -- and we've  
8 looked at this quite a bit now -- we do see  
9 correlations, we do see that they are related to one  
10 another in the direction we would expect.

11 But I also just want to point out that  
12 sometimes we need to triangulate on clinical status by  
13 looking at different data streams, not any one set of  
14 data. So I have more to say, but I'll stop there for  
15 now.

16 DR. KOVACS: Thank you. Bill, did you want to  
17 speak about this?

18 DR. BYROM: Sure. Yes.

19 DR. KOVACS: Thank you.

20 DR. BYROM: Thank you. And so those two  
21 questions -- I mean, number one I would -- I have to  
22 say, yes, of course I do think that these technologies



1 can be seen to be reflective of clinical benefit. And  
2 I think just linking back to some of the things that  
3 were said yesterday in particular, I think it's more  
4 about -- it doesn't actually -- it's not a question of  
5 what we use to measure something. It's a case of is  
6 the measurement meaningful.

7 And so if a digital technology can measure  
8 something that's meaningful and it's one of the  
9 concepts of interest of our study, then, well, why not,  
10 why not use it and why not use it to inform the  
11 regulatory decision-making.

12 And I think as Dr. Dunn said yesterday, and he  
13 said, you know, "We could consider these things in  
14 particular if they measure something better than other  
15 approaches that we've currently got. Or they measure  
16 something that we've been unable to measure before".  
17 And I think these digital technologies, you know, do  
18 tick those two boxes in some cases.

19 So as I thought about the second question, the  
20 second part of this, I came up with five reasons why --  
21 or how this data can add value to PRO data. And, yeah,  
22 I'll just run through those. I think the first one is

1 linked to what Brennan said. You know, it can help to  
2 explain or to provide additional evidence around the  
3 PROM data that we're collecting.

4 Now in that example it was a somewhat  
5 unexpected finding and that was quite an unusual one  
6 and I wasn't expecting you to say that around that  
7 slide, because one of the things I would have expected  
8 to see if we're measuring activity and pain is that as  
9 a patient's pain improves, they may get more active as  
10 a consequence, and because of their activity, they may  
11 actually feel more pain again.

12 So actually sometimes when you have a study  
13 when you're looking just to pain, those pain scores can  
14 be giving you a picture that you don't quite  
15 understand. But if you look at the activity data  
16 alongside it, you can really see actually the patient  
17 is improving because they're getting more active, but  
18 it's not showing up in the pain score because the  
19 additional activity is actually causing them pain  
20 again. The same might be true if we're measuring  
21 fatigue, for example.

22 So I think that's sort of number one: it can

1 help to add context and explain the PRO data. The  
2 second thing is, you know, it can measure something  
3 better. So back to Dr. Dunn's example. And I think  
4 activity again is a good example. We have the clinic-  
5 based functional test like the 6 minute walking test.  
6 They're very useful. We use them a lot in clinical  
7 trials.

8 But the question I suppose we're trying to  
9 answer from a test like that is: You know, is the  
10 patient showing improvements in activity that will be  
11 affecting their activities of daily living? Is it  
12 affecting or improving their quality of life? And  
13 actually a 6 minute corridor walk test doesn't really  
14 tell you that. What tells you that is, you know, the  
15 activity that they elect to do when they're at home.

16 And so if I'm a COPD patient, you know, maybe  
17 the thing that really affects my quality of life is if  
18 I can walk my granddaughter to school in the morning.  
19 And I'm not necessarily going to get that from a  
20 corridor walking test.

21 The other area where we've seen these  
22 approaches being used to supplement the PRO data is in

1 the development of composite endpoints. And I think a  
2 nice example of that is the IMI initiative, which  
3 looked at developing the PROactive tool again for COPD.  
4 And if you're familiar with that, it's a tool that  
5 combines both patient-reported data and accelerometer  
6 data together into a single composite endpoint.

7 The PRO data is measuring sort of difficulties  
8 with activities; it's asking questions about how easy  
9 it is to do certain things. And obviously the  
10 accelerometer data is measuring the amount of activity.  
11 And putting the two together into a single endpoint is  
12 an interesting concept.

13 So that was number three. Two more to go.  
14 Instrumentation of clinic-based performance test so I  
15 think is another really interesting way in which we can  
16 use digital technologies to supplement what we're  
17 doing.

18 So, you know, the timed up and go test, which  
19 was mentioned earlier, I think is a really great  
20 example. You know, if you're familiar again with this  
21 test: somebody -- the patient sits in a chair. They  
22 have to stand up, walk 4 meters, turn around, walk back

1 and sit back down again. And the conventional  
2 measurement is a stopwatch to time how long it takes  
3 them to do that.

4 If you instrument them by applying sensors and  
5 perhaps put a sensor on to each leg, for example, which  
6 you can obviously do in a clinic, you wouldn't do this  
7 at home, you can now learn a lot more about the  
8 movement involved in doing that timed up and go test.  
9 In particular you can learn more about the balance of  
10 the patient. You can learn about the actual -- the  
11 number of steps that they take and their balance in  
12 that turning movement where they turn around to go back  
13 to the chair.

14 And those additional bits of data can tell you  
15 much more about that patient. So, for example, you can  
16 correlate the way that they turn around to aspects of  
17 risk of falling, for example.

18 And I think the -- the final way that I think  
19 it supplements PRO data is linked to that, it's  
20 providing a richer picture of what's going on. And I  
21 think another nice example -- yesterday I mentioned the  
22 mPower app, which is for Parkinson's disease. And I

1 know Roche Pharmaceuticals have done a similar app for  
2 Parkinson's disease, which is very interesting, and  
3 they use the smartphone to deliver a number of  
4 performance tests at home.

5 One of those tests is where the patient holds  
6 the phone in their hand for 30 seconds and it uses the  
7 accelerometer in the phone to measure the tremor that  
8 the patient exhibits. And by being able to do that  
9 every day at home you get a much richer picture of that  
10 symptom than you would if you just simply assess it via  
11 a clinician assessment every 2 weeks when the patient  
12 comes into clinic, where in fact they don't show tremor  
13 every day.

14 So I think -- in summary, you know, I'm a big  
15 advocate of these approaches, if we can use them in one  
16 of those five ways, you know, to learn more or to  
17 improve the way we make measurements.

18 DR. KOVACS: Thank you. Megan, did you want  
19 to add something?

20 DR. MORENO: Sure. I think what I'd like to  
21 comment on is thinking about the ways that we can  
22 leverage digital health technology to use the data that

1 patients are generating for themselves. So thinking of  
2 the phone as your mHealth device and thinking about the  
3 ways that patients interact with their phones in their  
4 normal daily life and what information they may be  
5 willing to share that can enhance our understanding of  
6 their lived daily lives.

7           So in some ways we can think about some of  
8 this data to improve the accuracy when we're  
9 interacting with patients and what they report. So an  
10 example would be, we did a study with college students,  
11 where we asked them to do what's called a 28-day  
12 timeline follow back, where they walk through each of  
13 the days for the past 28 days and report events that  
14 happened on those days and how much alcohol they  
15 consumed.

16           What we tested was the standard procedure  
17 compared to the procedure when they could scroll  
18 through their photofeed. And what we found was if you  
19 allow them to scroll through their personal photofeed,  
20 even if you don't look at it, their accuracy is much  
21 improved. We've also tried this with just having them  
22 scroll through their text feed, and again it improves

1 their accuracy of being able to place the data in  
2 context using their own data without you even looking  
3 at it.

4           The second piece to me that comes to mind is  
5 thinking about where tools such as social media fit  
6 into the kind of data that may be helpful to understand  
7 the lived patient experience. So we've done studies,  
8 for example, looking at patients with depression and  
9 looking at how they describe their daily activities and  
10 their lived experience with depression over time and  
11 tracked how their social media disclosures related to  
12 depression are timed very closely to their self-  
13 reported depression experiences.

14           So are there ways that we can take some of  
15 this very context-rich data and be able to use it to  
16 try to understand the broader scope of what patients'  
17 experience? I think of the great example about the  
18 author writing. You know, I bet you if you'd seen her  
19 Instagram feed, you would see pictures of her sitting  
20 at her desk saying, "I am having a great writing day."  
21 And so I think there's opportunities to ethically and  
22 transparently work with patients to be able to look at



1 that data and help add that angle of context that the  
2 numbers just won't give us.

3 DR. KOVACS: Thank you. Chad, did you want to  
4 add something?

5 MR. GWALTNEY: First off, in previous sessions  
6 we've talked about not just focusing on the here and  
7 now, but also thinking about the future and where the  
8 field will be in 5 years and 10 years. And I really do  
9 want to thank Sarrit and the FDA for including this  
10 particular session, because I do think it's consistent  
11 with that mindset.

12 And I may be forgetting something, and correct  
13 me if I am, but I think this is the only session where  
14 we're not really reacting to something that's already  
15 in the draft of the guidance document, but really  
16 thinking about something new where best practices  
17 really are not all that well established yet. And I  
18 think that's a part of what our mandate is here, is to  
19 generate some ideas that could ultimately form a  
20 framework for those best practices and ultimately be  
21 incorporated at some point in the future in guidance  
22 documents. So again, I do think this is qualitatively

1 different from some of the sessions that we've had  
2 earlier.

3           And thinking about these questions. So if  
4 it's a yes/no question: Can the data be reflective of  
5 clinical benefit? You know, in the abstract I would  
6 say yes, in that we're potentially measuring an  
7 important part of patient functioning and changes in  
8 patient functioning can be reflective of direct  
9 clinical benefit.

10           So I would say yes. And in fact in doing so  
11 in the patient's natural environment rather than in a  
12 contrived clinic setting, we may be doing so in a way  
13 that has more ecological validity and more accurately  
14 reflects the patient's experience.

15           So in the abstract absolutely. And thinking  
16 more specifically, obviously the answer is a bit more  
17 complicated than that. Certainly, there are conceptual  
18 and methodological issues that need to be considered  
19 when using the sort of technology to support endpoints  
20 to evaluate treatment benefit.

21           For me, again, as not necessarily a technology  
22 expert, when I see data that's generated by some of

1 these wearable devices -- and there's a list of dozens  
2 of different types of wearables and they're measured  
3 over different time intervals and potentially -- and  
4 this is what I've seen in an actual study, there could  
5 be hundreds of thousands of data points that are  
6 generated by these types of devices. And that's just  
7 for one wearable. So multiply that by however many  
8 wearables we have. And again, it can be quite  
9 overwhelming for someone who's not an expert in  
10 understanding what each of those wearables mean.

11 And I would venture to guess that if I don't  
12 understand it, patients might have trouble  
13 understanding what those measures are actually  
14 capturing and how they're important for, again,  
15 reflecting treatment benefit and the way that it  
16 captures the patient's experience. So I think one of  
17 the task is really to make sure that whatever wearable  
18 we're using, that it really does measure something  
19 that's important in the patient's life.

20 And then thinking about using the data as a  
21 supplement to PRO data or other COA data, I want to  
22 echo something that Bill said. For me -- and thinking

1 about performance outcomes, there are certain types of  
2 tasks. The 6 minute walk test was what came to my mind  
3 as well as a performance task, where we have this  
4 contrived clinic setting -- and people don't just walk  
5 in 6 minute increments obviously -- but it has proven  
6 to be a useful task. And now we have the ability to  
7 look at actual walking in the natural environment. So  
8 that at the very least for me can provide a helpful  
9 complement to what we're measuring in the clinic and  
10 perhaps at some point in the future actually provide a  
11 substitute for some of these in-clinic tasks where the  
12 generalized ability to the patient's natural  
13 environment is somewhat questionable.

14 I certainly do not see these as a substitute  
15 for PRO data. You know, when I was thinking about my  
16 answer to this question, I thought maybe the sleep  
17 areas is one specific context where the activity  
18 monitor data may actually be more accurate than patient  
19 reports of things like number of awakenings. So maybe  
20 there are some specific examples where we would choose  
21 this type of data source over a patient-reported  
22 outcome.

1           But I think by and large it's going to be  
2           complementary and will give us context for -- the PROs  
3           will help give us context for what we're seeing with an  
4           activity monitor.

5           I think of examples where new treatments may  
6           lead to things like restlessness or agitation where we  
7           may see increased movement on the patient's part, but  
8           that's very much a negative aspect of their experience,  
9           not necessarily a positive. And I think that we need  
10          the patient-reported outcomes in order to better  
11          understand exactly what the patient is going through on  
12          these sorts of treatments.

13          Yeah. And another thing that Bill mentioned I  
14          think is important for us to consider is: Is there a  
15          pathway to a sort of composite endpoint that's based on  
16          both patient-reported outcomes and activity monitoring  
17          data like the PROactive initiative? I've heard wildly  
18          different opinions about the usefulness of that, but  
19          certainly there's a good model for it and I think it's  
20          worth considering.

21          DR. KOVACS: Thank you. Martin, did you have  
22          any comments?

1           MR. HO: Yes, I want to add on to the  
2 excellent comments before me. And I also am very  
3 optimistic about the opportunities provided by the  
4 digital health technology. Just think about -- I am a  
5 statistician by trade, so I analyze a lot of data as a  
6 result of a patient diary. And I -- when I analyze the  
7 data for a treatment for epilepsy, so to speak, I  
8 cannot imagine how painful it is for patients. At the  
9 end of the day they have to recall how many seizures  
10 they experienced and how intensive it is and how long.  
11 Because if it happened to me, I don't really,  
12 definitely have the energy.

13           And when I look at the diary log, I -- it  
14 really shows that whenever -- I mean, the data points  
15 tends to be clustered around the time that they have a  
16 study visit. And so it seems a lot of people are also,  
17 you know, filling out their forms last minute. So  
18 therefore, I think there are some low hanging fruit  
19 that digital health technologies can help us to  
20 overcome these obstacles.

21           And the other potential use of digital health  
22 to help us to collect more accurate information would

1 be that we are talking about -- when people are  
2 treating psychiatric patients, they use -- are trying  
3 to use different type of tricks to make sure that the  
4 patients comply with or adhere to their treatment  
5 regimens.

6           So if I -- I mean, there is a technology that  
7 the sensor is so little that it is being embedded in  
8 the tablet. So the -- so whenever patients are taking  
9 the medication, it can -- for few minutes it's not only  
10 being able to know whether the drugs are being taken or  
11 whether the patients have a full stomach or on fasting  
12 or even their activity level for a few minutes.

13           So I think these definitely can help enrich  
14 the information that we got from the clinical trials  
15 and see how we can improve the patients' experience  
16 when they are receiving the treatment.

17           And I would say that, yes, I agree with the  
18 composite or collaborative type of -- or, you know,  
19 composite endpoint. But from a statistician's point of  
20 view, analyzing composite endpoint has always been a  
21 very tricky issue. So -- on the other hand, I would  
22 also say that it also provides us with opportunities

1 that perhaps we can enrich the PROs and its meaning.  
2 We not only reflect depending on patients' reflection  
3 or interpretation of their daily life, you know, in a  
4 average sense whatever construct that we are assuming  
5 that patient are using, but also we can see how that  
6 information added on to the digital health technologies  
7 to provide us with a richer picture, so to speak.

8           So I agree those tools can be used in the  
9 context. But again, regardless of what -- regardless  
10 of PROs, Perfo or digital health, they all needs to go  
11 through a certain process so that we can interpret it  
12 with a clinical meaningfulness of the endpoint. And  
13 that I think is the most interesting exercise for us,  
14 to go through to make, you know, a measurement from  
15 digital health technology and make it into a claim that  
16 we can -- it can be meaningful to patients at the end.

17           DR. KOVACS: Thank you. Yeah, David.

18           MR. REASNER: Yeah. Just a brief moment to  
19 add something to the excellent discussion. We  
20 definitely have to learn to walk before we can run, but  
21 I want to point out another application where digital  
22 health technology can add value to our PRO work,



1 because it does create a lot of insight, right, to ask  
2 the patient to report. And that is where we use  
3 digital health technology to trigger a PRO.

4 So if you have a sensor that can detect that a  
5 patient has walked up the stairs, a COPD patient, you  
6 can probe them about their dyspnea. If you have low  
7 glucose, you can probe a diabetic about how they feel,  
8 right? Maybe you trigger the use of a peak flow meter  
9 in a adolescent who has been active.

10 So those interactions where I don't think in  
11 this context the health technology is a COA, it can add  
12 value and richness to the PRO, because moving our  
13 assessment out of the clinic has this great potential  
14 to create this qualitatively differentiated data. So  
15 maybe we can enhance that with this new technology.

16 DR. KOVACS: Thank you. Brennan?

17 DR. SPIEGEL: Thanks. I just want to briefly  
18 circle back after those excellent comments to the  
19 example that I started off with. Because that example  
20 that I showed on the screen for those of you that were  
21 in the room at the time might be interpreted to mean  
22 that we shouldn't be measuring these digital health

1 data, that it could mislead us. And I would say the  
2 same is true of any outcome measure.

3 My main purpose of showing you this is that we  
4 have to understand the behavior of that outcome in  
5 comparison to other outcomes like we always do with  
6 anchor-based, you know, construct validation or  
7 criterion validation.

8 But I also want to emphasis that the opposite  
9 could just as easily be true. There are, as we've  
10 heard in some of these discussions, examples where the  
11 goal of a patient is to be functional, to get through  
12 the day, to get through his or her activities of daily  
13 living regardless of the pain. So they say, "Yeah,  
14 well, you can ask me about my pain and I'm going to say  
15 it's bad. But my goal is not pain avoidance. My goal  
16 is to take care of my husband," or my wife or whomever,  
17 right?

18 So I don't -- I would give a full throated  
19 endorsement that the data we're talking about here can  
20 be a primary outcome, not a secondary outcome,  
21 depending on the situation. It's not just meant to  
22 supplement this or supplement that. In some instances,

1 it's the other way around. In some instances, the PROs  
2 may be supplementing the data from these sensors. It's  
3 not an either-or proposition.

4 At the end of the day, the comments we just  
5 discussed apply just as much to these data as anything  
6 else. We need to understand what is a minimally  
7 clinically important difference, you know, construct  
8 validity, content validity and all these basic measures  
9 of validity that we look at.

10 And the goal of us sitting here today is we  
11 take the zeros and ones, and that's data, and we turn  
12 the data into information. We turn information into  
13 knowledge and we turn knowledge into wisdom. That's  
14 the informatics pyramid, is to go from data to wisdom.  
15 And that pyramid applies just as much to all of the  
16 data we're talking about today as to any other type of  
17 outcome data that we could talk about.

18 So I just want to make that -- put a point on  
19 that in light of this example I gave here. Despite  
20 this example, this just points out that we need to be  
21 very careful and thoughtful as we enter this new era of  
22 digital health measurement.

1 DR. KOVACS: Thank you. Okay. So the next  
2 question under the same objective is: What evidence do  
3 we need to support whether COAs derived from digital  
4 health technology are fit-for-purpose? And Dr. Bill  
5 Byrom has a slide to present, so I'll ask him to speak  
6 first, if that's okay.

7 DR. BYROM: Okay. Thank you. And what I've  
8 got on this slide is really a summary of some work that  
9 was done by myself and colleagues in the ePRO  
10 Consortium, the Critical Path Institute's ePRO  
11 Consortium. And I can see some of the co-authors are  
12 in the audience, Stephen Coons, Sonya Eremenco and Paul  
13 O'Donohoe.

14 So we put this together as a starting point,  
15 really as a place to start the discussion about how can  
16 we be assured that if we use a mobile sensor in a  
17 clinical trial to perhaps derive and collect a clinical  
18 endpoint, how could we be assured the data that we  
19 provide in our regulatory submission would be  
20 acceptable? And, you know, whilst of course we're not  
21 qualified to make that decision, we wanted to start the  
22 discussion.

1           And so we looked at this in sort of three  
2 dimensions: so two aspects around evaluating the mobile  
3 sensor itself and then the final one around the  
4 clinical endpoint. And we've already heard a lot of  
5 these pieces throughout today and yesterday.

6           So as we think about the mobile sensor, we  
7 felt there was certain evidence we need to assess the  
8 safety and the suitability of a particular sensor,  
9 maybe a wearable device, for use in a particular  
10 clinical trial. And around safety that would be things  
11 like, you know -- the things that the manufacturer  
12 would probably provide, so the statement of electrical  
13 safety, for example.

14           But also if it's worn on the skin, you know,  
15 for the period of time that we want patients to wear  
16 it, do we know that it's hypoallergenic, do we know  
17 that it won't cause tissue inflammation or abrasion.  
18 You know, those sorts of things around that aspect of  
19 safety.

20           And then we come to suitability, you know,  
21 does it actually measure something that -- or does it  
22 claim to measure something that is our concept of

1 interest. So if we're interested in activity, does it  
2 claim to measure activity. And we'll come on to  
3 whether that's done in a valid way in a minute.

4 And then in terms of usability, so -- you  
5 know, there's a number of different aspects to this and  
6 its very target population specific; so, for example,  
7 the form factor of a particular device. What you  
8 notice with accelerometers is that the research-grade  
9 devices are often not quite as cool looking as the  
10 consumer devices. And if you -- perhaps if you're  
11 measuring activity in teenagers or a young population,  
12 young adults, they might not really want to wear these  
13 great big boxes around the wrist. They might prefer to  
14 wear a Fitbit or Garmin or something that's a bit more  
15 socially acceptable.

16 And so that form factor is important, but also  
17 just thinking about things around the wrist or around  
18 the waist. Just simply, you know, if I'm again  
19 studying perhaps a frail or elderly population, are the  
20 wrist straps simply too big even on this boy's hold --  
21 you know, is it still going to be too big and will it  
22 move around on the wrist of an elderly patient versus

1 perhaps, you know, an adult or a young person.

2           So those aspects around usability. But the  
3 other aspect then is around feasibility. So in the  
4 context of the actual clinical trial I want to use it  
5 in, do I think it's feasible to use this particular  
6 mobile sensor. And the kind of things we might want to  
7 think about there are the burden of using this in the  
8 context of everything else we're asking the patient to  
9 do, for example.

10           And then finally around suitability again is  
11 the -- perhaps the characteristics of the vendor. A  
12 good example here is the difference again between  
13 consumer and research-grade devices. So if I'm using a  
14 Fitbit and I'm providing patients with a Fitbit, I  
15 don't actually have any control over the automatic  
16 firmware updates that that device might push out to  
17 those patients. And so maybe that won't matter. But  
18 perhaps on one occasion that firmware update might  
19 adjust how it's calculating steps, and so I have a  
20 point in my study where I'm calculating steps one way  
21 and then after that particular time point I'm  
22 calculating steps in a different way.

1 I guess that's an extreme example. But  
2 clearly the research-grade devices, you know, control  
3 for that, you can -- you know, you can ensure that you  
4 use the same firmware version throughout your trial.

5 And then when it comes to the evidence to  
6 support the validity and the reliability of the device,  
7 there's the obvious things and we've talked about these  
8 already in this event. So, you know, the reliability,  
9 intra-and inter-device reliability, some of that can be  
10 done in the lab and some of that probably needs to be  
11 done in humans. Again, the vendor of the solution may  
12 well have data that support this.

13 The algorithm validation and the concurrent  
14 validity. So is it -- you know, is the data showing  
15 that it really does count steps if it's a step counter  
16 that we're using? Is there a study that shows that --  
17 you know, compared to a gold standard or an accepted  
18 approach in step counting it's giving me reliable  
19 figures?

20 In the particular patient population I'm  
21 looking at is there some more work I need to do? So if  
22 I'm looking at a Parkinson's disease patient population



1 where patients may shuffle rather than walk in a more  
2 normal way, does the device actually -- is it still  
3 able to measure steps in an appropriate way? And then  
4 responsiveness: is it able to detect change?

5           When we take all those -- that data that come  
6 from the sensors -- and I think to Chad's point, you  
7 know, quite often you get a load of derived data from  
8 these things. We then want to derive from that a  
9 clinical endpoint that we might then use in a  
10 submission. So, you know, does the endpoint measure  
11 the concept of interest appropriately? Does it have  
12 content validity? Is it responsive and able to detect  
13 change? And then finally, you know, is it  
14 interpretable? So what we heard in this really  
15 interesting session just before lunch around meaningful  
16 change: do we have a good handle on meaningful change?

17           One of the things that we've noticed in doing  
18 this piece of work is there's actually very few  
19 examples in the literature that you can go back to, to  
20 find estimates of meaningful change, whether it's  
21 responder definition of an MCID with a lot of these  
22 wearable devices, even things like activity monitors

1 which have been used for many years now. We could only  
2 find one or two examples of studies that estimated  
3 meaningful change in specific patient populations.

4 So I guess as we think about using these  
5 things, we know there's going to be work that needs to  
6 be done perhaps in phase 2 or perhaps separately to  
7 fill some of the gaps in some of this evidence.

8 But this was our starting point of -- in terms  
9 of what we felt was sensible for the evidence that's  
10 needed. And just to follow on from this piece of work,  
11 the Drug Information Association Study Endpoints  
12 Community, we -- and again, Emuella Flood is in the  
13 audience somewhere. So she is co-leading a wearables  
14 working group with myself and we're looking at a number  
15 of different things. But one of the things is how  
16 could we structure an evidence dossier in the same way  
17 that we perhaps do for the PRO dossier at the moment to  
18 support the use of perhaps a wearable device or a  
19 mobile sensor in clinical trials. And I know we've had  
20 some input from Wen-Hung and others at FDA as we've  
21 been doing this piece of work.

22 DR. KOVACS: Thank you. Suz?

1 MS. SCHRANDT: Sure. So I'll probably touch  
2 on some of the same points. But I would start with  
3 kind of the same ethos we use when we're talking about  
4 PROs, which is, just because something is patient-  
5 reported, doesn't mean it's patient-centered. So I  
6 think as a piece of the evidence base, do we know that  
7 this is something that actually matters to patients, is  
8 it meaningful to them, or is it related to something  
9 that's meaningful to them.

10 The second piece is almost more of a construct  
11 validity issue and I think it kind of speaks to the  
12 data divergence slide that Brennan presented. I'm  
13 really wearing my rheumatology hat when I think about  
14 this, because for me it -- you know, we talk about the  
15 difference between "is it walking speed versus step  
16 count?" And I'm thinking about a person with advanced  
17 RA, maybe it's either one, step or speed. Does it pay  
18 attention or does it have the ability to know whether  
19 there's a severe limp? Is it a person who's not  
20 bending their knees because there's too much damage and  
21 they're just propelling themselves forward?

22 I think as a community, we, RA patients,

1 invent bizarre and amazing ways to get from point A to  
2 point B. And I do worry about that physical context  
3 and what are these tools actually able to discern and  
4 do -- can we lay that context on top somehow or is it  
5 not giving us the data we think we're getting.

6 I think sort of a related piece then is this  
7 issue of what's the important clinical difference to a  
8 patient. And I worry a lot again in the rheumatology  
9 space, although I'm sure it would be relevant for many  
10 other diseases, about baseline. And again, if you're  
11 looking at a person with advanced RA who has already  
12 got significant joint damage and mobility issue, the  
13 difference for that person -- the success is going to  
14 be much smaller, much harder to get at than someone who  
15 starts out healthy.

16 And so it's not just that the tool needs to be  
17 validated and appropriate for the community of  
18 patients, but maybe even specifically, you know,  
19 calibrated -- I'm not a digital expert -- for that  
20 unique person given where they're starting from and  
21 where they want to go.

22 So these are all pretty complicated, but I

1 think it's again a lot of opportunity. I just want to  
2 make sure we're embedding all of that appropriate  
3 context.

4           And then the last piece just because -- in my  
5 role I deal with a lot of different age ranges and  
6 people with different comfort levels with technology  
7 and I think there is some skepticism about failure of  
8 the device itself. And when I think about the other  
9 COAs, it doesn't seem like anything else is quite as  
10 vulnerable to failure. I mean, you could administer  
11 something incorrectly. The person, you know, doing the  
12 test or performing something could do it wrong. But  
13 the -- if it's a paper-based tool, the paper isn't  
14 going to suddenly change itself, it's not going to  
15 malfunction.

16           And so I do think there's almost skepticism  
17 about "how do we know that the machine as a tool itself  
18 isn't going to fail?" And it kind of goes back to my  
19 smartphone example. We have to sort of be extra  
20 vigilant that if something doesn't quite look right or  
21 smell right, we need to again validate what the patient  
22 is telling us and the rest of the clinical context and

1 not be too beholden to -- be too beholden to whatever  
2 the data says from the tool.

3 DR. KOVACS: Thank you. Okay. So our final  
4 question for the session is: How do we show flexibility  
5 while maintaining regulatory standards when using COAs  
6 derived from this type of technology to support  
7 clinical trial endpoints? And, Martin, did you want to  
8 provide comments?

9 MR. HO: Thank you. So I myself -- or I was --  
10 - I mean, as I mentioned before, when something is  
11 useful, then I don't really care whether it's a  
12 specific type of endpoint. And so therefore, I think  
13 here we are -- it sounds like these questions -- I  
14 wanted to see if we can show some flexibility for some  
15 evolving technology, so to speak, so that as time goes  
16 by then the technology can get a foothold and mature to  
17 be a clinical trial endpoint.

18 But I just want to say that perhaps -- and --  
19 my word is that we see the trackers or sensors that are  
20 supposed to be just tracking, have now -- they  
21 themselves are being made as a diagnostic or screening  
22 devices. For example, recently our center has cleared

1 Apple Watch for detecting Afib. And for that, I think  
2 is really the extreme of using the sensor and detect  
3 clinical condition.

4 So therefore, I think to me is -- perhaps we  
5 may not need to have extra flexibility. In fact I  
6 don't really have a good, clear understanding of what  
7 flexibility means. But in this case -- but I will say  
8 that for choosing the correct target and with the --  
9 with a good technology, then perhaps we can be -- you  
10 know, we can be getting to the point that we wanted to  
11 get to.

12 And adding to that comment, I wanted to say  
13 that when we are discussing these endpoints and these  
14 data characteristics, it's quite rare for me to see  
15 there's, you know, biomedical engineers who are  
16 developing these sensors in the mix. And when I do  
17 site visits to the West Coast, going to talk with those  
18 companies, they are the opposite, they are dominated by  
19 biomedical engineers. They don't have measurement  
20 scientist. They don't have PRO experts.

21 And so therefore, they are -- it seems like  
22 they have a silo discussion, that perhaps just by

1 bridging those two, you know, the manufacturer's  
2 perspective and the scientist's perspective, then  
3 perhaps we can already have some -- we can mix them  
4 that way without, you know, treating the digital health  
5 technology as a special entity, that they serve some  
6 special treatments.

7 DR. KOVACS: Thank you. David?

8 MR. REASNER: Yes, thanks. Well, a far way  
9 for me to define flexibility at the agency. But I  
10 guess where as a sponsor who would like to innovate  
11 with digital health technology where flexibility will  
12 be very valuable is to keep in mind I think the  
13 principles from the PRO guidance, which have now been  
14 tempered by our practical experience over the last few  
15 years, apply those to this new opportunity, but  
16 generalizing, you know. So we have to bring it up a  
17 level.

18 And I accept what Kevin said yesterday, that  
19 our terminology might be a little bit too PRO specific.  
20 But I think the underlying principles are often the  
21 same. So we can use known groups to assure that we can  
22 differentiate patient subgroups using these endpoints -



1 - or these assessments -- we'll get to endpoints later  
2 -- these assessments. And that could be disease  
3 severity. It could be developmental stage. There  
4 could be a number of very real differences that we can  
5 use to validate these assessments. So that's one  
6 point.

7           Also, the anchoring may be a little different.  
8 Maybe global assessment is not an appropriate anchor.  
9 Maybe you need to use a clinic technology to help  
10 develop anchoring for your new novel assessment, okay.  
11 So it's a slightly different use. Maybe it's not a  
12 gold standard, but a silver standard, but you can use  
13 it in terms of establishing your anchoring and trying  
14 to get to clinically meaningful improvement. So I  
15 think those principles apply.

16           The other aspect of flexibility is just that  
17 it's going to be more open-ended. We have a very rich  
18 data stream. There's a lot you can do. Sponsors  
19 usually address this by throwing out data or averaging  
20 data because it's too complex. So if we actually start  
21 using this data at the resolution that we have access  
22 to, there are just a lot of possibilities. So, you

1 know, I think there's a lot of directions that we can  
2 go in.

3           And then lastly I'll just point out that --  
4 along the lines of some of the discussion yesterday,  
5 the temporal aspect. The patient journey, the disease  
6 history are very rich and now you're going to get  
7 access to that. So there's a lot of variability that's  
8 interesting, a lot of change over time. People are not  
9 necessarily stable in every indication. So being sure  
10 we're not losing that richness of data as we try to  
11 derive algorithms is going to be very important.

12           DR. KOVACS: Thank you. Chad?

13           MR. GWALTNEY: Well, first off, the fact that  
14 we're even being asked a question about how the agency  
15 could show flexibility to me -- makes me really, really  
16 happy and I think already demonstrated flexibility just  
17 by asking the question "how do we show flexibility?"

18           You know, for me -- yeah, I think a part of  
19 showing flexibility is in encouraging sponsors to  
20 collect the sort of data as secondary or exploratory  
21 endpoints in trials or to support secondary and  
22 exploratory endpoints in studies. And, you know, I

1 think to a certain degree that's already happening,  
2 rather than closing that door right now because we  
3 don't know maybe enough in a particular area about how  
4 to use the data to evaluate treatment benefit. So I  
5 think that encouragement and having discussions like  
6 this is really important.

7           Additionally, technology changes so fast,  
8 right, and we're going to have different variations of  
9 these types of wearable devices. You know, I don't  
10 know that they will necessarily be entirely different  
11 from one another, but I think acknowledging that  
12 different iterations are not completely different  
13 entities and that we may already know quite a bit about  
14 new devices based on old devices be it from their  
15 underlying scoring algorithms or about what they're  
16 measuring, that we don't have to consider each new  
17 iteration as a de novo product or device.

18           You know, alternatively -- I think there are  
19 some areas where maybe we don't want to be overly  
20 flexible and I'm thinking about understanding  
21 meaningful with patient changes on some of these types  
22 of wearables that we get from the devices. You know,

1 to me it seems like that may be along with content  
2 validity are the two areas where we maybe know the  
3 least at this stage.

4           And thinking about the example that Bill  
5 raised earlier in MS (ph), my understanding, correct me  
6 if I'm wrong, is that the anchors used there were  
7 really important changes in overall functioning and  
8 aspects of the patient's daily life. It wasn't the  
9 typical global impression of change type anchor,  
10 something else that we would use for a patient-reported  
11 outcome, for example.

12           I don't really know what the right anchors are  
13 in this context for the types of data we would get from  
14 wearable devices. So I think it's understanding that  
15 issue and how to establish that kind of threshold are  
16 really important.

17           And then this may be -- is a part of an answer  
18 to question three rather than four. When I think about  
19 content validity -- I don't think if I can say it any  
20 better than what Suz was saying earlier about, yeah --  
21 so how do we really know exactly what the patients are  
22 going through and how that maps on the sorts of data

1 that we get from these devices? That's a really  
2 important question.

3 And again, thinking about patient-reported  
4 outcomes, I can speak with patients. They tell me that  
5 they have pain in their knee and I can build an item  
6 that asks them about pain in their knee. And that link  
7 is pretty direct. And I can show them those items and  
8 they can tell me if I'm on target.

9 And here to me we're doing something very  
10 different. We're taking what the patient is saying and  
11 almost translating that into a new metric that is more  
12 indirectly related to the patient's language. And we  
13 can't easily go back and do a kind of cognitive  
14 interview to say, "Okay, this is how this is all  
15 calculated and here's what the score is and does this  
16 really get at what you're talking about?" We can do  
17 that to a certain degree, but again to me it's more  
18 indirect than what we would do with a patient-reported  
19 outcome.

20 So I think, you know -- and thinking about the  
21 consultation stage where we would identify what's  
22 important to patients, we really have to be careful in

1 our interviews to ask very nuanced and detailed  
2 questions about where the functional limitations are,  
3 what patients are going through so that we can make  
4 that translation in a more valid way rather than simply  
5 understanding may be walking is a problem, but not  
6 understanding why, what that's like for each patient  
7 and then taking that number of steps is the right way  
8 to capture that.

9           So I do think that those two issues, content  
10 validity and interpretation, are where we maybe need  
11 more evidence than some of the other areas at this  
12 point.

13           DR. KOVACS: Thank you. I'm going to try to  
14 summarize the main themes that we heard during the  
15 session and then open it up for audience questions. We  
16 heard that sometimes -- yeah, did you have a comment?

17           MR. HO: Yes.

18           DR. KOVACS: Sure.

19           MR. HO: Yes, I just want to add one more  
20 comment. When we're talking about our -- when the  
21 patients are using these digital health technologies,  
22 we don't know what they went through or what -- perhaps

1 there's some misunderstanding of how it works. And so  
2 as a result, we may get some wrong data. But in fact  
3 we may already have no more than we do, because when  
4 we're using digital health app, they're not -- for a  
5 reasonable or good companies, they're not only  
6 monitoring whether patients are opening the apps. They  
7 would also collect how quickly the patients are using  
8 their apps from step to another, what buttons they  
9 push, and how quickly they answer one question to  
10 another.

11 And these are also very, very detailed  
12 tracking system in place and it's almost like an  
13 industry standard now. So when they are observing the  
14 patient's response or usage of these devices, they are  
15 in indirect way to observe every click and every swap  
16 of the patients. And as a result, they improve the  
17 interface and get the result they want.

18 So I think that is yet another type of  
19 information that they collect to improve either the  
20 information collection or the intervention itself.

21 Thank you.

22 DR. KOVACS: Thanks. So sometimes COA data

1 derived from digital health technology may fit within a  
2 performance or PerfO category, for example, when  
3 wearing a wearable sensor when it's used to capture  
4 data from a standardized active performance task like a  
5 timed walking task.

6           Yesterday Dr. Billy Dunn mentioned that  
7 digital sensor data may fit within an ObsRO or PerfO  
8 COA types and that the definitions could possibly  
9 incorporate different types of monitoring or reporting.  
10 And also panelists today in this session mentioned that  
11 digital monitoring could be a subtype of ObsRO.

12           In contrast, we heard that sometimes COA data  
13 derived from digital health technology does not fit  
14 well within the established four COA categories and  
15 perhaps should be considered a separate fifth category  
16 that capture passive data that are collected while  
17 subjects are conducting their activities of daily  
18 living and that perhaps a dotted line should be drawn  
19 between PRO measures and digital monitoring to show  
20 that they should be connected.

21           We also learned that COA data obtained from  
22 these digital tools can be reflective of clinical



1 benefit and used to inform regulatory decision-making  
2 if the data are truly capturing aspects of functioning  
3 that are relevant and important to how patients feel,  
4 function and survive.

5           And that just because these data are coming  
6 from or reported by the patient does not necessarily  
7 mean that they are patient centric, as Suz mentioned  
8 and Elektra mentioned yesterday when introducing  
9 Guidance 3.

10           Patient input is critical in capturing what is  
11 really important in patient's functioning in their  
12 daily lives. We heard that technology can be used to  
13 help improve accuracy of clinical outcomes and that  
14 social media sources can be used to understand the  
15 broader picture of what patients are experiencing and  
16 provide context for some of the patient's data.

17           We also heard that the COA data from --  
18 obtained from these digital tools can supplement and  
19 add value to PRO data and data from other COA types.  
20 For example, a patient can report experiencing a  
21 symptom such as pain and then one can measure the  
22 impacts on pain -- of that pain, sorry, on patient's

1 functioning using a wearable sensor and this could  
2 provide a fuller or richer picture of the patient's  
3 functioning in their daily lives.

4 Dr. Paul Kluetz mentioned in one of the  
5 sessions yesterday that data from PRO tools can be used  
6 to give meaningfulness to wearable sensor data and that  
7 the two can be used together to complement each other.

8 However, we saw on Brennan's slide that  
9 improvement in patient-reported symptoms such as pain  
10 does not always relate to an increase in activity level  
11 depending on how it's measured and perhaps the wrong  
12 aspect of functioning is being measured. And this  
13 becomes clear when it is supplemented by PRO data,  
14 which gives context to the digital monitoring data.

15 Another thing we heard that was -- was that  
16 perhaps we should explore composite endpoints,  
17 including PRO and digital monitoring data, but that  
18 this may be tricky statistically. And we heard that  
19 events detected or reported by a digital monitor may  
20 trigger probing PRO questions about symptoms or  
21 activities that could be helpful.

22 We discussed what evidence would be needed to

1 support whether COAs derived from digital health  
2 technology are fit-for-purpose. For example, in order  
3 to maximize a wearable sensors' ability to be sensitive  
4 in detecting a treatment effect, instructions to  
5 subjects should be standardized, for example, regarding  
6 where or how to wear a sensor to reduce unwanted  
7 variability and noise in the data, in addition to the  
8 good measurement principles presented in the Guidance 3  
9 discussion document.

10 The precision and accuracy of the mobile  
11 technology tool used to measure a clinical outcome are  
12 both important when determining whether a tool and its  
13 algorithm are fit-for-purpose. It's important to  
14 establish methods to determine what concepts are truly  
15 being measured by digital health technology tools and  
16 to determine more suitable anchors or well-established  
17 silver standard tools to confirm the validity and  
18 reliability of the data derived from digital tools.

19 We also heard that the acceptability of the  
20 sensor, the size, the look, the feel is important for  
21 compliance as well as the feasibility of its use in the  
22 target population. What if people do not take clear

1 steps, they may shuffle their feet or have a severe  
2 limp, this is all important to consider.

3 Finally, we discussed how to show flexibility  
4 while maintaining regulatory standards when using COAs  
5 derived from this type of technology to support  
6 clinical trial endpoints. The agency is open and  
7 flexible to consider the -- considering the use of  
8 digital health technology tools and approaches and  
9 methods to validate these tools and algorithms.

10 It is important to mention that we should not  
11 use digital tools just because they're new and  
12 exciting, but rather only if they're going to be  
13 providing useful data above and beyond that which is  
14 already being captured well to inform evaluation of  
15 clinical benefit.

16 We heard that the magnitude of improvement  
17 that is considered clinically meaningful depends on the  
18 condition or disease and that the -- and also the  
19 baseline level of patient's functioning. Also, we  
20 heard that an opportunity would be to collect digital  
21 monitoring data in an exploratory manner to test and  
22 evaluate it.

1           So thank you very much to our panelists. It's  
2 now time for audience question and answer -- sorry, the  
3 question and answer portion of this session. So the  
4 microphones in the center of the aisle are available.

5           And as I mentioned earlier, we do encourage  
6 you to submit any and all comments and feedback that  
7 you may have related to the Guidance 3 discussion  
8 document to the public docket, which closes on December  
9 14th. And we look forward to your helpful feedback.

10                           AUDIENCE QUESTION AND ANSWER

11                   UNIDENTIFIED SPEAKER: Hi. It's not on?  
12 Okay. It was very interesting to hear everyone's  
13 comments and perspectives, especially from such a wide  
14 range of sort of positions within the field.

15           I'd like to go back to the issue of whether we  
16 should name another category of clinical outcome  
17 assessment. And I think that it would be helpful to  
18 have an additional category. The four categories are  
19 really different in terms of the patient's relationship  
20 to the assessments. So I think that's one very useful  
21 way that they're different. We could think about the  
22 patient's role in this.

1           And then also from a logistics of the data  
2 collection perspective each of those four categories  
3 are also very different. Are you doing surveys? Do  
4 you need to bring in an expert to do an evaluation?  
5 And then of course I think, as many of us know, the  
6 digital sensor-based assessments open up a whole new  
7 basket of issues.

8           So I think particularly for the clinical  
9 operations groups of -- you know, running these trials,  
10 I think it's helpful for us all to communicate that,  
11 you know, once you bring in this additional type of  
12 COA, you need to call these people.

13           And then I think it would be helpful that --  
14 you know, I think we've talked about a lot of different  
15 types of sensors, wrist worn, wrist patches. Then  
16 there are things that could be installed in the home.  
17 There are sleep sensors that go across the bed. And so  
18 I'm thinking about sort of a phrase, something like  
19 sensor-based, because that's sort of the relationship  
20 of the patient to the assessment and then also the  
21 point to differentiate it from a performance measure  
22 that this is a daily living, sort of, free living or

1 daily living task. So I would be interested in  
2 people's reactions to that. And I'd also be really  
3 interested if someone can come up with sort of a more  
4 jazzier, you know, condensed term, but I think the  
5 aspect of it being sensor based and that this is a  
6 daily living type of outcome measure could be useful to  
7 capture.

8 UNIDENTIFIED SPEAKER: Yeah, I think those are  
9 excellent comments and sort of consistent with how I  
10 have been thinking about this as well. As said earlier  
11 I'm more of a lumper and I'd love to find a way to make  
12 it -- to shoehorn it in. But one other distinction is  
13 -- which we haven't really addressed head on is this  
14 notion of sort of active versus passive, I've -- we've  
15 discussed it. But each one of these requires some  
16 active exercise, going to fill out a questionnaire,  
17 going to observe a standardized, you know, performance  
18 -- or activity.

19 I'm going to, you know, make this observation  
20 under these circumstances and write them down in a  
21 piece of paper or in a computer. Whereas, the data  
22 we're talking about generally, although not always is

1 passive. It's not standardized. We're not asking  
2 anyone to do anything in particular.

3           And one of the benefits is that overcomes the  
4 Hawthorne effect to some degree. The notion, you know,  
5 we all watch reality TV, the cameras are around, but  
6 people forgot about those cameras after a couple of  
7 days and they just do whatever they're going to do.  
8 Right now, my heart rate is being monitored. I have no  
9 idea what it is, but it's in this computer right now.  
10 I'm not keeping track of it. I'm not trying to change  
11 my heart rate in any way shape or form. I've been  
12 walking around all day keeping its -- this is being  
13 keeping track of it. This is the ecological validity  
14 of these -- of this type of data. So I think that is  
15 another distinction that sets it quite apart from these  
16 traditional categories.

17           UNIDENTIFIED SPEAKER: Yes, I think or I've  
18 heard about the sensor based categories. I think that  
19 is one way to look at it. From my center's experience,  
20 the sensors has been getting more and more sensitive,  
21 and they can deal quite a bit of small details in terms  
22 of movements or signals that they try to detect. But



1 it also comes with larger amount of data and probably  
2 comes with also noise. And so therefore for us, our  
3 experience has been that the breakthrough for the last  
4 few years is actually not coming from the sensor or the  
5 mobility of the sensor, but rather the hour firms (ph)  
6 and the computational power behind it that can help  
7 squeeze the signal out of the noise, so that we can  
8 have things that are measuring PerfO and somehow it got  
9 related to AVIO (ph) so to speak.

10 So therefore our -- we wanted to -- our -- as  
11 a result, we wanted to acknowledge that the software  
12 and the hardware are equally important. And as you  
13 said that the patients -- one day perhaps those hour  
14 firms can be highly customized or personalized as well.  
15 And so therefore, I think that's -- as a sensor the  
16 term is nice, but I also wanted to now perhaps to pitch  
17 for -- perhaps to have something called digital health  
18 would be helpful. Thank you.

19 UNIDENTIFIED SPEAKER: I think Antonio (ph)  
20 and I are kind of thinking along the same lines. But I  
21 have always been confused as to why we think these  
22 things are clinical outcomes assessments to begin with.

1 I mean if we really think about it, what you're  
2 measuring as far as I know is really an underlying  
3 clinical process which makes them closer to a biomarker  
4 in my mind than it does a clinical outcomes assessment.  
5 I mean, you know, for one thing, this is the only kind  
6 of clinical outcomes assessment that can really only be  
7 understood through another clinical outcomes  
8 assessment, which is getting kind of meta in my  
9 estimation. And so you know, it might just be a matter  
10 of what we call it and a rose might be a rose. But I  
11 think it is worth considering what this thing actually  
12 is and how we want to understand its properties and to  
13 understand how valid and reliable it is, given how  
14 those properties are measured in clinical outcomes  
15 assessments.

16 UNIDENTIFIED SPEAKER: Okay, the gentleman,  
17 back.

18 MR. FISCHER: Hi, oh. We're good. Okay.

19 UNIDENTIFIED SPEAKER: Yeah.

20 MR. FISCHER: Ryan Fischer, I'm with PPMD. I  
21 just wanted to comment that I think special  
22 considerations should be made for pediatrics when it

1 comes to wearable devices. I work with the rare  
2 disease community. Many times these boys are socially  
3 isolated. You're going to add a sensor to them,  
4 sometimes looking like a prison ankle bracelet, and  
5 they're going to be presented with even more questions  
6 and curiosity. So I just think this is something that  
7 needs to be anticipated and some guidance needs to be  
8 done around it. The other comment I have is for  
9 companies that are investing in wearables. When  
10 several companies are working within one disease space  
11 and collecting wearable data. You know, I implore  
12 those companies to work with patient advocacy to agree  
13 to donate that placebo arm data of the wearables  
14 studies to add to our understanding of the natural  
15 history, because I think it's only going to advance the  
16 science and the use of these technologies within our  
17 overall understanding in natural history in the disease  
18 progressions. Those were my two comments.

19 UNIDENTIFIED SPEAKER: Thank you. Go ahead.

20 UNIDENTIFIED SPEAKER: As the pediatrician of  
21 the room, I would just echo that -- I think -- thinking  
22 about special considerations for minors and -- and my

1 population of interest is adolescents. So thinking  
2 about what do we with data that shows adolescents  
3 engaging in illicit activities or being in places that  
4 they shouldn't be that has nothing to do with the  
5 clinical trial really needs to be protected at a very  
6 specific and special level.

7 UNIDENTIFIED SPEAKER: Brennan?

8 DR. SPIEGEL: Brief remarks on both the last  
9 two comments. Not just -- not just children, but  
10 adults, we were using an echo bracelet essentially that  
11 our engineers thought was really great, and our  
12 patients did not think was really great. And they  
13 stopped using it. It looked like, you know, it looked  
14 like a prison, you know, it just really did. So we  
15 have to be -- we have to be very thoughtful about how  
16 intrusive these -- these devices are and their physical  
17 appearance and those are really, really important  
18 concepts.

19 I'm a little perplexed about the last comment  
20 about whether this is a clinical outcome or not or  
21 whether it's a biomarker or not. I don't know that it  
22 matters it could be a rose is rose, but you know, it's

1 a 6 minute walk test a biomarker. In a way it is. I'm  
2 a gastroenterologist, so in irritable bowel syndrome, a  
3 major outcome which is sort of a PRO is which one of  
4 these bowel movements looks like your bowel movements.  
5 Pick it out on a scale from 1 to 7, that's a biomarker.  
6 I mean that's a piece of poop coming out of your  
7 bottom, and you get to take a picture of it. So, you  
8 know, I don't know where a biomarker ends and biometric  
9 starts and clinical outcome continues. I don't know if  
10 it really matters. I think pragmatically connect to --  
11 from my colleague's comments. If the thing matters and  
12 it could be measured -- and as I say, has a very strong  
13 relationship to what people care about. I don't know  
14 that sounds like a clinical outcome to me.

15 UNIDENTIFIED SPEAKER: Yes.

16 UNIDENTIFIED SPEAKER: Thank you. Martin and  
17 then Linda's question --

18 UNIDENTIFIED SPEAKER: Sure.

19 UNIDENTIFIED SPEAKER: -- will be the last  
20 question.

21 MR. HO: A very quick comment. I was been --  
22 I was told before the meeting that once we hit the

1 biomarker discussion, we would encourage this -- the  
2 audience to provide their comments about these  
3 classifications, biomarkers are or how we record these  
4 things into the docket, so that we can enrich our data  
5 collection. And so that we can also focus on other  
6 issues that are more burning. So thank you.

7 MS. DEAL: So Linda Deal, Pfizer. I just  
8 wanted to pick up on the ability for this category to  
9 be complementary to COAs. And while I agree with that,  
10 I think we need to be careful about how that's  
11 expressed. And what I mean is a COA or a human  
12 reported outcome may measure something that's extremely  
13 important, and the sensor device or something may also.  
14 You provided, Dr. Spiegel, the example with pain in  
15 steps, and a decision had to be made, do I believe the  
16 device data or do I believe what the human told me?  
17 And I think that's important but -- but I think what we  
18 need to do to make them complementary and avoid having  
19 to figure out the principles for deciding who to  
20 believe or what to believe is to make sure that they  
21 are measuring something unique to what the human can  
22 report. So it's funny. I was thinking, you know, if I

1 got clocked doing 16 or 35, the officer would come to  
2 my window and say, "Do you know why I'd stopped you?"  
3 And I'd say, I have no idea. But he is going to  
4 believe his radar device, right?

5           So I think that we're going to -- to sort of  
6 avoid that because we have that even with two different  
7 COAs that may measure the same concept, we can get  
8 discordant data and then you have to talk to the agency  
9 about which one -- give them an argument for what to  
10 believe. So I think with this digital help, it should  
11 be something that is uniquely measured and not -- not  
12 similar to what maybe a human report. And then you've  
13 got yourself in the corner of coming up with a rule on  
14 who or what to believe.

15           UNIDENTIFIED SPEAKER: Thank you. Okay, so we  
16 are concluding this session. Thank you to our  
17 panelists and to the audience.

18           (Applause)

19           UNIDENTIFIED SPEAKER: Hi, everyone. Final  
20 stretch, almost there. We will take a full 15 minute  
21 break. We won't be cutting into the next session. We  
22 don't have a full list of folks signed up for the open

1 public comments. We'll be able to take some of that  
2 time. So we'll see you all again at 3:00 p.m. Thank  
3 you.

4 (Recess)

5 BREAK

6 IDENTIFYING KEY THEMES AND NEXT STEPS

7 MS. CHALASANI: Hi, all. I'm just going to  
8 slowly ask you all to make your way back to your seats.  
9 We'd like to get our last closing session started.  
10 Thank you. Great. Hello again. My name is Meghana  
11 Chalasani in the Office of the Center Director, in the  
12 Center for Drug Evaluation and Research. I have the  
13 honor of moderating our workshop's closing session.

14 It's truly been an insightful 2 days of really  
15 robust conversation. And I know that our FDA experts  
16 that we have a lot of information that we're going to  
17 be taking back with us and hopefully much more in the  
18 public docket that we have consistently and constantly  
19 been reminding you all of. And I hope that everyone  
20 else joining us in person and on the web have also  
21 found the discussions informative and helpful.

22 To kick off our closing panel, I'll ask that



1 each of our panelists briefly introduce themselves.  
2 We'll start with Stephen and then work our way down the  
3 line.

4 DR. COONS: Stephen Coons, and I'm the  
5 executive director of the Patient-Reported Outcome  
6 Consortium and program officer for Clinical Outcome  
7 Assessment Programs at the Critical Path Institute.

8 DR. GROSSMAN: I'm Cindy Grossman. I'm  
9 director of FasterCures, which is a center of the  
10 Milken Institute. And I lead a program to help patient  
11 perspectives inform medical product, discovery,  
12 development and delivery.

13 MS. HALLING: Hi, I'm Katarina Halling, and I  
14 head up the patient-reported outcomes group at  
15 AstraZeneca.

16 DR. JOHNSON: I'm Laura Lee Johnson, director  
17 of Biometrics III in the Office of Biostatistics in  
18 CDER and I am our clinical outcome assessment and rare  
19 disease liaison.

20 DR. LEIDY: Good afternoon. My name is Nancy  
21 Kline Leidy. I'm the senior vice president of  
22 Scientific Affairs and Patient-Reported -- no, Patient-

1 Centered Outcomes -- it's late, right -- at Evidera.

2 DR. PAPADOPOULOS: Hi, I'm Elektra  
3 Papadopoulos, associate director for the Clinical  
4 Outcome Assessments staff in CDER.

5 DR. SLAGLE: Hi, I'm Ashley Slagle, principal  
6 at Aspen Consulting, where I provide scientific and  
7 regulatory advice to instrument developers, sponsors  
8 and patient advocacy organizations who are developing  
9 patient-centered COAs and endpoints.

10 DR. WEINFURT: Good afternoon. I'm Kevin  
11 Weinfurt. And I am a professor and vice chair research  
12 in the Duke Department of Population Health Sciences  
13 and a member of our Center for Health Measurement  
14 directed by Bryce Reeve.

15 MS. CHALASANI: Thank you. Thank you all. So  
16 the purpose of this closing panel is to really  
17 highlight some of the key takeaways from our workshop  
18 discussions, primarily focusing on those topics related  
19 to methods to select, develop or modify fit-for-purpose  
20 clinical outcome assessments. So discussion of  
21 document 3 topics. And then after that I really ask  
22 our panel to reflect on the bigger picture, larger

1 themes and thinking about next steps.

2           So I'd like to open our panel discussion with  
3 one guiding question to really focus on the key  
4 takeaways. And so does the discussion document for  
5 Guidance 3 present information about best practices of  
6 clinical outcome assessments selection, development or  
7 modification in a manner that can be reasonably and  
8 rigorously implemented in medical product development?  
9 And so as our panel responds, I'll ask that in addition  
10 to sharing your perspectives on the document itself,  
11 also reflect on one to two of the most important  
12 messages you have taken away from the workshop  
13 discussion itself yesterday afternoon and today.

14           I know Stephen, Nancy and Kevin, you had an  
15 opportunity to comment on the document yesterday  
16 afternoon, so perhaps your comments can particularly  
17 focus on the discussions themselves. And I know that  
18 we can spend the entire 1 hour discussion during this  
19 panel on this one question alone, so I'll also ask our  
20 panelist to be brief and succinct, so that we can move  
21 onto some of the other -- other questions that I have  
22 laid out there.

1           So Stephen, we'll get started with you.

2           DR. COONS: Sure. One of the things I wanted  
3 to talked about just briefly in terms of -- for many of  
4 you who know me, terminology is something that I obsess  
5 on. And one of the things is in the document, we refer  
6 to or the -- the FDA refers to measures instruments,  
7 tools and assessments. These four different terms.  
8 And I -- I think that we need to consider or there  
9 needs to be consideration of landing on one or two of  
10 those. One of the things about the PRO guidance in  
11 2009 is it made a distinction between measures and  
12 instruments. And there was a glossary at the end of  
13 the guidance that essentially defined the instrument as  
14 the measure in all of the information that accompanies  
15 it to enable it to be administered. Essentially the --  
16 the scoring algorithm, the user manual et cetera. And  
17 I didn't know if -- if FDA is continuing that  
18 distinction, but I think it's an important issue to  
19 consider.

20           The other thing is the difference between  
21 something or the distinction we need to make to be more  
22 precise between PRO, like a patient-reported outcome

1 which is could be pain, and how would you measure that  
2 or what tool you use to measure that, and that would be  
3 a patient-reported outcome measure. And I think that  
4 that's one of the things throughout this document that,  
5 that distinction has to be made between the what is  
6 being measured, what is the outcome and then what is  
7 the tool that's measuring it.

8           But in terms of, you know, some of the  
9 takeaways or, you know, in principle, you know, there's  
10 -- there -- as I said yesterday, they are some very  
11 significant advances in Guidance 3 from the 2009 PRO  
12 guidance. And there are some -- still some things that  
13 have to be fleshed out, specifically related to more  
14 specifics about the uniqueness of performance outcome  
15 measures and clinician reported outcome measures. And  
16 it's important to remember that this series of PFDD  
17 guidance document is -- is broadly addressing,  
18 appropriately capturing the patient experience. But  
19 Guidance 3 really is a guidance for industry. It's not  
20 necessarily -- it shouldn't be trying to be all things  
21 to all people. The target audience has to be the  
22 scientists that are involved in medical product

1 development. So I think that's an important principle  
2 and an important message, takeaway message.

3 And also this guidance, Guidance 3, has to  
4 remain focused on assessing the outcomes of disease and  
5 its -- its treatment that are meaningful to patients  
6 and treatable by a medical product. And this guidance  
7 is not on patient preference research or risk  
8 assessment or safety reporting or assessment. And it's  
9 not to say that COA data couldn't be used particularly  
10 in patient preference research, but that's not within  
11 this scope of this guidance. So I think we have to not  
12 be distracted by these other things that are important  
13 and related, but that aren't within this scope of this  
14 guidance. So with that, I'll finish with my remarks.

15 MS. CHALASANI: Thank you, Stephen. Cindy?

16 DR. GROSSMAN: Thanks. So I think that I  
17 heard a lot over the last day and a half about how this  
18 is, I think a significant improvement in terms of  
19 clarifying and adding to the 2009 guidance. And in  
20 particular heard that sort of expanding the decision  
21 tree and kind of getting away from that. The circular  
22 diagram in terms of the development and process behind

1 clinical outcome assessments is really important. I  
2 should also say one caveat, I don't do measurement  
3 development or anything like that. So my perspective  
4 is really going to be from the perspective of trying to  
5 help make this guidance, and set of guidances as  
6 accessible to the stakeholders that would want to  
7 partner with industry, in trying to create this -- to  
8 have an -- I agree with Stephen that the primary  
9 audience does seem to be sort of sponsors and  
10 potentially measure developers within the context of a  
11 clinical development pipeline. But certainly, patient  
12 advocacy organization, we heard from them throughout  
13 the last day and half, have a vested interest in these  
14 measures in developing and are key partners throughout.

15 And so one area, I think that I heard was that  
16 there needs to be a bit better pull through across the  
17 document to talk a little bit about what Phil (ph) has  
18 talked about in terms of the, what we're doing and also  
19 the how we're doing it. And so this implementation  
20 piece, while I think there was a lot of guidance on the  
21 selection and development and modification processes  
22 behind COA, the implementation piece was I think a

1 little less present. And so a little bit more  
2 information about the implementation across the  
3 development and selection process.

4 And then I think one word caution that for  
5 somebody like me, it is a little tricky to flip back  
6 between fit-for-purpose, context of use. If you modify  
7 a COA, at what point does it become a new COA because  
8 you modified it so darn much that you can't really tell  
9 it's the same instrument or it looks even remotely the  
10 same. And so those were just sort of brass tacks  
11 questions for kind of a bit more of a lay person. And  
12 again if it's not a relevant or isn't directed toward  
13 that, then I understand that. But that was a little  
14 bit more challenging to figure out, and I did get that  
15 the fit-for-purpose in context of user are essential,  
16 but exactly where does one stop and where does one end?

17 Similarly for determining an outcome, at what  
18 point does sort of an outcome exactly flip over to an  
19 endpoint. And exactly sort of again and a bit more in  
20 lay terms, how does that -- how are -- how are those  
21 two things differentiated? And then finally, just a  
22 moment about, I think interacting with FDA throughout



1 the process of selection, development and modification  
2 of the COA. There were presented in the documents  
3 multiple doors in which people could go through,  
4 whether that's the qualification process through the  
5 PRO consortium or the IND process or a bit more around  
6 sort of formative conversations with FDA. And I think  
7 different doors may attract different stake holders,  
8 and I wasn't sure if that was okay. And would help  
9 facilitate an efficient development program around COAs  
10 kind of making it through the process.

11 I can understand the need for different doors,  
12 but their relationship in the document was a little  
13 less clear to me, so maybe thinking about the  
14 relationship of the different doors and when you would  
15 make a decision and -- and maybe whose -- which  
16 stakeholders are appropriate -- more appropriate for  
17 which doors would be useful. So that's about it.

18 MS. HALLING: So I think that the way that the  
19 guidance is put together now has come a really long  
20 way, and I think it's a really good place to be in with  
21 the collaboration between the COA group and the  
22 patient-focused drug development, Theresa's group and

1 the division from the FDA. I think it's really nice to  
2 see how you all come together and presents your  
3 thinking. How can this reasonably and rigorously be  
4 implemented in medical product development? From a  
5 pharma company perspective, I have high hopes that this  
6 dramatically will change how we develop medicines.

7           So the way that you push and the way that many  
8 of us in our companies have pushed for understanding  
9 the patient perspective already very early on in  
10 development will be very important, and I think a game  
11 changer. And I see that as a huge achievement and  
12 something to be proud of so far. There is more work to  
13 be done. I see that foundation of understanding the  
14 patient perspective very early on in development as the  
15 foundation for the strategy. So yesterday, we heard a  
16 lot about let's start with the end in mind what's the  
17 strategy, what's the research question? And I think  
18 and I hope that this patient experience work that we'll  
19 be doing and pushing more for early on will provide  
20 that foundation and be extremely important.

21           One thing we heard also yesterday was the way  
22 that this information is being structured. So we heard

1 both voices to make the strategy very clear and make  
2 the intent very clear for all sections. And then to  
3 Stephen's point, there are many sections such as the  
4 Guidance 3 that obviously is very relevant for those of  
5 us who develop endpoints. I think that we'd like to  
6 push ourselves to be in a place where the information  
7 that is on the higher level strategy is accessible and  
8 understandable to everybody, all the key stakeholders,  
9 even if you don't develop measurements. And then that  
10 the right amount of details are in the appendices and  
11 in the specific guidances. And we heard a lot of  
12 suggestions of what more detail to put in there. I  
13 think one of the suggestions that I liked was also  
14 adding more about the implementation piece, and not to  
15 stop the guidance when we do have a good strategy and a  
16 good plan, but really to ensure that we have principles  
17 to actually implement the assessments and measurements  
18 in clinical trials, so that we really drive home,  
19 really good data because only if we have very good  
20 compliance and very good data, will we be able to use  
21 the data for its intended purpose for regulatory  
22 discussions to -- to feedback to patients and to inform

1 decision making and also for peers.

2           So I would like to see that strategy very  
3 clear for all stakeholders and then clear guidance.  
4 And then the final thing that I would like to ask for  
5 is and I know that came up yesterday as well is really  
6 clear guidance where -- where the FDA really know,  
7 where the "no-no"s are and where you know where the  
8 best practices are, please be comfortable to spell  
9 those out. I know that there is great with -- it's  
10 really great with flexibility, but it's a double edged  
11 sword. So if you present good principles and then at  
12 the end say, "But we are flexible," there will be  
13 always people who say "Well, you know, we -- they're  
14 flexible, so we can -- we can do whatever we want." So  
15 I'd encourage you to think about, you know, the key  
16 principles where you really don't want to negotiate and  
17 many of us have seen you, not negotiate on those things  
18 and spell them out. I think that'd be really helpful.  
19 But overall, I think that the answer to the question is  
20 -- is yes.

21           MS. CHALASANI: Thank you. Laura Lee?

22           DR. JOHNSON: Sure. So I sometimes show a

1 slide that I showed the high jump and then I showed the  
2 limbo bar where like the stick is right by the ground  
3 and like there is a certain point after which you can't  
4 be flexible sometimes. So as you were saying that  
5 reminded me of this. I think, some of my key  
6 takeaways, and I want to thank everybody for all of  
7 your input, because it's always -- it's been a rich  
8 discussion, and I think I walked past someone who said,  
9 "I have 14 pages and notes," and I think I'm around  
10 there too. And really thinking about you focusing on  
11 what we are doing, why we are doing it and how we are  
12 doing it. And that transparency in kind of that  
13 thought process which we try to put down, it's a little  
14 hard because then you -- you will never know until you  
15 sit here how much people read into what you write and -  
16 - and can interpret it in ways you never imagined. But  
17 that is something that I think we're trying to balance  
18 in thinking about especially with the implementation  
19 piece is kind of what should go online and what should  
20 go in guidance. And so I've been to trying to make  
21 notes to myself about that over time because a lot of  
22 these case studies or our thoughts about implementation

1 may change dramatically 3 years from now or even 6  
2 months from now.

3           And so how do we stay fresh while actually  
4 having a really useful document and not something  
5 that's just like, okay, these are some high principles  
6 and nobody knows how to really implement it?

7           And really also thinking about -- and this  
8 came from one of my colleagues in the audience thinking  
9 about that digital health technology. And it's useful,  
10 but I think we did have a very robust discussion about  
11 how to best try to integrate this and how to really  
12 think about, and this is true across any of these, how  
13 do we really think about meaningfulness. But this is  
14 not all that easy to figure out. And so how are we  
15 going to approach that and how we're going to keep  
16 updating that over time?

17           DR. LEIDY: I think it's a -- this is a -- a  
18 very good what I would call a transition draft.  
19 Transitioning from PRO to COA. And what struck me in  
20 the conversations in the last couple of days as well as  
21 re-looking at the draft, is that some -- a lot of the  
22 elements of the PRO are still there. So the

1 recommendation I would make actually is to for the  
2 editors, as they're going through, is to ask yourself,  
3 is this a PRO specific example? Is this a PRO specific  
4 terminology? And to what extent can we make it more  
5 generic, so that it actually is a framework for  
6 clinical outcomes assessment. And then be specific  
7 around for example, for PRO measures, such and such and  
8 such and such could be done, while for ObsRo measures,  
9 X, Y and Z might be done. So it's very clear that it's  
10 a generic framework for this COA categories, but the  
11 PROs are a subset of that.

12 Right now, it's kind of -- it's a little bit -  
13 - I think we can all it's driven by the PRO, which is  
14 great, it's a perfect transition, but something that we  
15 want to do.

16 The other thing that was brought up which I  
17 thought was a very good point as we want to go beyond  
18 the classical test theory. And so if every example is  
19 classical test theory, we may be tying ourselves in  
20 unintentionally. So I'd spread out the examples a  
21 little bit more or scale them back a little bit more,  
22 or possibly again sprinkle a COA example, the Perfo

1 example with a PRO example, so it's clearly a COA  
2 broader guidance document.

3           The other piece of it is you want it to be  
4 guidance and not prescriptive, so that allows you to  
5 actually give more examples without necessarily  
6 proscribing or what should be done or -- or leaving  
7 impression that they -- people have to use specific  
8 techniques. The other piece of it is that I love the  
9 reference to modification, but as I mentioned  
10 yesterday, it scares me a lot, and I think we need to  
11 really take page -- I think it's page -- I got to fold  
12 it over here -- the modification page could be actually  
13 cleaned up a little bit, so that it really does  
14 describe when do you modify or why do you modify or  
15 what represents different levels of modification for  
16 example. What would be a minor modification, what  
17 would be a major modification, and then what do we do  
18 when this maybe another topic of conversation and  
19 discussion, what do we do about, is this a new measure?  
20 Is this a modification of an old measure? What's going  
21 to happen with it?

22           And then you -- I'm a little bit concerned



1 that people will read that and say, "Oh, I can just  
2 take any measure I want from the literature or off the  
3 web, and just to make changes." Well, there's  
4 copyright and intellectual property that we need to  
5 deal with as well. And so we need to make sure that IP  
6 is respected in that -- in that regard as well.

7           So the modification piece, I think we've just  
8 got to get that. We got to get that down. That's  
9 really, really important. And then other examples that  
10 came up this -- the last couple of days that are -- in  
11 addition to IRT and Rasch and other techniques that  
12 could be mentioned as sort of a wave of the future and  
13 the past as well. Or things like item banks that came  
14 up quite a bit. And that seems to be an opportunity  
15 for us going forward and are there could -- could some  
16 examples be included in there -- in the guidance too?  
17 Let people realize that that could potentially be a --  
18 a potential approach.

19           You mentioned the doors that were mentioned on  
20 page 9, the figure 2. I think we would benefit from  
21 hearing a little bit more about those doors. And  
22 specifically, again what -- which door is best for

1 which people perhaps or -- or some sort of examples of  
2 what -- when you might want to use which door, but also  
3 potentially how we can maybe not part of this guidance,  
4 but as part of the discussion, how can we improve the  
5 speed with which we can call through those doors. And  
6 how do we know when the door could actually be opened,  
7 and how do we know when the door is closed. So a  
8 little bit more around, you know, the -- maybe the  
9 advantages and disadvantages.

10 I don't know that that necessarily is a  
11 guidance per se, but may be and this PRO taskforce  
12 could write an article or something like that, that  
13 would give people an idea of what to do about the  
14 doors, so --

15 Let's see what other ideas or thoughts I have  
16 here. Yeah, I think those -- those are my main  
17 comments. So and to address the question, does the  
18 discussion document present information for best  
19 practices, rather than a dichotomist yes, no, I'd like  
20 to answer that on a -- on a scale of 1 to 10. And with  
21 1 being, "Yeah, forget it, this isn't going to work at  
22 all", to 10, "Brilliant, let's go as is". I would -- I

1 would probably give it a 6, because I think we're well  
2 on our way. But I think four more points will get us  
3 closer to 10, so --

4 MS. CHALASANI: Thank you, Nancy. Elektra?

5 DR. PAPADOPOULOS: I -- so, I agree with a lot  
6 of what's been said and I just wanted to reassure folks  
7 that we are taking all of this advice, this feedback  
8 very seriously. We're listening very carefully and --  
9 to the advice that we're getting, and this workshop as  
10 well as to the docket. So I, you know, I'm going to  
11 say a few words after this session but I just wanted to  
12 say that, and I appreciate it.

13 MS. CHALASANI: Thanks, Electra. Ashley?

14 DR. SLAGLE: Great. So, first I just want to  
15 thank the FDA for this what has I'm sure been a  
16 Herculean effort to get these discussion documents out,  
17 I mean across center collaboration and all the  
18 clearances and the time lines you did it under. So I  
19 agree with Nancy that this is well on its way and I'm  
20 really impressed with how quickly you did it and how  
21 thoughtful it was. So I hope that the comments that  
22 you've heard have been constructive and I'm going to

1 point out some things, where I think there can be  
2 improvement but overall I think they're really great  
3 documents. We did hear and I agree that the new Figure  
4 6 to replace the wheel and spokes -- that seemed to  
5 resonate well with people. I really appreciate that  
6 you're talking about modifications in the guidance now  
7 rather than starting from a place where Denovo  
8 Instrument (ph) is assumed. I think that, and this has  
9 been said by a number of people most recently, Nancy.  
10 There needs to be a little bit more discussion around  
11 thinking about the process of modification and Nancy  
12 mentioned minor versus major modifications and I would  
13 actually hope to see even a little bit more specific  
14 information about when you modify and if you're --

15 MS. CHALASANI: Ashley, sorry. Could you  
16 speak a little bit closer to the mic?

17 DR. SLAGLE: Yeah.

18 MS. CHALASANI: Thank you.

19 DR. SLAGLE: When you modify item content then  
20 it's -- that would be a major revision but the type of  
21 evidence that you would need to generate for item  
22 revision versus a type of modification where you may

1 have a legacy instrument, you know that that people  
2 that the population understands the items but you're  
3 just creating a new score with a subset. That's a very  
4 different process for evidence generation, so just some  
5 examples around that I think could be really helpful.  
6 I really like the appendix one, where you lay out the  
7 different types of things that you're reviewing and  
8 kind of the steps you go through to review. People did  
9 mention that that seemed very classical test theory  
10 based and my bias is towards classical test theory. So  
11 that didn't bother me. I think -- I do think though  
12 there are some really important advances that we've  
13 made and there are some really useful purposes for some  
14 of the new modern psychometric methods. And so adding  
15 something even if it's just into the preamble that  
16 says, here's what kind of the minimum that we want to  
17 see but there are a lot of other emerging methods or  
18 methods that can be really useful. And just opening  
19 that door that these are not -- people are not limited  
20 to what's in that review section. This is getting down  
21 into the weeds a little bit so I won't spend a lot of  
22 time on it. But it would be nice to have just a little

1 bit more information around thinking about scoring.  
2 And so again I'm more traditional where I like raw  
3 scores, I think they're easier to interpret, we can  
4 anchor them back to the original response options, it's  
5 easier to communicate to patients. But there are  
6 benefits sometimes with using some more complicated  
7 scoring algorithms that can help improve sensitivity,  
8 sometimes that's at the risk or the threat of making it  
9 less interpretable or less easy to be communicated. So  
10 just some thinking around or some thoughts around how  
11 to think about scoring decisions. And I wouldn't  
12 imagine that you would take a stand on that or should  
13 take a stand on that but just giving people some  
14 thoughts about what to think about when you're making  
15 those decisions.

16 The context of use discussion, I think, is  
17 really good. I was a little concerned yesterday when I  
18 heard a few people mention that in step one of Figure 6  
19 it's too early to be thinking about endpoints, and I  
20 would strongly disagree with that. So I would hope you  
21 would keep that in step one. I think we need to at  
22 that point -- clearly you can't specify the actual

1 endpoint that's going to be in your future SAP. But  
2 having some idea if you're looking at symptom  
3 improvement or time to deterioration can drive your  
4 qualitative research sample, it can drive decisions  
5 about the items in your instrument, it can even -- and  
6 you should be thinking about your ultimate patient.  
7 The sponsor should be thinking about their ultimate  
8 patient population in their trials. And so I think not  
9 thinking about endpoints that early is really a  
10 mistake.

11 I love the examples in the guidance. I think  
12 they're extremely helpful. I learn best when I see bad  
13 examples and so if there are examples where things  
14 haven't worked out well it might be nice. And I know  
15 it's difficult for FDA to put examples out in guidance  
16 because it's difficult to get that through the  
17 attorneys, the lawyers probably.

18 But so I'll ask the audience a plea for our  
19 FDA colleagues to please send in your examples to the  
20 docket and I'll be doing that by December 14th, I  
21 understand. So I liked the examples and I think we  
22 could build on even more examples. And I'll talk about

1 this probably later in the questions but I think we can  
2 think about a framework to communicate information in  
3 different places and so maybe the guidance isn't a  
4 place for all the examples necessarily. And I think  
5 I'll stop there.

6 MS. CHALASANI: Thank you, Ashley. And to  
7 close us off, Kevin?

8 DR. WEINFURT: Thank you. This really has  
9 been a very interesting last 2 days, wonderful  
10 discussions and as I was putting together my thoughts I  
11 was just noting that pretty much all of the good things  
12 have been said but I'm bringing the academic  
13 perspective on the panel. So I'll just restate them in  
14 a tedious pedantic way. I guess -- to -- I've got  
15 about three things I wanted to note. The first is  
16 toward this issue -- well, let me let me say to that  
17 that I really enjoyed these guidance documents. I  
18 think they reflect much better now where our field is.  
19 And so some of the opportunities I think we have for  
20 sharpening here are opportunities that the field has.  
21 These are not shortcomings of the guidance in  
22 particular. They really is reflecting where we are as



1 a field. So, I just wanted to make that clear.

2 And I think regarding the issue of how well  
3 can people reasonably and rigorously implement these  
4 things in development? This issue of examples has come  
5 up many times and I just can't underscore enough how  
6 important that is. Right toward the beginning  
7 yesterday, Tara Symonds mentioned that you know, over  
8 10 years ago when we met for the first guidance, what  
9 we got was a list of ingredients and absent any other  
10 guidance people tended to think that the only thing the  
11 FDA would eat is something that had all these  
12 ingredients in it. And so people just dumped these  
13 things in. I don't think a lot of them tasted  
14 particularly good, they didn't really all go together  
15 well.

16 In this one we've got a list of potential  
17 ingredients with more statements that FDA is not a  
18 picky eater, we're open to all sorts of types of  
19 cuisine and stuff and you can even use some leftovers  
20 and maybe put it in a new sauce or something. And so  
21 that is good but what we still need and there are  
22 examples of more specific things like best technique to

1 dice an onion or something. But we really need recipes  
2 that have worked, ways to combine these things in a way  
3 that makes a compelling dish.

4           And I guess that brings me to the second  
5 point. The compelling dish here is a compelling  
6 argument and I would love to see in the guidance more  
7 explicit language that touches on what some of our  
8 colleagues have mentioned in the past here because some  
9 people can take terms like "Fit for purpose and  
10 qualified" and they'll just interpret that as  
11 validated. It's just now it's sort of a property of  
12 the measure. And it doesn't encourage thoughtfulness  
13 that wasn't the intent of the terms but I think we see  
14 that people tend to use them that way.

15           And so it would be great to have some language  
16 that was really underscoring that we're trying to make  
17 a claim and we're going to make an argument about the  
18 truth of that claim. And the argument about the truth  
19 of the claim includes many parts. One important part  
20 in that argument is the suitability of the measure. So  
21 fit for purpose is a convincing -- to say a measure is  
22 fit for purpose is to say it is a convincing part of

1 the argument for the claim and how do I make that  
2 argument. And so I think that kind of language would  
3 be helpful for people in thinking about, "Okay I need  
4 to put together a story that's going to back up the  
5 truth of the claim that I'm hoping to get at the end."  
6 I think making it more explicit would be better.

7 And the last thing I wanted to mention then  
8 was an important part of the story that I think is  
9 missing and it's going to be very difficult for people  
10 to make a compelling story about a fitness for purpose  
11 without this other picture. And the picture is a model  
12 of the measure, what is the rationale for how this  
13 measurement works. And this addresses somewhat the  
14 concern with the different types of COAs in here.

15 What we've got in like Figure 7 the conceptual  
16 framework, an example; 8 is another example of that.  
17 We have some boxes, and some boxes are underneath other  
18 boxes. And so it's good, it's more explicit than not  
19 having any boxes or labels. But we still don't know  
20 how is this measure supposed to work. Because when I  
21 know how it's supposed to work I then know what  
22 properties would be relevant to see whether it is

1 working or not.

2           So for example I might have some boxes with  
3 boxes underneath them and what is describing is really  
4 a composite index. For example, activities of daily  
5 living; these are activities that patients in this  
6 community have said were sort of the basic critical  
7 things for them to be able to do during the day and we  
8 want to know whether or how well they can do those  
9 things. And we're going to put them all in one  
10 category and give the label activities of daily living.

11           It's a composite index, they don't need to be  
12 correlated necessarily, right Cronbach's alpha,  
13 dimensionality analysis will not be relevant there,  
14 it's a different type of a measure, it's a composite  
15 index.

16           And so if we communicated that that's how that  
17 measure is supposed to work then I would know what to  
18 look for to see is this making a good argument. Where  
19 did they get the opinions that these were the right  
20 activities to be listed under there, did they talk to  
21 the right people, was there enough consensus on those,  
22 right? Maybe the picture of how the measure works is

1 that these are multiple -- the items are all multiple  
2 fallible indicators of some underlying thing. It's a  
3 latent variable, I'm trying to estimate either through  
4 classical test 3 methods or IRT or whatever. But  
5 that's how this is supposed to work. And now I know  
6 that I need to offer evidence that the dimensionality  
7 is there, a relevant measure of reliability would be  
8 internal consistency and so somewhere in between the  
9 argument for the claim and the rationale for the model  
10 is my argument about the fitness for purpose right  
11 here. So I think without giving people examples of the  
12 different models and maybe I've got a performance  
13 measure that's tracking my movements. What is --  
14 what's the mechanism by which this measure is supposed  
15 to work, and what's the evidence that it's working in  
16 that way that variation's and the concept of interest  
17 are reflected in variations in the output of this  
18 measure. So there are some common principles that  
19 could apply across all the different types of measures  
20 we've got here and I think it would be beneficial to go  
21 through and as others have noted to be very clear about  
22 the higher level properties of a measure that we need

1 to see and giving the examples and being clear to link  
2 the examples of properties specific to their  
3 measurement models. I think that was pedantic enough,  
4 was that? I'm sorry. I'm done, Meghana, right.

5 MS. CHALASANI: Okay. Thanks Kevin.

6 DR. WEINFURT: Meghana, I'm sorry.

7 MS. CHALASANI: He warned me that when he  
8 first said his first comments he's going to address all  
9 the questions in one. And I think you set it out quite  
10 nicely Kevin, thank you. There is a lot that I do want  
11 to probe on and we had a really full panel, so I'm  
12 going to start back here with something's that Stephen  
13 said and probably slowly make our way back over the  
14 other -- to the other direction.

15 The first thing Stephen, I think, you raise  
16 which was a really good point and we didn't touch upon  
17 it as much in this workshop but we did talk a lot about  
18 it at the December workshop last year, which was  
19 terminology. And I think that at the agency we are  
20 very conscious and supportive of consistent and  
21 standardized terminology especially in this space,  
22 especially considering it's such a new and evolving

1 space. But we can of course be more conscious, but I  
2 do want to put a plug in for the glossary. At this  
3 time I think that's appropriate. The PFDD, Patient  
4 Focused Drug Development glossary is intended to be a  
5 glossary for the entire series of documents. And so  
6 while we presented a version at the December workshop  
7 and already had some feedback on it, that has been  
8 updated to include some new terminology based on these  
9 guidance documents. So if folks can take a look at  
10 that and provide us comments to the docket on the  
11 glossary as well, that would be very, very helpful.  
12 Feel free to give us a line edits, I know, with the  
13 glossary it needs to be very specific.

14 The other thing that I -- another theme that I  
15 heard was audience. And I think Cindy you nicely  
16 captured it in that the entire PFDD guidance series  
17 overall. So the four guidance documents does have a  
18 broader audience than typical FDA guidance. Typical  
19 FDA guidance maybe for product developers and  
20 methodologists and researchers, and for this guidance  
21 series we did want to make it more accessible to a  
22 broader range of stakeholders.

1           But specifically in Guidance 3, the audience  
2           that's described is more once again the developers and  
3           the experts. But I do think we envision that it's  
4           still accessible and provides opportunities for  
5           patients stakeholders and other community members to  
6           partner along side in the process. I look to our FDA  
7           colleagues, Laura Lee and Elektra, and say, do you  
8           agree that that was the end vision and the audience  
9           that we intended for Guidance 3 and that's coming off  
10          clearly? And then I'll ask for others folks on the  
11          panel to see if that did come across clearly. So,  
12          Elektra?

13                 DR. PAPADOPOULOS: I completely agree. I  
14                 think you stated it very well Meghana. I mean, in  
15                 general we try to use plain language in all of our  
16                 documents. And so this is no exception and we also try  
17                 to illustrate some of the principles with examples to  
18                 again make things more accessible.

19                 MS. LEE: Yeah, I want to echo that. And I do  
20                 think as we are working on the discussion documents of  
21                 preparing for these 2 days of meetings, we did realize  
22                 that kind of our language was shifting in what we were



1 doing for 3. And part of that may be kind of where we  
2 were coming from but also if folks do have a way to  
3 kind of make more plain language, because I think we  
4 all understand that eventually the patients are going  
5 to have -- they are partners all the way along was way  
6 and really in many ways -- this is my personal view --  
7 the ultimate consumers of what we're doing.

8           And so I mean there a lot of other people  
9 consuming this information but also at the same time, I  
10 mean, I work in an office with about 220 statisticians,  
11 the majority of whom have no background in this area.  
12 So for them also they are approaching it, they need a  
13 non-technical way of thinking about even though they  
14 have a technical background. So there are a variety of  
15 different groups there. But yes I think you'll notice  
16 our language did slightly change. And as we look  
17 forward to Guidance 4, in that development we're also  
18 going to have I think the struggle of trying to think  
19 about who are those stakeholders.

20           So we're very interested in hearing from  
21 others kind of where are we balancing, where can we do  
22 better, what should we be looking at.

1 MS. CHALASANI: And I think Laura Lee just  
2 basically said this next question that I had for folks,  
3 which is; did we strike the right balance? Now that  
4 you know that that was the vision of our audience that  
5 we intended this document for, I don't know if folks on  
6 the panel want to respond, perhaps Cindy if you want to  
7 kick us off?

8 DR. GROSSMAN: Yeah, I mean I think it's a  
9 good start to striking the balance. I still think  
10 though that there are some ways in which it's harder  
11 for other types of stakeholders to enter in. And I  
12 actually was really also struck by the fact that some  
13 folks talked about the other stakeholders in their  
14 companies too, so it's not just -- it's not just out --  
15 external to the sponsor, it's also within sponsor and  
16 organizations or entities that other stakeholders need  
17 to be considered.

18 And so I think -- so if you look external to  
19 sponsors or non-sponsor activities, we see a great  
20 activity across patient advocacy organizations or  
21 patient organizations that collect data in the context  
22 of trying to understand the natural history of the

1 disease. And to the degree to which that data needs to  
2 be in a particular form to be able to inform the  
3 processes, COA development and sort of enter into this  
4 guidance, I think that's a critical point. We would  
5 really -- obviously the goal is to have those groups  
6 also be partnered with sponsors, but to be honest there  
7 are some sponsors that just aren't interested in their  
8 disease area or aren't working in their disease area  
9 yet.

10           And so to the degree to which those  
11 organizations are standing up work on their own around  
12 this data collection figuring how to touch point to  
13 this I think is -- and having this be accessible enough  
14 to them, to guide some of their efforts is going to be  
15 critical.

16           But then I also think, and maybe it's -- if I  
17 followed all of Kevin's pedantic points, I think it  
18 actually that maybe telling the right story is also  
19 very important for the stakeholders in other parts of  
20 the sponsor company to understand why a particular COA  
21 is fit for purpose, how it drives the end goal of  
22 making a claim, I think is critically important. And

1 so maybe being able to -- your comments about spelling  
2 that out more clearly would serve that purpose as well.  
3 So those were some of my thoughts. If I can slip in  
4 one more into this?

5 MS. CHALASANI: Thanks.

6 DR. GROSSMAN: Which is just about whether or  
7 not some of this work -- for some stakeholders this  
8 work of COA modification and development happens in a  
9 pre-competitive space, and in other ways it's not  
10 competitive or it's not transparent, it's more  
11 competitive and sort of behind a wall. And I think to  
12 the degree to which this guidance or if it's the  
13 discussion document or some way of pulling out and  
14 highlighting some of the pre-competitive opportunities,  
15 would be one way stakeholders could potentially insert  
16 into this in a way that would be appropriate.

17 MS. CHALASANI: Thank you, Cindy. One thing  
18 that I want to probe a little further into what you  
19 just said Cindy is that it's not just medical product  
20 developers and the other stakeholders but within an  
21 organization, within a medical product developers,  
22 organization and company like within their different

1 teams and I think this is something that Katarina when  
2 we had our prep call we've had briefly discussed. I  
3 think you were talking about you may have patient  
4 engagement or PFDD staff and then you have your PRO or  
5 other co-staff for example. So would you mind speaking  
6 to that a little bit? Thank you.

7 MS. HALLING: Sure. And I do find that the  
8 language, I mean, building on what you talked about in  
9 terms of terminology I think some of the changes now  
10 moving into also patient experience has actually in the  
11 past couple of months helped us to engage with our  
12 internal colleagues and really helped realize that this  
13 is not -- actually had a great colleague who said the  
14 other week, "What? So, you're not only patient  
15 reported outcomes instrument that we put in at the end  
16 of the clinical program that gives us quality of life?"  
17 Well, this is very different. And I think that we have  
18 a great opportunity, I mean, to your point Nancy, that  
19 now when we broaden from just being PRO to actually  
20 being the things that matters in terms of the endpoints  
21 that's really important. And I think it's worth  
22 highlighting as you just said Meghana, that the PRO

1 experts many of who are here were in one part of the  
2 organization. And many organizations have the patient  
3 engagement experts in another part of the organization.  
4 And on top of that we have our digital colleagues with  
5 wearables in the commercial part of the organizations.  
6 And anything you can do to kind of help us to  
7 collaborate is of greatness. I think we -- as I said,  
8 I think with the language and with this broader scope  
9 we've made some really important steps. But that's  
10 clearly important and to that point I mean I would hope  
11 that when our clinical colleagues go into the FDA  
12 website and look in their specific disease areas, they  
13 will also find these guidances so that the PRO experts  
14 are no longer the advocates for this work within our  
15 companies. And I know Paul asked yesterday "Where are  
16 the clinicians?" And I think that's what we need to  
17 start thinking about, how can we engage across in a  
18 different way.

19 MS. CHALASANI: Thank you. That's perfect  
20 Katarina. I think we would agree. Elektra, I think  
21 you wanted to add to the dialogue?

22 DR. PAPADOPOULOS: Yes. I was -- I have a

1 follow-on question, and that is you know the strategy I  
2 think we were trying to use as to sort of keep the more  
3 strategic information in the main document and then  
4 maybe some of the more technical information as the  
5 attachments or appendices. And I'm wondering if that  
6 kind of helps to serve the purpose of making it more  
7 useful to a broader audience of stakeholders?

8 MS. CHALASANI: Maybe we'll just do a quick  
9 "Yes" or "No" down the line; is that fair? Stephen?

10 DR. COONS: Well, I agree with that approach,  
11 but I think what we have in the current discussion  
12 documents is a mix of that. There's a lot of technical  
13 content within the body of the guidance. And then  
14 there is other technical content in the appendices. So  
15 I can't say a straight yes or no at this point. I can  
16 say that's a good idea.

17 But again, I hate to lose the fact that this  
18 target audience does have to be the scientists that are  
19 working on COA instrument development within the  
20 industry. I think it's a guidance for industry. We  
21 make -- we can make it to some degree accessible to  
22 others, but it's the industry -- it's those scientists

1 like me even in a nonindustry position who bring in the  
2 partners to be a part of the process.

3 But we still need that technical guidance  
4 around the evidentiary expectations that FDA is going  
5 to have when we bring these evidence dossiers to them  
6 to be used as -- and for measures that are to be used  
7 for endpoints in clinical trials.

8 DR. JOHNSON: I agree with that spirit. As  
9 I read it, it got more technical to me. So I don't  
10 know if that was just me or if that was actually how it  
11 ended up playing out. But that's how it felt. It felt  
12 like it started out meeting that spirit more than it  
13 did ending up meeting that spirit.

14 DR. GROSSMAN: And I agree with you, Stephen,  
15 that this -- the detailed guidance is really for those  
16 who are going to build the strategies, but I think for  
17 us really to change drug development, we do need  
18 something like that that gives that fuller picture in  
19 order to bring everyone along and to help our  
20 colleagues understand when they need to reach out to  
21 us. And that's in the TPP stage. And at the TPP stage  
22 we want to -- we need to know what the patient



1 experience is. So to me it would be helpful with some  
2 kind of framework like that. And I don't see -- I  
3 don't think that will work against us. I think that we  
4 can frame it so that there is technical and very  
5 specific guidance for those who are going to do the  
6 actual work.

7 MS. CHALASANI: Nancy?

8 DR. LEIDY: I was very struck by what you  
9 said, Laura Lee, about how this document helps the  
10 nonpsychometrician understand what's going on  
11 especially within FDA as well as outside of FDA within  
12 the sponsor organizations. So it -- I think it needs  
13 to be technically accessible. So these are  
14 sophisticated readers. So they understand the research  
15 process, they understand the issues, the tradeoffs et  
16 cetera. They should be able to look at it and realize  
17 that they understand maybe 50% of it. They'll call  
18 Katarina for the other 50%, because that's the  
19 technical piece of it.

20 I think if you try to make it too accessible,  
21 you're going to dilute it and then it's not going to be  
22 the user manual we absolutely have to have in order to

1 implement these things. So to me maybe what again  
2 during the editing process, maybe what you should do is  
3 think about the introduction. I like the idea of the  
4 details in the appendix and some of the more generic in  
5 the body of the paper but -- or the guidance but the  
6 introduction explains that and gives an overview so  
7 that when you're looking for something that you can  
8 understand, you say, okay, I see what this document is  
9 for and it really is more of a technical document. But  
10 the key issues that I need to understand as a non-  
11 technician are X, Y and Z and then leave the rest of it  
12 really to the people who absolutely need this as a user  
13 manual, don't dilute it in order to make it too  
14 accessible.

15 It will be accessible through the  
16 introduction. It'll be accessible through the learning  
17 process, through the partnerships that we should be  
18 having here. But I wouldn't dilute it.

19 DR. SLAGLE: I agree that we should not make  
20 the entire guidance plus the attachments diluted and  
21 less complicated. But I think, we can structure it so  
22 that the main body of the guidance is higher level

1 strategy. We've talked about -- a little bit about the  
2 what high level, the how? But I also think the why for  
3 some of those clinical colleagues that think we're just  
4 doing just the check boxes but to talk about the  
5 thoughtful approach that needs to be taken and the  
6 risks if you don't go through these processes. And  
7 then refer those who are doing the work or need to have  
8 that level of detail to the attachments. And I like  
9 the idea of attachments, especially for things like  
10 whatever it's -- we're going to eventually call it but  
11 the digital health, that's still evolving. If it's in  
12 an attachment it's easier to update that as we gain  
13 more evidence and more knowledge. Then we don't have  
14 to go through the whole guidance redevelopment process.  
15 It's just that specific piece of it.

16 And then having a third stream which is not  
17 part of the guidance but where maybe on the website  
18 there can be additional examples that are more of the  
19 living document I think is what people were suggesting  
20 yesterday. They can be updated much more easily as we  
21 have more examples to include.

22 DR. WEINFURT: I very much like that idea of

1 the suite of different resources that Ashley is  
2 describing. And I like Nancy's idea of an  
3 introduction. And at the same objective as the  
4 introduction might be achieved through letting folks  
5 know that the -- first of all there's a nice  
6 introduction and there's an italicized paragraph at the  
7 beginning of each section that explains in very plain  
8 language what -- what's the rationale here for this.  
9 And I wonder whether that might actually be useful for  
10 some of us technical folks too because I think there  
11 are lot of technical people who are reading the  
12 guidance, trying to understand FDA's thinking and a  
13 repetition of some of the principles in very simple  
14 language to help teach that might be very useful for us  
15 as well. And then, for folks who aren't interested in  
16 the geek stuff, they can just -- they know they can  
17 skim through and just read all the italicized sections,  
18 but that might be useful.

19 MS. CHALASANI: Thank you, Kevin.

20 DR. PAPADOPOULOS: I think that that's so  
21 important because as has been brought up and as I  
22 completely agree with that, we want to get away from

1 the check box mentality. And so having -- this is the  
2 motivation for this. This is one way, there are other  
3 ways and I think that's a really good idea, I like it.

4 MS. CHALASANI: Thank you, Electra. I think  
5 every FDA guidance actually starts off with a statement  
6 that the purpose of this guidance is to illustrate  
7 FDA's thinking, to share what FDA's thinking. And so I  
8 guess as we were trying to get really into the  
9 technical and provide all these details, we may have  
10 lost that along the way. And so I think bringing that  
11 back is kind of the resounding theme that I'm hearing  
12 from our panelists here.

13 The third question on the slide is really  
14 getting at flexibility but I do think we've managed to  
15 weave that throughout all of our discussions and even  
16 earlier in our opening statements from the panelists.  
17 We heard that it's a double-edged sword but maybe there  
18 are ways for FDA to provide more detail around what we  
19 mean by flexibility, whether it's more examples or  
20 recipes as Kevin called it and so forth. And so I do  
21 want to switch gears a little bit and go to -- talking  
22 a little bit about how the good measurement principles

1 presented in this document and that we discussed during  
2 our workshop, how they can apply to PerfO measures and  
3 ClinRO measures and what other evidence may be needed.

4           Yesterday, Electra, during her presentation  
5 laid out how we envision having these supplements to an  
6 eventual guidance document. That go into more detail  
7 about the specifics for a specific type of COA for  
8 example. So I'd really look forward to hearing the  
9 panelists thoughts on some of the principles going  
10 forward and how -- which ones can be applied and how  
11 they should be applied and what other evidence may be  
12 needed here? Perhaps, I'll turn to Kevin. Would you  
13 mind getting us started on that?

14           DR. WEINFURT: Yeah. Just make a brief  
15 comment. It's just to reiterate something I said  
16 earlier. First of all, I think the idea of having  
17 these supplements is really important. What would help  
18 in the main document though is to describe how  
19 important it is for people to describe the rationale  
20 for the measure. Whatever the measure is, how is it  
21 constructive? How is it supposed to do what it's doing  
22 so that if we've got a standardized task, we've got the

1 concept of interest.

2           What's the theory about how the person's, say,  
3 day-to-day functioning, the core elements of that are  
4 reflected in this standardized task, what parts of  
5 their functioning are reflected there and how does the  
6 process of the task and its assessment give us some  
7 indication of that. So for whatever it is, the  
8 clinician reported the performance, the PRO observer.  
9 We should be able to ask people to provide a rationale  
10 that right now says conceptual framework, and I'm  
11 afraid that as it stated it's anemic with respect to  
12 what we really need which is a more detailed theory  
13 about how it's working so that we know what evidence to  
14 bring to bear to help convince someone that we think it  
15 is working that way to inform us about the concept of  
16 interest to help us make this argument for the truth  
17 value of the claim. But put all the details in the  
18 supplement stuff.

19           MS. CHALASANI: Okay. Thank you, Kevin.  
20 Anyone else on the panel that would like to address or  
21 provide a comment on this, Stephen?

22           DR. COONS: Well, I do think it's incredibly

1 important to provide more detail. We do have a --  
2 there is going to be an ISPOR taskforce that is going  
3 to address Perfo assessments. And so that will be  
4 critical in terms of flushing out some of these issues.  
5 But I do think the guidance has to, as intended, has to  
6 have an appendix that does provide some more details on  
7 the unique aspects of particularly performance outcome  
8 assessment, because they are the most abstract of the  
9 clinical outcome assessments.

10           And as you were saying, Kevin, there has to be  
11 -- we're evaluating the performance of structured tasks  
12 in a sort of clinical environment that are intended to  
13 represent activities that patients are needing to  
14 perform in their daily lives to fulfill their goals in  
15 terms of remaining independent and functioning on a  
16 daily basis.

17           And so there is a -- it's very different from  
18 asking a person about how is their pain today or what  
19 is the worst rating of pain that they've experienced  
20 today? And so I think that's where we need, all of us  
21 need the most guidance around these clinical outcome  
22 assessments. And it doesn't, in this current situation



1 doesn't help to just say refer to that new description  
2 of the steps of COA development and apply whatever of  
3 those, apply to a performance -- the development of a  
4 performance outcome assessment tool.

5           So I think that it'll be critical to have a  
6 little more guidance in terms of what are the unique  
7 elements of the development or selection of a  
8 performance outcome assessment that are going to demand  
9 different evidence to bring to bear on whether indeed  
10 the instrument is fit for purpose in terms of the  
11 assessment of endpoint in a trial.

12           DR. PAPADOPOULOS: I just wanted to follow-up  
13 on this because we had the Duke-Margolis Conference on  
14 this topic, on the topic of performance outcome  
15 assessments and then published a paper. And this  
16 discussion was really intended to inform how we address  
17 this in future guidance. And so what I wanted to see  
18 is whether, you know, the information, say, that's in  
19 the publication to what degree can we leverage that,  
20 does -- is anything missing, and so on.

21           DR. COONS: Well, I think and I could even do  
22 this as a thought exercise on my own in terms of

1 because I know what -- I know the situation that we're  
2 all in right now because there's a lot that's unknown  
3 but can I even in terms of those steps in the  
4 development and/or selection of a COA measure that  
5 later on figure at the bottom of Figure 6, could I even  
6 develop that in a way that would be meaningful for a  
7 performance -- specifically for a performance outcome  
8 assessment. And maybe it can't be done and maybe I'm  
9 asking for something that is more of a challenge than  
10 it's worth but I think that's the level of detail that  
11 ultimately would be the most useful in terms of what  
12 are the steps, what are the -- what's really unique  
13 about a performance outcome assessment, that isn't  
14 really covered by the general issues that are addressed  
15 in the steps for a COA -- for the COA measure as  
16 currently stated.

17 MS. CHALASANI: A thought exercise that  
18 regardless of outcome that you'll submit through the  
19 public docket hopefully.

20 DR. COONS: Yeah, we'll see about that. Yeah.

21 MS. CHALASANI: Cynthia, I think you -- Cindy?

22 DR. GROSSMAN: I think for these two the real

1 challenge for me is seeing how the patient voice gets  
2 carried through in the development because I can see it  
3 dropping off precipitously like we could start at the  
4 beginning but then once you get -- it starts to get  
5 more abstract as you go through the development. And  
6 it's so -- I think that's to me the biggest problem.  
7 The other piece is -- and this is just from my own sort  
8 of unique vantage point of looking at sort of tracking  
9 some of the digital health space alongside some of this  
10 other work is I think these two areas are the most  
11 right for digital health disruption.

12           And I almost think, you know, we didn't want  
13 to get into this place of trying to say okay, could we  
14 take what's relevant for PROs and sort of filter it  
15 through and see how that could affect these other kinds  
16 of COAs and go through all of that investment when in  
17 fact it really could potentially be solved or addressed  
18 in a large part by the use of digital technologies.

19           And so that's not super helpful for you  
20 because that's sort of like a futuristic thing and you  
21 have to do something now. But I guess that's just to  
22 say, you know, maybe some of this needs to crosswalk if

1 you're going to put a digital health or digital  
2 technologies component to it, cross-walking these two  
3 COAs would be particularly important.

4 MS. CHALASANI: Thank you, Cindy. I do want  
5 to save some time for question and answers. So I will  
6 ask folks in the audience that may want to ask a  
7 question to slowly make their way to a microphone. In  
8 the meantime, I'm looking at Shanon to make sure that  
9 we can go a little bit into the Open Public Comment  
10 session. I think we only had a few folks signups. So  
11 we may be able to go into a little bit at that time.

12 I think we've really started talking about  
13 next steps with this last discussion component. And so  
14 I do want to look to all of our panelists for perhaps a  
15 closing remark or something really thinking about  
16 what's next and what's that more work that can be done.  
17 We talked about the implementation phase, for example,  
18 but if there's anything else that, you know, kind of  
19 falls into that what's next bucket perhaps we can hear  
20 some thoughts on that. I feel like I've started with  
21 Steven so many times. We'll move on to Cindy and then  
22 work our way back if that works.

1 DR. GROSSMAN: I do have two things that I  
2 haven't had a chance to say and that one is to make --  
3 to increase the volume and urgency of the need for case  
4 studies, the call for studies. I think that that again  
5 sort of alluded to the fact that some of this work is  
6 happening in a more competitive environment versus a  
7 pre-competitive environment. I think it's super  
8 important to have these case studies. I will do our  
9 part in trying to populate the docket with that or  
10 encourage our community to do that. But the other  
11 piece is has to do with the special populations as  
12 called out in the document. And I think for me one  
13 thought -- about and I don't know if this is future  
14 work or if it could be done now is to think about --  
15 instead of special populations thinking about what is  
16 it that the special population represents? So what I  
17 mean by that is when you talk about kids in pediatrics,  
18 it's not so much their age that I heard, it was more  
19 their developmental stage and what they could do.

20 When you think about women, it's not so much  
21 that they're of a particular age thus they're  
22 childbearing. It's maybe more about whether they

1 intend to ever get pregnant or whether they have the  
2 capacity to be pregnant. And so I guess we could -- I  
3 think that this document and our future work really  
4 needs to be a bit more clear about what is it about  
5 sort of special populations or select groups that make  
6 or pose certain types of considerations, rather than  
7 just adding demographic characteristics or other kinds  
8 of specialness of a population to that. So I snuck  
9 that in. I know.

10 MS. CHALASANI: Okay. Katarina?

11 MS. HALLING: So two things -- so just to add  
12 to the digital health one. So I would strongly  
13 encourage the FDA to make some statements around what  
14 can be done and what cannot be done at this stage  
15 because this is, as we heard in the great session  
16 before, this is already on its way. And one of the  
17 things that I'm really keen on is what we heard from  
18 Suze (ph) that there is a -- there was raised concern  
19 that this is not representing the patient voice. So if  
20 we could at least say something like a digital health  
21 monitoring cannot substitute the patient's feelings or  
22 feelings. Something like that would be extremely

1 helpful and then we can work on all the details.

2           The second thing is, I think the modification  
3 piece as has been mentioned I just want to reiterate, I  
4 think there are more examples on good practices and  
5 particularly very quick solutions which is of interest  
6 to all of us. And then finally, when we more  
7 consistently as part of this new way of developing our  
8 medicines, listen to patients we all know that we will  
9 find that some of the instruments that we see as  
10 standards does not represent the patient experience in  
11 a good way. So let's not close the door to continue to  
12 push forward de novo development, when that is  
13 absolutely needed and continue to find a speedy way to  
14 do that and move as quickly as we can.

15           And I want to reiterate what Tara mentioned, I  
16 refer to it as her FDA hot button system or something  
17 like that, just to continue the dialogue between us,  
18 because we will have to develop de novo tools as well.

19           MS. CHALASANI: Thank you. Laura Lee?

20           DR. JOHNSON: I was going to defer to the  
21 others.

22           MS. CHALASANI: Okay. Nancy?

1 DR. LEIDY: Okay. I actually would like to  
2 make a couple comments related to flexibility, contexts  
3 of use and fit for purpose. And some of the discussion  
4 that happened these last couple of days, because as I  
5 think these are very difficult terms, because it's --  
6 if you're really very specific about context of use and  
7 fit for purpose, the more specific you are, the more  
8 precise you're going to be but the harder it's going to  
9 be to be flexible. And I heard opportunities for  
10 flexibility around -- in fact one thing I heard under  
11 rare disease discussion was the global nature of  
12 disease burden for example.

13 I also heard or at least I'm starting to hear  
14 rumblings around, can we select or develop or use  
15 common outcomes across diseases. We do that I think  
16 for pain. We're talking about doing that for fatigue.  
17 What about function across different types of oncology  
18 indications for example. What about exercise  
19 tolerance. And then, what about leveraging existing  
20 resources. That type of discussion really demands the  
21 flexibility that you're talking about. So we really  
22 have to really think about the context of use and fit



1 for purposes with a little bit more breathing space,  
2 because if you're going to get together in a pretty  
3 competitive space to develop an instrument that's  
4 suitable for multiple sponsors to use in their drug  
5 development studies, the context of use is not yet  
6 fully baked. The fit for purpose isn't completely  
7 baked. It's partially baked and it can be done. But I  
8 think we need. That's where your flexibility needs to  
9 really come in.

10 The other piece of that is the item banks. If  
11 we're going to use item banks, there's a flexibility  
12 that's required there as well. So I guess I would urge  
13 us to really think about how these three things can --  
14 I guess it's more that you can't do yin and yang with  
15 three things, but it's really three things that need to  
16 fit together nicely in a pie so that we really can be  
17 flexible and also have measurement that's suitable for  
18 both the context of use and fit for purpose, so.

19 The other comment I would have also related to  
20 that is where our trial design is going. And I heard  
21 some really interesting comments related to future of  
22 trial -- different trial designs. And I know we're

1 hearing things like can we use real world evidence in  
2 some cases for certain types of approval processes or  
3 approvals and what about adaptive trials and what are  
4 we going to do about combo products. So that also says  
5 this fit for purpose context of use is in a flex -- I  
6 think in a flex time a little bit. And so if we can be  
7 flexible to meet that that would be great, so.

8 MS. CHALASANI: Ashley?

9 DR. SLAGLE: So one of the drawbacks of being  
10 one of the last people to speak in the last panel is  
11 that all of the good comments have been said. I do  
12 want to just touch on flexibility a little bit. And  
13 those who know me may be surprised with these comments,  
14 because when I was at the FDA I was definitely a  
15 champion on flexibility. But now as I reflect on it a  
16 little bit more and I think about it in terms of the  
17 guidance or these guidances, in some cases flexibility  
18 means regulatory uncertainty and that worries me a  
19 little bit.

20 And so I think we need to define what  
21 flexibility is. We need to be really cautious about  
22 giving very clear examples of when flexibility is

1 appropriate. And I think Laura Lee said this earlier.  
2 And I'm sorry, I missed your limbo bar but where there  
3 just can't be flexibility and you have to think about  
4 labeling and making sure that the measured labels,  
5 what's being described in labeling and to me that's a  
6 place where you just can't be overly flexible, but  
7 maybe in terms of reliability, some things are little  
8 noisier than you would like, a big treatment effect  
9 will overcome that. And so that is an example of a  
10 case you can be a little bit more flexible potentially.

11 So I think we just need to be really careful  
12 about what we mean by flexibility so that we don't have  
13 Katarina's colleagues who think that just means they  
14 can do anything that they want to do or not hold to  
15 account. The people Katarina overheard at lunch.

16 MS. CHALASANI: Thank you. Kevin?

17 DR. WEINFURT: Yeah. All the good stuff has  
18 been said. I just will end though by saying there  
19 wasn't time nor would have been very interesting to go  
20 through. And for me to just highlight all the places  
21 in this -- in both guidances, where there was clearly  
22 so much work, so much thought things are very clear,

1 such an advance over prior documents we've had. And so  
2 I just want to underscore that we're talking about  
3 opportunities for changing and modifying and building  
4 on this, but I just don't want to lose this gratitude  
5 we have to the FDA for all of the hard work that's gone  
6 into this and we're looking forward to being partners  
7 in trying to get this document reflecting what all of  
8 us are trying to do.

9 MS. CHALASANI: Thank you, Kevin. And to wrap  
10 up us, Steven?

11 DR. COONS: Sure. And dido to that that,  
12 Kevin. And the only other thing that I'll say is that  
13 the -- you'll get some feedback on ECOA section because  
14 I think there are some things that need to be beefed up  
15 in that and because one of the things it says  
16 specifically is that paper as a backup to an electronic  
17 data capture device is possible. And then the next  
18 line says, but don't mix electronic and paper. So I  
19 think there's some little details like that. And I  
20 think that -- and then I agree with Katarina that  
21 something has to be said around the mobile devices and  
22 the data that are going to be generated by mobile

1 devices.

2           But I don't know how much you can get into  
3 that yet because there's so much for us to learn about  
4 how those data will be used to produce endpoints for  
5 efficacy trials or treatment trials. But we can't --  
6 it can't be avoided, it has to be discussed in a little  
7 more in depth. And I agree with Nancy that the  
8 modification area is -- it's wonderful that it's  
9 highlighted as opposed to just de novo instrument  
10 development. But there are some concerns around the  
11 modification of instruments. And if we can use  
12 instruments as is, I think that should be our default.  
13 And that's the beauty of these item banks. That's the  
14 beauty of all the work that Promise (ph) has done in  
15 these domains scores that we may be able to apply to a  
16 variety of diseases, fatigue, depression or these  
17 domains that we can apply to a variety of diseases as  
18 is or as subsets obviously, short forms from the item  
19 banks. So I think there's a great future in that, but  
20 the modification -- there are -- it's fraught with a  
21 number of challenges. But -- and we can't necessarily  
22 describe them all in the guidance documents, so it's

1 complicated.

2 MS. CHALASANI: Thank you Stephen. I do want  
3 to open the floor to questions now, I see several  
4 folks, so please go ahead. I just ask that you please  
5 state your name and affiliation before you ask your  
6 question. Thank you.

7 AUDIENCE QUESTION AND ANSWER

8 MS. LEETMAN: My name is Amy Leetman (ph), a  
9 patient advocate, I'm the Director of Advocacy and  
10 Policy for NTMN phone Research (ph). So I wanted to  
11 touch on a point that was made earlier about the  
12 technical content that's in the guidance document, and  
13 perhaps removing some of it and putting it in  
14 appendices. You know, I'm actually one of those people  
15 that would actually benefit from that because my  
16 background isn't in science, so I'm always googling  
17 things and e-mailing epidemiologists and asking  
18 questions.

19 And it's a -- it's been a big learning curve  
20 for me but that's what I consider part of my job,  
21 because part of my job is to bridge the gap between our  
22 patients and the researchers, and the physicians, and

1 the industry and the regulators who are all trying to  
2 help them.

3           So for me getting a handle on all this in a  
4 more technical sense is kind of important. For the  
5 patients, maybe not so much, and I get that. They  
6 don't necessarily want to sit and take the same amount  
7 of time that I need to take to learn it, but my concern  
8 is that it would perhaps dilute the strength of the  
9 document to move too much of the technical content  
10 because of who this really is geared towards. Yes, we  
11 want the patients to understand and appreciate what's  
12 going on.

13           I just -- my question I guess is almost  
14 towards the FDA, have you considered just writing a  
15 plain language summary, like really drawing a line from  
16 A to B to C plain language summary for patients,  
17 explaining what this document is and what it says.  
18 Because my experience with our patients is that when  
19 I've done that, explain to them, well this is why we're  
20 doing all these market research studies, this is why  
21 it's so important. They stop complaining, they're  
22 like, oh, now, I understand why this is important. And

1 then they start showing up in droves for these studies.

2           So those are the kinds of things I think that  
3 might be a little more helpful, sort of getting back to  
4 that, sort of plain language summary of each section.  
5 And those kinds of documents, if you were, you know, to  
6 produce like a summary, a plain language summary,  
7 doesn't have to be long, but that's something that  
8 could be disseminated widely. For a lot of patients,  
9 organizations, they could put it out for their patients  
10 and say, this is what the FDA has been doing with their  
11 patient-focused drug development initiatives and this  
12 is where it's gone and this is where it's heading to  
13 and this is how it's going to impact drug development  
14 for us and how it's going to help you.

15           I don't know if that's something that is  
16 possible to consider but --

17           MS. CHALASANI: So I know that our NIH  
18 colleagues, many of them follow this practice of  
19 developing and communicating with a plain language --  
20 plain language summary, so definitely a really helpful  
21 comment, Amy, that I -- I know that we can take back,  
22 and we'll definitely consider.



1 MS. LEETMAN: Yeah. And Just one thing about  
2 those NIH summaries, they're great, but some of our  
3 patients look at them too and they're like we don't  
4 understand. So when I say plain language summary I  
5 mean you really have to draw down to the people who are  
6 not doing any of the science. And that really sort of  
7 speaks to what these patients are going through too.  
8 It's like for my patients they're doing hours of  
9 treatments every day, they just don't have the time to  
10 sit and try and wrap their heads around it, and, you  
11 know, a lot of them are dealing with the kind of mental  
12 fatigue where they just can't. So to really make it as  
13 easy as possible for them to digest I think would be  
14 more helpful.

15 MS. CHALASANI: Okay. Thank you, Amy. We'll  
16 definitely take that comment back. Thank you.

17 MS. SYMONDS: Hi, Tara Symonds from Clinical  
18 Outcomes Solutions. Just a comment or a plea because I  
19 think we're moving from PRO to COA now and I still have  
20 clients who see PRO synonymous with quality of life or  
21 health-related quality of life. I have to caveat, do  
22 you want me to build a PRO strategy that has symptoms

1 and treatment satisfaction and have relative quality of  
2 life. And I felt with the guidance as Nancy and  
3 Katarina have outlined with the guidance three that it  
4 is still a bit PRO centric. You do add in the -- an  
5 intra-rater reliability but I do think you need to put  
6 in the information around ClinROs and PerfOs, and that  
7 can be an appendix and a simple statement next to that  
8 inter and intrarater reliability by stating. And these  
9 require different study designs and power  
10 considerations. And then, you could put that into an  
11 appendix and I think that will give you more  
12 legitimacy, because what I don't want the COA guidance  
13 to be seen as is, oh, that's just for PROs and then  
14 that PRO is just the quality of life. It will devalue  
15 exactly what we're trying to do here.

16 And what you're trying to do, as I said  
17 yesterday, one of the things we need to hammer home  
18 and, you know, I've been party to the ISPOR or the  
19 International Society for Pharmacoeconomics and  
20 Outcomes Research, there's a COA SIG, Special Interest  
21 Group, that they're putting together and I've been  
22 party to pushing that forward.

1           The struggle I had with them changing the  
2 name, they wanted it to be PRO SIG, I said, well, we've  
3 moved on guys, it's COA SIG, well why -- and I had to  
4 put -- well it's just an FDA term, sorry, you know.  
5 And I was like, well, it is but what we're trying to do  
6 here is measurement site for outcomes assessment, and  
7 what we're trying to do is show you what you need to do  
8 to have precise measurement with these outcome  
9 measures. So they've kind of allowed us to call it the  
10 COA SIG but there's still a lot of work for us to  
11 educate that audience. So if that audience can't  
12 understand what we're doing, we need to make it so in  
13 the guidance. So you can have your strategy and then  
14 your appendices and you need more on the ClinRO and  
15 PerfO. And so the patient advocate that just spoke and  
16 I was going to also say that this is fantastic idea.  
17 Don't dumb down this guidance for industry, it will do  
18 a disservice to all those people working in industry  
19 trying to push this forward as Katarina has outlined,  
20 but, yes absolutely, have something that the patients  
21 can really understand and take away as well. Okay,  
22 thank you.

1 MS. CHALASANI: Thank you for that comment,  
2 Tara.

3 MS. CHRISTOPHER: Stephanie Christopher from  
4 the Medical Device Innovation Consortium. And why the  
5 medical device innovation consortium has been here at a  
6 drug development guidance for the last 2 days is  
7 because all of the issues that you've been talking  
8 about here are also things that the medical devices  
9 industry is thinking about. And first of all I want to  
10 applaud you for bringing folks from your sister  
11 agencies from CDRH and from CBRE and into this meeting,  
12 but -- and I do view medical device companies as a  
13 stakeholder in this conversation.

14 And to the point that was made earlier today  
15 about terminology and making sure we were very clear on  
16 terminology. I would encourage you to keep that  
17 terminology, explanations of terminology, glossary of  
18 terms keep those in there because medical device  
19 companies -- they're looking to this document as well,  
20 not necessarily because it's guidance but because it's  
21 helping us to better define what it means to do  
22 patient-centered clinical outcomes research.

1           And so those terminologies are helpful to all  
2 of us that are looking to advance this across the  
3 spectrum of medical product development. So I'd  
4 encourage you to keep that in and help us to continue  
5 to work together. And as, you know, the work, you  
6 know, going on in ISPOR and other places, it's not  
7 siloed to particular like this is how we develop drugs,  
8 this is how we develop devices, but it's going to --  
9 something that's going to be helpful to all of us. So  
10 help us continue to bring a medical device companies  
11 including those really small innovative companies doing  
12 cool things like digital health and combination  
13 products and bring -- continue to bring them into this  
14 good work.

15           MS. CHALASANI: Thank you, thank you. This  
16 workshop, the discussion documents and the eventual  
17 guidance are actually all cross-center efforts, Center  
18 for Drug, Center for Biologics and Center for Devices,  
19 so thank you for that comment.

20           MS. LATASH: Hi, Wendy Latash from Astellas  
21 Pharma, patient experience and outcomes. Two points.  
22 The first thing is I'd like to underscore point from

1 our patient advocate colleague about trying to develop  
2 something that is really plain language. And I think  
3 for us in -- as a sponsor I think having something like  
4 that would help us to engage our patient advocates much  
5 earlier on to bring them to the table as we're trying  
6 to, you know, develop the different COAs and getting  
7 their feedback. So really underscore that point, I'm  
8 glad she said that. The second point I like to make  
9 and just really request really, you know, one of things  
10 I noticed about the last panel when we were talking  
11 about digital health, you know, I kind of feel like  
12 when we get 10 people in a room and try to define what  
13 digital health is, we get about 15 different opinions.

14 And, you know, what I heard a lot of the  
15 discussion was around devices and wearables and looking  
16 at, you know, performance type of data that could be  
17 correlated could not be correlated. What I'd like to  
18 pose and try to bring in, I think it was lightly  
19 touched on during that panel is the fact that digital  
20 health is not just about wearables, it can also be a  
21 tool, a means to an end to pull through those  
22 classically developed COA instruments. And that's

1 something that we have looked at, I know, you know,  
2 other industry members have looked at and want to make  
3 sure that that gets treated in some sort of definition,  
4 in some sort of language, so that as we're going to the  
5 different, you know, groups within the FDA and trying  
6 to get feedback, you know, that distinction is made so  
7 that it is not, you know, it doesn't get confused with,  
8 oh, are you just trying to do this to have a different  
9 measure? No this is just a means to an end to pull  
10 through, you know, some of the classical, you know,  
11 COA. So, you know, I would request that, so thank you.

12 MS. CHALASANI: Thank you for that comment. I  
13 don't know if anyone on the panel would like to add to  
14 that or anything? No? Okay, I think we'll definitely  
15 make a note of that comment. Thank you.

16 MS. LATASH: Okay. Thank you.

17 MS. CHALASANI: I think with that I think we  
18 can close this panel. I'm not really going to provide  
19 a summary because I know Elektra is going to be up here  
20 in a few minutes and in the interest of time I'll leave  
21 the summary to her. But I would like to thank all of  
22 our panelists that are up here today, that are here up

1 here right now as well as all of our other panelists  
2 throughout the workshop sessions for a truly rich  
3 discussion. It's been a very insightful 2 days, so  
4 thank you all.

5 (Applause)

6 OPEN PUBLIC COMMENT

7 MS. CHALASANI: So with that I'd like to  
8 invite Dr Shannon Woodward to facilitate the open  
9 public comment session.

10 DR. WOODWARD: Hi, everyone. My name is  
11 Shannon Woodward. I'm part of the Office of the Center  
12 Director and first off I want to thank you all for  
13 hanging in there 2 whole days with us. So right now  
14 we're moving into the open public comment session, and  
15 the purpose of this part of the workshop is to allow an  
16 opportunity for people to comment on topics other than  
17 our workshop discussion topics. This is also a chance  
18 for many other stakeholders other than, of course, our  
19 panelists and speakers to also share with us.

20 So keep in mind, the FDA won't address  
21 comments that we hear during this session, but all of  
22 the comments are being transcribed as part of the



1 public record. And of course we would like this to be  
2 a transparent process so we encourage you to know any  
3 financial interests that may be relevant to your  
4 comment. And if you do not have any such interest you  
5 may want to state that for the record. Or if you  
6 prefer not to share that information with us, you are  
7 still welcome to provide your comment. We collected  
8 signups for open public comment beginning this morning  
9 and also during the breaks of the workshop and we have  
10 five speakers signed up. For each speaker you will  
11 have 2 minutes to provide a comment. We won't be using  
12 a timer and light system, but I will use my cell phone  
13 which I'm going to grab now.

14           So of course, I don't have a buzzer or  
15 anything like that but I will kindly nudge you a little  
16 bit once you get close to your 2 minutes. And also if  
17 I call your name and you're no longer interested in  
18 sharing your comment or you may have shared during the  
19 Q&A, feel free to let me know and I'm happy to move on  
20 to the next speaker. So with that our first speaker is  
21 Danielle Friend with BIO. You're welcome to approach  
22 whichever mic is closest.

1 MS. FRIEND: Good afternoon. As you  
2 mentioned, I'm Daniel Friend. I'm a Director of  
3 Science and Regulatory Affairs at BIO. I don't have  
4 anything to disclose today. Bio or the Biotechnology  
5 Innovation Organization thanks FDA for the opportunity  
6 to provide the oral comments at the meeting today.  
7 We'd like to commend the FDA for the tremendous amount  
8 of work that the agency has done in order to better  
9 ensure that patients' experiences are more  
10 systematically collected and used to inform drug  
11 development and regulatory review.

12 In order to support transparency, as FDA  
13 begins drafting the next series of guidance documents,  
14 we have a couple of points that we'd like the FDA to  
15 consider. Specifically specifying in guidance when and  
16 how industry sponsors and other stakeholders can  
17 consult with FDA regarding the conduct of studies and  
18 the incorporation of patient experience into regulatory  
19 decisions.

20 BIO requests that FDA consider increasing the  
21 length of milestone meetings and sponsors will be  
22 discussing patient experience data, providing dedicated

1 meeting opportunity to sponsors, to discuss patient  
2 experience data, for example, through Type C meetings  
3 or providing opportunities for sponsors to receive  
4 written agreement with FDA on study design.

5 It's BIO's belief that in order to truly support  
6 patient-centric drug development, patient experience  
7 data should be considered for use throughout the entire  
8 product lifecycle including regulatory review. Such  
9 data may inform important decisions such as benefit  
10 risk assessments, labeling post market studies, and  
11 others. To encourage all stakeholders to collect  
12 patient experience data we request the FDA to more  
13 clearly indicate the regulatory decisions for which  
14 they will consider patient experience data.

15 BIO also requests that the FDA make clear in  
16 the draft guidance the delineation between collection  
17 of patient experience data to inform clinical studies  
18 and patient experience data collected within a clinical  
19 study meant for submission to the FDA to inform a  
20 regulatory decision. Because the level standards  
21 needed for generating patient experience data can vary  
22 across studies and will depend upon the intended use,

1 we request that the FDA clearly describe how the  
2 evidentiary standards may vary depending upon the  
3 intended use of the data.

4 DR. WOODWARD: Any final thoughts?

5 MS. FRIEND: Finally, we like to ask the FDA  
6 or we appreciate that the FDA has made comments  
7 regarding specific patient populations that may be  
8 difficult to collect patient experience data around.  
9 And we're hopeful that the coming guidance documents  
10 will contribute solutions to still collecting patient  
11 experience data for those populations.

12 Again, thank you for the opportunity to speak  
13 and we'd also like to thank the patients and patient  
14 organizations who've contributed widely to this effort  
15 as well. BIO will be submitting comments to the  
16 docket. So thank you so much.

17 DR. WOODWARD: Thank you, Danielle. Next, we  
18 have Elizabeth Manning of UCB Biosciences.

19 MS. MANNING: Hi again, Elizabeth Manning, UCB  
20 Biosciences, I'm taking a little bit different approach  
21 here. I don't have anything to disclose. Sorry. I  
22 want to highlight some of the interpersonal focus that

1 came out of that last discussion and show true  
2 appreciation for it. I think this is a real  
3 opportunity of a turning point for FDA as a partner  
4 with industry and for us as multi stakeholders within  
5 industry to practice the position of empathy with each  
6 other. We're trying to empathize with our patients but  
7 it's the only way we're going to succeed, is if we  
8 figure out how to relate to each other and we figure  
9 out how to combine our efforts. And if FDA can help us  
10 by facilitating those conversations, removing  
11 obstacles, letting us accelerate, and helping clear  
12 that path, I think that's a huge role that could be  
13 different and differently relayed through the guidance.

14 I challenge you to take the exercise tonight  
15 when you brush your teeth, use your other hand. That's  
16 how everyone feels, that's how patients feel when they  
17 get the new diagnosis, that's how we feel as we're  
18 trying to revolve -- evolve how we do our work and  
19 accelerate it. And then, I want to highlight a  
20 specific point that only came up briefly, but if you  
21 could give guidance around how gender identity and the  
22 evolution of that paradigm is, should, should not,

1 will, will not play a role in this conversation around  
2 patient experience where it could be impactful while  
3 sex is still critical to our clinical setting and how  
4 we can help educate the public when both of those  
5 paradigms become active in our space. Thank you.

6 DR. WOODWARD: Thank you. Next we have Berett  
7 Yufe (ph) from FAIR (ph). My apologies, if I  
8 misspelled or misspoke your name.

9 MS. YUFE: Hi, my name is Berett Yufe, and  
10 it's okay. I'm a 16 year old junior at Georgetown Day  
11 School, and I've lived with a multitude of life-  
12 threatening food allergies since infancy. And even  
13 with my parents' and my own constant vigilance, I've  
14 had many allergic reactions over the course of my life.  
15 Because the magnitude of allergy attacks increases  
16 every time one reacts, by the time I was 10 my allergy  
17 reactions were truly life threatening.

18 At 10 years old I suffered from an extremely  
19 bad anaphylactic reaction and almost died even with the  
20 immediate aid of epipens and hospitalization. In  
21 America someone is sent to the emergency room because  
22 of food allergy induced anaphylaxis every 3 minutes,

1 and my one experience affects me to this day. Nothing  
2 that I consume that night had any warning of allergens  
3 or cross contaminations and yet -- cross contamination,  
4 and yet, within an hour of eating I found myself  
5 covered in hives being pumped full of steroids and  
6 relying entirely on an oxygen tank for life. My  
7 parents and brother thought I would die at just 10  
8 years old. Although I physically recovered, I still  
9 suffer from extreme allergy related anxiety. And for  
10 the month -- and for many months after the attack, I  
11 refused to eat, because how could I be sure that  
12 nothing was contaminated. And the answer is that I  
13 can't be sure.

14           There's nothing that I put in my body that is  
15 guaranteed to be a 100 percent free of the slightest  
16 cross-contamination and medically there are no  
17 preventative measures that I nor the 15 million  
18 allergic Americans can take to guarantee our safety.  
19 Epipens are only to be used as a rescue and even  
20 epipens don't always save lives. The only medical  
21 treatment that can decrease one's likelihood of death  
22 as a result of anaphylaxis is desensitization which is

1 not only a long obstructive process, but also has  
2 little impact on people like me who have multiple life  
3 threatening food allergies many of which are not  
4 treatable by the current desensitization program.

5 With staggering statistics that show 377%  
6 increase in anaphylactic reactions between just 2007  
7 and 2016 --

8 DR. WOODWARD: Any final thoughts Berett?

9 MS. YUFE: Yeah. With the exponential growth  
10 of food allergic Americans now is the time to act  
11 before many more people's lives are taken or tarnished.  
12 We, the allergic community, are in dire need of  
13 preventative treatments and cures, because our lives  
14 and our quality of life depends on it. Thank you.

15 DR. WOODWARD: Thank you. Next we have Maria  
16 Osobal of FAIR. And my apologies on your name, feel  
17 free to clarify.

18 MS. OSOBAL: You actually did really well.  
19 It's Osobal, but you were close. In August of 2003 my  
20 husband and I rushed our toddler to the emergency room  
21 after she took a tiny bite of a peanut butter cracker.  
22 One of those very orange crackers with peanut butter



1 inside. She only bit off a small corner before handing  
2 it back to me with I don't like this at all face. I  
3 turned my back to her to find a trash can to throw the  
4 cracker away. And when I turned back around, Nina's  
5 (ph) lips were huge and red blotches were covering her  
6 face and neck. By the time we got to the emergency  
7 room her eyes were swollen shut and her face was  
8 unrecognizable. She was vomiting violently, red hives  
9 covered her entire body and she was wheezing. The  
10 first shot of epinephrine did nothing and for those few  
11 minutes before the doctors gave her another dose my  
12 world came to a standstill.

13 That day it took two shots of epinephrine to  
14 get her anaphylactic reaction under control and I have  
15 never been so grateful for a medication in all my life.  
16 Fast forward 15 years, and today my toddler is 17.  
17 We're very lucky she's enrolled in a clinical trial  
18 that offers immunotherapy treatment for a peanut  
19 allergy. But as you all know there is no FDA approved  
20 treatment for patients outside of the clinical trial  
21 setting. Meaning that the vast, vast majority of the  
22 50 million Americans with food allergy are excluded

1 from treatment.

2           And even for those of us fortunate to be in a  
3 trial, there are enormous limitations to the outcomes  
4 currently available to patients that I think few  
5 patients -- few people are aware of. What has changed  
6 for Nina after more than a year of constant visits to  
7 the hospital, she can now tolerate 300 milligrams of  
8 peanut powder. When she started, she had an  
9 anaphylactic reaction to just 6 milligrams. So that is  
10 a big, big step. But what does that translate to into  
11 the real world, 300 milligrams is the equivalent of one  
12 peanut. The cost of getting her to be able to tolerate  
13 one peanut has included four anaphylactic reactions,  
14 two requiring multiple doses of epinephrine, ambulance  
15 rides and countless stress.

16           DR. WOODWARD: Any final thoughts, Maria?

17           MS. OSOBAL: Yes. We ask for the FDA's  
18 partnership to accelerate research to answer critical  
19 unknown questions and to help all the patients with  
20 multiple food allergies that if we continue on the  
21 current path and schedule it will be more than 20 years  
22 out before any treatment is available for them. Thank

1 you so much.

2 MS. CHALASANI: Thank you. Next we have Kathy  
3 Lash (ph) of Pharmerit International. Kathy, are you  
4 still in the room? Calling once. Calling twice.  
5 Okay, I think that concludes our open public comment  
6 session. So I'm going to turn it over to my colleague,  
7 Elektra, to provide closing remarks.

8 CLOSING REMARKS

9 DR. PAPADOPOULOS: So thank you so much for  
10 everyone to -- for staying till the very end. And I  
11 also think it's so appropriate that, you know, that  
12 we're closing the meeting with patients' voices. So  
13 it's very, very much appreciated. I just really again  
14 would like to thank everyone who participated in  
15 person, on the web, and who have come from long  
16 distances, all of our panelists, very, very much  
17 appreciate it. All of the comments will be taken back,  
18 discussed, and very seriously considered.

19 And also really want to thank everyone here at  
20 the FDA involved in the planning of this meeting. Not  
21 only the clinical outcome assessment staff, but  
22 colleagues from other parts of the CDER, the Office of

1 the Center Director, Biostatistics, CDRH, CBER. This  
2 is really a cross center effort and it's very  
3 important.

4 I think our leadership at the highest level of  
5 all three medical products centers have been extremely  
6 supportive of these efforts. And I can just say one  
7 quote that we frequently hear from our Center Director,  
8 Dr. Woodcock is that patients are the true experts in  
9 their disease, and I think, you know, we all really,  
10 you know, that that rings true for all of us.

11 I can highlight some of just the key themes  
12 from the meeting, but I think this has been done very  
13 well up until now. One of the things I think we need  
14 to think very carefully about is, you know, the need to  
15 strike a balance between, you know, having too much  
16 detail, perhaps advice that might be construed as  
17 prescriptive and not enough detail. So there does need  
18 to be that balance. And we've heard different advice  
19 from different people.

20 But at the end of the day, I think what I did  
21 hear from everyone was examples, examples, examples,  
22 case studies that people find them very helpful. And I

1 think that's something that we can work on and  
2 encourage our external stakeholders to also provide  
3 examples. And not just positive examples but lessons  
4 learned. So, you know, we don't want to have a kind of  
5 a bias towards only positives, we want it to be  
6 balanced. I think the other very interesting area is,  
7 you know, this area is such a rapidly evolving field,  
8 it's a science, you know, how do we take the input, how  
9 do we go from the anecdote to, you know, to developing  
10 or selecting a measure to actually interpreting at a  
11 group level, at a population level how a treatment can  
12 be impacting patients' lives.

13           And it is a science, and it's an art as well  
14 as a science and it's a rapidly evolving area. And as  
15 we learned, you know, with new technology, with new  
16 methods, we need to be positioned to be able to adapt.  
17 And we don't want to lock ourselves in. So this is I  
18 think another very important key theme that we've taken  
19 away.

20           And I so very much appreciated Michelle  
21 Tarver's and others' comments about, you know, we have  
22 to consider that we're part of a bigger ecosystem and

1 we're not the only, you know, as regulators, we're not  
2 the only people who are going to be using the data, the  
3 clinical trial data. And there are so many post  
4 regulatory stakeholders. And we need to, I think,  
5 listen and work very closely together so that, you  
6 know, how -- we can be most efficient and meeting  
7 different stakeholders needs, and, you know, using core  
8 outcome measure sets where possible I think is going to  
9 be really useful going forward, so that's another area  
10 of great interest.

11 So I think, again, just resounding thanks to  
12 everyone for staying until the end. Please submit your  
13 comments. Docket closes December 14th. Thank you very  
14 much.

15 (Applause)

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CERTIFICATE OF NOTARY PUBLIC

I, MICHAEL FARKAS, the officer before whom the foregoing proceeding was taken, do hereby certify that the proceedings were recorded by me and thereafter reduced to typewriting under my direction; that said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.



MICHAEL FARKAS

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State of Maryland





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