PATIENT-FOCUSED DRUG DEVELOPMENT

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

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P R O C E E D I N G S

WELCOME

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

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

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

agenda for today.

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

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

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

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

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

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

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

OPENING REMARKS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The other concept that will probably come up

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

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

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

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

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

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

podium.

(Applause)

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

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

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

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

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

SPEAKER: (Off mike).

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

SPEAKER: (Off mike).

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

SPEAKER: Minority population.

DR. PEIRIS: Minority populations. I heard orphans.

SPEAKER: Women of childbearing age.

DR. PEIRIS: Women of childbearing age, great.

SPEAKER: Elderly.

DR. PEIRIS: The elderly, perfect.

SPEAKER: Organ impairment.

DR. PEIRIS: Organ impairment.

SPEAKER: Mobility impaired.

DR. PEIRIS: Mobility impaired. This is good.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. LAPTEVA: Good morning. My name is

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

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

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

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

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

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

(Applause)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

unable to express themselves in words or even writing. I don't know if that helps.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. PEIRIS: Please go ahead.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

MS. CRUZ: I wanted to circle back to your

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

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

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

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

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

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

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

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

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

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

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

AUDIENCE QUESTION AND ANSWER

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

way as well.

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

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

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

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

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

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

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

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

DR. PEIRIS: Sure.

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

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

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

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

favorable for pediatrics.

DR. PEIRIS: Perfect. Go ahead.

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

DR. PEIRIS: It's not just me.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(Applause)

BREAK

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

So I really appreciate that those details are

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

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

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

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

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

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

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

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

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

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

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

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

DR. WIRTH: No.

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

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

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

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

measurement science as a whole.

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

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

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

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

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

DR. CAMPBELL: Well, thank you for those

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

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

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

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

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

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

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

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

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

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

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

DR. CAMPBELL: Thank you.

MS. DEAL: There's lot of meaning.

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

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

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

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

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

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

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

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

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

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

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

So I'll stop there.

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

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

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

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

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

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

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

one of the PIs.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. WIRTH: Right.

DR. CAMPBELL: RJ?

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

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

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

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

DR. REEVE: Oh, go ahead.

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

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

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

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

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

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

DR. CAMPBELL: Thank you Bryce. And Linda,

final thought?

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

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

AUDIENCE QUESTION AND ANSWER

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. CAMPBELL: Leah?

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

DR. CAMPBELL: Next comment please.

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

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

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

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

DR. CAMPBELL: Thank you. Dagmar?

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

DR. CAMPBELL: It's okay.

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

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

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

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

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

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

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

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

(Applause)

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

(Lunch Recess)

LUNCH

EMERGING TECHNOLOGIES TO SUPPORT FIT-FOR-PURPOSE CLINICAL OUTCOME ASSESSMENTS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(Laughter)

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

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

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

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

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

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

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

to hear what other panelists say about this.

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

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

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

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

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

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

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

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

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

technology measurements.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. BYROM: Sure. Yes.

DR. KOVACS: Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. KOVACS: Thank you. Yeah, David.

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

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

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

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

DR. KOVACS: Thank you. Brennan?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. KOVACS: Thank you. Suz?

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

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

I think as a community, we, RA patients,

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

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

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

So these are all pretty complicated, but I

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

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

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

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

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

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

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

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

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

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

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

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

DR. KOVACS: Thank you. David?

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

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

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

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

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

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

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

DR. KOVACS: Thank you. Chad?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

MR. HO: Yes.

DR. KOVACS: Sure.

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

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

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

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

DR. KOVACS: Thanks. So sometimes COA data

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

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

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

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

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

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

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

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

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

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

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

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

We discussed what evidence would be needed to

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

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

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

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

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

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

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

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

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

AUDIENCE QUESTION AND ANSWER

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

UNIDENTIFIED SPEAKER: Okay, the gentleman, back.

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

UNIDENTIFIED SPEAKER: Yeah.

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

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

UNIDENTIFIED SPEAKER: Thank you. Go ahead.

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

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

UNIDENTIFIED SPEAKER: Brennan?

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

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

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

UNIDENTIFIED SPEAKER: Yes.

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

UNIDENTIFIED SPEAKER: Sure.

UNIDENTIFIED SPEAKER: -- will be the last question.

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

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

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

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

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

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

(Applause)

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

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

(Recess)

BREAK

IDENTIFYING KEY THEMES AND NEXT STEPS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

themes and thinking about next steps.

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

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

So Stephen, we'll get started with you.

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

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

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

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

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

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

MS. CHALASANI: Thank you, Stephen. Cindy?

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

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

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

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

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

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

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

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

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

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

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

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

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

decision making and also for peers.

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

MS. CHALASANI: Thank you. Laura Lee?

DR. JOHNSON: Sure. So I sometimes show a

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

MS. CHALASANI: Thank you, Nancy. Elektra?

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

MS. CHALASANI: Thanks, Electra. Ashley?

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

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

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

DR. SLAGLE: Yeah.

MS. CHALASANI: Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

working or not.

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

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

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

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

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

MS. CHALASANI: Okay. Thanks Kevin.

DR. WEINFURT: Meghana, I'm sorry.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

MS. CHALASANI: Thanks.

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. JOHNSON: I agree with that spirit. As I read it, it got more technical to me. So I don't know if that was just me or if that was actually how it ended up playing out. But that's how it felt. It felt like it started out meeting that spirit more than it did ending up meeting that spirit.

DR. GROSSMAN: And I agree with you, Stephen, that this -- the detailed guidance is really for those who are going to build the strategies, but I think for us really to change drug development, we do need something like that that gives that fuller picture in order to bring everyone along and to help our colleagues understand when they need to reach out to us. And that's in the TPP stage. And at the TPP stage we want to -- we need to know what the patient

experience is. So to me it would be helpful with some kind of framework like that. And I don't see -- I don't think that will work against us. I think that we can frame it so that there is technical and very specific guidance for those who are going to do the actual work.

MS. CHALASANI: Nancy?

DR. LEIDY: I was very struck by what you said, Laura Lee, about how this document helps the nonpsychometrician understand what's going on especially within FDA as well as outside of FDA within the sponsor organizations. So it -- I think it needs to be technically accessible. So these are sophisticated readers. So they understand the research process, they understand the issues, the tradeoffs et cetera. They should be able to look at it and realize that they understand maybe 50% of it. They'll call Katarina for the other 50%, because that's the technical piece of it.

I think if you try to make it too accessible, you're going to dilute it and then it's not going to be the user manual we absolutely have to have in order to

implement these things. So to me maybe what again during the editing process, maybe what you should do is think about the introduction. I like the idea of the details in the appendix and some of the more generic in the body of the paper but -- or the guidance but the introduction explains that and gives an overview so that when you're looking for something that you can understand, you say, okay, I see what this document is for and it really is more of a technical document. But the key issues that I need to understand as a non-technician are X, Y and Z and then leave the rest of it really to the people who absolutely need this as a user manual, don't dilute it in order to make it too accessible.

It will be accessible through the introduction. It'll be accessible through the learning process, through the partnerships that we should be having here. But I wouldn't dilute it.

DR. SLAGLE: I agree that we should not make the entire guidance plus the attachments diluted and less complicated. But I think, we can structure it so that the main body of the guidance is higher level

strategy. We've talked about -- a little bit about the what high level, the how? But I also think the why for some of those clinical colleagues that think we're just doing just the check boxes but to talk about the thoughtful approach that needs to be taken and the risks if you don't go through these processes. And then refer those who are doing the work or need to have that level of detail to the attachments. And I like the idea of attachments, especially for things like whatever it's -- we're going to eventually call it but the digital health, that's still evolving. If it's in an attachment it's easier to update that as we gain more evidence and more knowledge. Then we don't have to go through the whole guidance redevelopment process. It's just that specific piece of it.

And then having a third stream which is not part of the guidance but where maybe on the website there can be additional examples that are more of the living document I think is what people were suggesting yesterday. They can be updated much more easily as we have more examples to include.

DR. WEINFURT: I very much like that idea of

the suite of different resources that Ashley is describing. And I like Nancy's idea of an introduction. And at the same objective as the introduction might be achieved through letting folks know that the -- first of all there's a nice introduction and there's an italicized paragraph at the beginning of each section that explains in very plain language what -- what's the rationale here for this. And I wonder whether that might actually be useful for some of us technical folks too because I think there are lot of technical people who are reading the guidance, trying to understand FDA's thinking and a repetition of some of the principles in very simple language to help teach that might be very useful for us as well. And then, for folks who aren't interested in the geek stuff, they can just -- they know they can skim through and just read all the italicized sections, but that might be useful.

MS. CHALASANI: Thank you, Kevin.

DR. PAPADOPOULOS: I think that that's so important because as has been brought up and as I completely agree with that, we want to get away from

the check box mentality. And so having -- this is the motivation for this. This is one way, there are other ways and I think that's a really good idea, I like it.

MS. CHALASANI: Thank you, Electra. I think every FDA guidance actually starts off with a statement that the purpose of this guidance is to illustrate FDA's thinking, to share what FDA's thinking. And so I guess as we were trying to get really into the technical and provide all these details, we may have lost that along the way. And so I think bringing that back is kind of the resounding theme that I'm hearing from our panelists here.

The third question on the slide is really getting at flexibility but I do think we've managed to weave that throughout all of our discussions and even earlier in our opening statements from the panelists. We heard that it's a double-edged sword but maybe there are ways for FDA to provide more detail around what we mean by flexibility, whether it's more examples or recipes as Kevin called it and so forth. And so I do want to switch gears a little bit and go to -- talking a little bit about how the good measurement principles

presented in this document and that we discussed during our workshop, how they can apply to PerfO measures and ClinRO measures and what other evidence may be needed.

Yesterday, Electra, during her presentation laid out how we envision having these supplements to an eventual guidance document. That go into more detail about the specifics for a specific type of COA for example. So I'd really look forward to hearing the panelists thoughts on some of the principles going forward and how -- which ones can be applied and how they should be applied and what other evidence may be needed here? Perhaps, I'll turn to Kevin. Would you mind getting us started on that?

DR. WEINFURT: Yeah. Just make a brief comment. It's just to reiterate something I said earlier. First of all, I think the idea of having these supplements is really important. What would help in the main document though is to describe how important it is for people to describe the rationale for the measure. Whatever the measure is, how is it constructive? How is it supposed to do what it's doing so that if we've got a standardized task, we've got the

concept of interest.

What's the theory about how the person's, say, day-to-day functioning, the core elements of that are reflected in this standardized task, what parts of their functioning are reflected there and how does the process of the task and its assessment give us some indication of that. So for whatever it is, the clinician reported the performance, the PRO observer. We should be able to ask people to provide a rationale that right now says conceptual framework, and I'm afraid that as it stated it's anemic with respect to what we really need which is a more detailed theory about how it's working so that we know what evidence to bring to bear to help convince someone that we think it is working that way to inform us about the concept of interest to help us make this argument for the truth value of the claim. But put all the details in the supplement stuff.

MS. CHALASANI: Okay. Thank you, Kevin. Anyone else on the panel that would like to address or provide a comment on this, Stephen?

DR. COONS: Well, I do think it's incredibly

important to provide more detail. We do have a -- there is going to be an ISPOR taskforce that is going to address PerfO assessments. And so that will be critical in terms of flushing out some of these issues. But I do think the guidance has to, as intended, has to have an appendix that does provide some more details on the unique aspects of particularly performance outcome assessment, because they are the most abstract of the clinical outcome assessments.

And as you were saying, Kevin, there has to be -- we're evaluating the performance of structured tasks in a sort of clinical environment that are intended to represent activities that patients are needing to perform in their daily lives to fulfill their goals in terms of remaining independent and functioning on a daily basis.

And so there is a -- it's very different from asking a person about how is their pain today or what is the worst rating of pain that they've experienced today? And so I think that's where we need, all of us need the most guidance around these clinical outcome assessments. And it doesn't, in this current situation

doesn't help to just say refer to that new description of the steps of COA development and apply whatever of those, apply to a performance -- the development of a performance outcome assessment tool.

So I think that it'll be critical to have a little more guidance in terms of what are the unique elements of the development or selection of a performance outcome assessment that are going to demand different evidence to bring to bear on whether indeed the instrument is fit for purpose in terms of the assessment of endpoint in a trial.

DR. PAPADOPOULOS: I just wanted to follow-up on this because we had the Duke-Margolis Conference on this topic, on the topic of performance outcome assessments and then published a paper. And this discussion was really intended to inform how we address this in future guidance. And so what I wanted to see is whether, you know, the information, say, that's in the publication to what degree can we leverage that, does -- is anything missing, and so on.

DR. COONS: Well, I think and I could even do this as a thought exercise on my own in terms of

because I know what -- I know the situation that we're all in right now because there's a lot that's unknown but can I even in terms of those steps in the development and/or selection of a COA measure that later on figure at the bottom of Figure 6, could I even develop that in a way that would be meaningful for a performance -- specifically for a performance outcome assessment. And maybe it can't be done and maybe I'm asking for something that is more of a challenge than it's worth but I think that's the level of detail that ultimately would be the most useful in terms of what are the steps, what are the -- what's really unique about a performance outcome assessment, that isn't really covered by the general issues that are addressed in the steps for a COA -- for the COA measure as currently stated.

MS. CHALASANI: A thought exercise that regardless of outcome that you'll submit through the public docket hopefully.

DR. COONS: Yeah, we'll see about that. Yeah.

MS. CHALASANI: Cynthia, I think you -- Cindy?

DR. GROSSMAN: I think for these two the real

challenge for me is seeing how the patient voice gets carried through in the development because I can see it dropping off precipitously like we could start at the beginning but then once you get -- it starts to get more abstract as you go through the development. And it's so -- I think that's to me the biggest problem. The other piece is -- and this is just from my own sort of unique vantage point of looking at sort of tracking some of the digital health space alongside some of this other work is I think these two areas are the most right for digital health disruption.

And I almost think, you know, we didn't want to get into this place of trying to say okay, could we take what's relevant for PROs and sort of filter it through and see how that could affect these other kinds of COAs and go through all of that investment when in fact it really could potentially be solved or addressed in a large part by the use of digital technologies.

And so that's not super helpful for you because that's sort of like a futuristic thing and you have to do something now. But I guess that's just to say, you know, maybe some of this needs to crosswalk if

you're going to put a digital health or digital technologies component to it, cross-walking these two COAs would be particularly important.

MS. CHALASANI: Thank you, Cindy. I do want to save some time for question and answers. So I will ask folks in the audience that may want to ask a question to slowly make their way to a microphone. In the meantime, I'm looking at Shanon to make sure that we can go a little bit into the Open Public Comment session. I think we only had a few folks signups. So we may be able to go into a little bit at that time.

I think we've really started talking about next steps with this last discussion component. And so I do want to look to all of our panelists for perhaps a closing remark or something really thinking about what's next and what's that more work that can be done. We talked about the implementation phase, for example, but if there's anything else that, you know, kind of falls into that what's next bucket perhaps we can hear some thoughts on that. I feel like I've started with Steven so many times. We'll move on to Cindy and then work our way back if that works.

DR. GROSSMAN: I do have two things that I haven't had a chance to say and that one is to make -- to increase the volume and urgency of the need for case studies, the call for studies. I think that that again sort of alluded to the fact that some of this work is happening in a more competitive environment versus a pre-competitive environment. I think it's super important to have these case studies. I will do our part in trying to populate the docket with that or encourage our community to do that. But the other piece is has to do with the special populations as called out in the document. And I think for me one thought -- about and I don't know if this is future work or if it could be done now is to think about -- instead of special populations thinking about what is it that the special population represents? So what I mean by that is when you talk about kids in pediatrics, it's not so much their age that I heard, it was more their developmental stage and what they could do.

When you think about women, it's not so much that they're of a particular age thus they're childbearing. It's maybe more about whether they

intend to ever get pregnant or whether they have the capacity to be pregnant. And so I guess we could -- I think that this document and our future work really needs to be a bit more clear about what is it about sort of special populations or select groups that make or pose certain types of considerations, rather than just adding demographic characteristics or other kinds of specialness of a population to that. So I snuck that in. I know.

MS. CHALASANI: Okay. Katarina?

MS. HALLING: So two things -- so just to add to the digital health one. So I would strongly encourage the FDA to make some statements around what can be done and what cannot be done at this stage because this is, as we heard in the great session before, this is already on its way. And one of the things that I'm really keen on is what we heard from Suze (ph) that there is a -- there was raised concern that this is not representing the patient voice. So if we could at least say something like a digital health monitoring cannot substitute the patient's feelings or feelings. Something like that would be extremely

helpful and then we can work on all the details.

The second thing is, I think the modification piece as has been mentioned I just want to reiterate, I think there are more examples on good practices and particularly very quick solutions which is of interest to all of us. And then finally, when we more consistently as part of this new way of developing our medicines, listen to patients we all know that we will find that some of the instruments that we see as standards does not represent the patient experience in a good way. So let's not close the door to continue to push forward de novo development, when that is absolutely needed and continue to find a speedy way to do that and move as quickly as we can.

And I want to reiterate what Tara mentioned, I refer to it as her FDA hot button system or something like that, just to continue the dialogue between us, because we will have to develop de novo tools as well.

MS. CHALASANI: Thank you. Laura Lee?

DR. JOHNSON: I was going to defer to the others.

MS. CHALASANI: Okay. Nancy?

DR. LEIDY: Okay. I actually would like to make a couple comments related to flexibility, contexts of use and fit for purpose. And some of the discussion that happened these last couple of days, because as I think these are very difficult terms, because it's -- if you're really very specific about context of use and fit for purpose, the more specific you are, the more precise you're going to be but the harder it's going to be to be flexible. And I heard opportunities for flexibility around -- in fact one thing I heard under rare disease discussion was the global nature of disease burden for example.

I also heard or at least I'm starting to hear rumblings around, can we select or develop or use common outcomes across diseases. We do that I think for pain. We're talking about doing that for fatigue. What about function across different types of oncology indications for example. What about exercise tolerance. And then, what about leveraging existing resources. That type of discussion really demands the flexibility that you're talking about. So we really have to really think about the context of use and fit

for purposes with a little bit more breathing space, because if you're going to get together in a pretty competitive space to develop an instrument that's suitable for multiple sponsors to use in their drug development studies, the context of use is not yet fully baked. The fit for purpose isn't completely baked. It's partially baked and it can be done. But I think we need. That's where your flexibility needs to really come in.

The other piece of that is the item banks. If we're going to use item banks, there's a flexibility that's required there as well. So I guess I would urge us to really think about how these three things can -- I guess it's more that you can't do yin and yang with three things, but it's really three things that need to fit together nicely in a pie so that we really can be flexible and also have measurement that's suitable for both the context of use and fit for purpose, so.

The other comment I would have also related to that is where our trial design is going. And I heard some really interesting comments related to future of trial -- different trial designs. And I know we're

hearing things like can we use real world evidence in some cases for certain types of approval processes or approvals and what about adaptive trials and what are we going to do about combo products. So that also says this fit for purpose context of use is in a flex -- I think in a flex time a little bit. And so if we can be flexible to meet that that would be great, so.

MS. CHALASANI: Ashley?

DR. SLAGLE: So one of the drawbacks of being one of the last people to speak in the last panel is that all of the good comments have been said. I do want to just touch on flexibility a little bit. And those who know me may be surprised with these comments, because when I was at the FDA I was definitely a champion on flexibility. But now as I reflect on it a little bit more and I think about it in terms of the guidance or these guidances, in some cases flexibility means regulatory uncertainty and that worries me a little bit.

And so I think we need to define what flexibility is. We need to be really cautious about giving very clear examples of when flexibility is

appropriate. And I think Laura Lee said this earlier. And I'm sorry, I missed your limbo bar but where there just can't be flexibility and you have to think about labeling and making sure that the measured labels, what's being described in labeling and to me that's a place where you just can't be overly flexible, but maybe in terms of reliability, some things are little noisier than you would like, a big treatment effect will overcome that. And so that is an example of a case you can be a little bit more flexible potentially.

So I think we just need to be really careful about what we mean by flexibility so that we don't have Katarina's colleagues who think that just means they can do anything that they want to do or not hold to account. The people Katarina overheard at lunch.

MS. CHALASANI: Thank you. Kevin?

DR. WEINFURT: Yeah. All the good stuff has been said. I just will end though by saying there wasn't time nor would have been very interesting to go through. And for me to just highlight all the places in this -- in both guidances, where there was clearly so much work, so much thought things are very clear,

such an advance over prior documents we've had. And so I just want to underscore that we're talking about opportunities for changing and modifying and building on this, but I just don't want to lose this gratitude we have to the FDA for all of the hard work that's gone into this and we're looking forward to being partners in trying to get this document reflecting what all of us are trying to do.

MS. CHALASANI: Thank you, Kevin. And to wrap up us, Steven?

DR. COONS: Sure. And dido to that that, Kevin. And the only other thing that I'll say is that the -- you'll get some feedback on ECOA section because I think there are some things that need to be beefed up in that and because one of the things it says specifically is that paper as a backup to an electronic data capture device is possible. And then the next line says, but don't mix electronic and paper. So I think there's some little details like that. And I think that -- and then I agree with Katarina that something has to be said around the mobile devices and the data that are going to be generated by mobile

devices.

But I don't know how much you can get into that yet because there's so much for us to learn about how those data will be used to produce endpoints for efficacy trials or treatment trials. But we can't -- it can't be avoided, it has to be discussed in a little more in depth. And I agree with Nancy that the modification area is -- it's wonderful that it's highlighted as opposed to just de novo instrument development. But there are some concerns around the modification of instruments. And if we can use instruments as is, I think that should be our default. And that's the beauty of these item banks. That's the beauty of all the work that Promise (ph) has done in these domains scores that we may be able to apply to a variety of diseases, fatigue, depression or these domains that we can apply to a variety of diseases as is or as subsets obviously, short forms from the item banks. So I think there's a great future in that, but the modification -- there are -- it's fraught with a number of challenges. But -- and we can't necessarily describe them all in the guidance documents, so it's

complicated.

MS. CHALASANI: Thank you Stephen. I do want to open the floor to questions now, I see several folks, so please go ahead. I just ask that you please state your name and affiliation before you ask your question. Thank you.

AUDIENCE QUESTION AND ANSWER

MS. LEETMAN: My name is Amy Leetman (ph), a patient advocate, I'm the Director of Advocacy and Policy for NTMN phone Research (ph). So I wanted to touch on a point that was made earlier about the technical content that's in the guidance document, and perhaps removing some of it and putting it in appendices. You know, I'm actually one of those people that would actually benefit from that because my background isn't in science, so I'm always googling things and e-mailing epidemiologists and asking questions.

And it's a -- it's been a big learning curve for me but that's what I consider part of my job, because part of my job is to bridge the gap between our patients and the researchers, and the physicians, and

the industry and the regulators who are all trying to help them.

So for me getting a handle on all this in a more technical sense is kind of important. For the patients, maybe not so much, and I get that. They don't necessarily want to sit and take the same amount of time that I need to take to learn it, but my concern is that it would perhaps dilute the strength of the document to move too much of the technical content because of who this really is geared towards. Yes, we want the patients to understand and appreciate what's going on.

I just -- my question I guess is almost towards the FDA, have you considered just writing a plain language summary, like really drawing a line from A to B to C plain language summary for patients, explaining what this document is and what it says. Because my experience with our patients is that when I've done that, explain to them, well this is why we're doing all these market research studies, this is why it's so important. They stop complaining, they're like, oh, now, I understand why this is important. And

then they start showing up in droves for these studies.

So those are the kinds of things I think that might be a little more helpful, sort of getting back to that, sort of plain language summary of each section. And those kinds of documents, if you were, you know, to produce like a summary, a plain language summary, doesn't have to be long, but that's something that could be disseminated widely. For a lot of patients, organizations, they could put it out for their patients and say, this is what the FDA has been doing with their patient-focused drug development initiatives and this is where it's gone and this is where it's heading to and this is how it's going to impact drug development for us and how it's going to help you.

I don't know if that's something that is possible to consider but --

MS. CHALASANI: So I know that our NIH colleagues, many of them follow this practice of developing and communicating with a plain language -- plain language summary, so definitely a really helpful comment, Amy, that I -- I know that we can take back, and we'll definitely consider.

MS. LEETMAN: Yeah. And Just one thing about those NIH summaries, they're great, but some of our patients look at them too and they're like we don't understand. So when I say plain language summary I mean you really have to draw down to the people who are not doing any of the science. And that really sort of speaks to what these patients are going through too. It's like for my patients they're doing hours of treatments every day, they just don't have the time to sit and try and wrap their heads around it, and, you know, a lot of them are dealing with the kind of mental fatigue where they just can't. So to really make it as easy as possible for them to digest I think would be more helpful.

MS. CHALASANI: Okay. Thank you, Amy. We'll definitely take that comment back. Thank you.

MS. SYMONDS: Hi, Tara Symonds from Clinical Outcomes Solutions. Just a comment or a plea because I think we're moving from PRO to COA now and I still have clients who see PRO synonymous with quality of life or health-related quality of life. I have to caveat, do you want me to build a PRO strategy that has symptoms

and treatment satisfaction and have relative quality of life. And I felt with the guidance as Nancy and Katarina have outlined with the guidance three that it is still a bit PRO centric. You do add in the -- an intra-rater reliability but I do think you need to put in the information around ClinROs and PerfOs, and that can be an appendix and a simple statement next to that inter and intrarater reliability by stating. And these require different study designs and power considerations. And then, you could put that into an appendix and I think that will give you more legitimacy, because what I don't want the COA guidance to be seen as is, oh, that's just for PROs and then that PRO is just the quality of life. It will devalue exactly what we're trying to do here.

And what you're trying to do, as I said yesterday, one of the things we need to hammer home and, you know, I've been party to the ISPOR or the International Society for Pharmacoeconomics and Outcomes Research, there's a COA SIG, Special Interest Group, that they're putting together and I've been party to pushing that forward.

The struggle I had with them changing the name, they wanted it to be PRO SIG, I said, well, we've moved on guys, it's COA SIG, well why -- and I had to put -- well it's just an FDA term, sorry, you know. And I was like, well, it is but what we're trying to do here is measurement site for outcomes assessment, and what we're trying to do is show you what you need to do to have precise measurement with these outcome measures. So they've kind of allowed us to call it the COA SIG but there's still a lot of work for us to educate that audience. So if that audience can't understand what we're doing, we need to make it so in the guidance. So you can have your strategy and then your appendices and you need more on the ClinRO and PerfO. And so the patient advocate that just spoke and I was going to also say that this is fantastic idea. Don't dumb down this guidance for industry, it will do a disservice to all those people working in industry trying to push this forward as Katarina has outlined, but, yes absolutely, have something that the patients can really understand and take away as well. Okay, thank you.

MS. CHALASANI: Thank you for that comment, Tara.

MS. CHRISTOPHER: Stephanie Christopher from the Medical Device Innovation Consortium. And why the medical device innovation consortium has been here at a drug development guidance for the last 2 days is because all of the issues that you've been talking about here are also things that the medical devices industry is thinking about. And first of all I want to applaud you for bringing folks from your sister agencies from CDRH and from CBRE and into this meeting, but -- and I do view medical device companies as a stakeholder in this conversation.

And to the point that was made earlier today about terminology and making sure we were very clear on terminology. I would encourage you to keep that terminology, explanations of terminology, glossary of terms keep those in there because medical device companies -- they're looking to this document as well, not necessarily because it's guidance but because it's helping us to better define what it means to do patient-centered clinical outcomes research.

And so those terminologies are helpful to all of us that are looking to advance this across the spectrum of medical product development. So I'd encourage you to keep that in and help us to continue to work together. And as, you know, the work, you know, going on in ISPOR and other places, it's not siloed to particular like this is how we develop drugs, this is how we develop devices, but it's going to -- something that's going to be helpful to all of us. So help us continue to bring a medical device companies including those really small innovative companies doing cool things like digital health and combination products and bring -- continue to bring them into this good work.

MS. CHALASANI: Thank you, thank you. This workshop, the discussion documents and the eventual guidance are actually all cross-center efforts, Center for Drug, Center for Biologics and Center for Devices, so thank you for that comment.

MS. LATASH: Hi, Wendy Latash from Astellas Pharma, patient experience and outcomes. Two points. The first thing is I'd like to underscore point from

our patient advocate colleague about trying to develop something that is really plain language. And I think for us in -- as a sponsor I think having something like that would help us to engage our patient advocates much earlier on to bring them to the table as we're trying to, you know, develop the different COAs and getting their feedback. So really underscore that point, I'm glad she said that. The second point I like to make and just really request really, you know, one of things I noticed about the last panel when we were talking about digital health, you know, I kind of feel like when we get 10 people in a room and try to define what digital health is, we get about 15 different opinions.

And, you know, what I heard a lot of the discussion was around devices and wearables and looking at, you know, performance type of data that could be correlated could not be correlated. What I'd like to pose and try to bring in, I think it was lightly touched on during that panel is the fact that digital health is not just about wearables, it can also be a tool, a means to an end to pull through those classically developed COA instruments. And that's

something that we have looked at, I know, you know, other industry members have looked at and want to make sure that that gets treated in some sort of definition, in some sort of language, so that as we're going to the different, you know, groups within the FDA and trying to get feedback, you know, that distinction is made so that it is not, you know, it doesn't get confused with, oh, are you just trying to do this to have a different measure? No this is just a means to an end to pull through, you know, some of the classical, you know, COA. So, you know, I would request that, so thank you.

MS. CHALASANI: Thank you for that comment. I don't know if anyone on the panel would like to add to that or anything? No? Okay, I think we'll definitely make a note of that comment. Thank you.

MS. LATASH: Okay. Thank you.

MS. CHALASANI: I think with that I think we can close this panel. I'm not really going to provide a summary because I know Elektra is going to be up here in a few minutes and in the interest of time I'll leave the summary to her. But I would like to thank all of our panelists that are up here today, that are here up

here right now as well as all of our other panelists throughout the workshop sessions for a truly rich discussion. It's been a very insightful 2 days, so thank you all.

(Applause)

OPEN PUBLIC COMMENT

MS. CHALASANI: So with that I'd like to invite Dr Shannon Woodward to facilitate the open public comment session.

DR. WOODWARD: Hi, everyone. My name is Shannon Woodward. I'm part of the Office of the Center Director and first off I want to thank you all for hanging in there 2 whole days with us. So right now we're moving into the open public comment session, and the purpose of this part of the workshop is to allow an opportunity for people to comment on topics other than our workshop discussion topics. This is also a chance for many other stakeholders other than, of course, our panelists and speakers to also share with us.

So keep in mind, the FDA won't address comments that we hear during this session, but all of the comments are being transcribed as part of the

public record. And of course we would like this to be a transparent process so we encourage you to know any financial interests that may be relevant to your comment. And if you do not have any such interest you may want to state that for the record. Or if you prefer not to share that information with us, you are still welcome to provide your comment. We collected signups for open public comment beginning this morning and also during the breaks of the workshop and we have five speakers signed up. For each speaker you will have 2 minutes to provide a comment. We won't be using a timer and light system, but I will use my cell phone which I'm going to grab now.

So of course, I don't have a buzzer or anything like that but I will kindly nudge you a little bit once you get close to your 2 minutes. And also if I call your name and you're no longer interested in sharing your comment or you may have shared during the Q&A, feel free to let me know and I'm happy to move on to the next speaker. So with that our first speaker is Danielle Friend with BIO. You're welcome to approach whichever mic is closest.

MS. FRIEND: Good afternoon. As you mentioned, I'm Daniel Friend. I'm a Director of Science and Regulatory Affairs at BIO. I don't have anything to disclose today. Bio or the Biotechnology Innovation Organization thanks FDA for the opportunity to provide the oral comments at the meeting today. We'd like to commend the FDA for the tremendous amount of work that the agency has done in order to better ensure that patients' experiences are more systematically collected and used to inform drug development and regulatory review.

In order to support transparency, as FDA begins drafting the next series of guidance documents, we have a couple of points that we'd like the FDA to consider. Specifically specifying in guidance when and how industry sponsors and other stakeholders can consult with FDA regarding the conduct of studies and the incorporation of patient experience into regulatory decisions.

BIO requests that FDA consider increasing the length of milestone meetings and sponsors will be discussing patient experience data, providing dedicated

meeting opportunity to sponsors, to discuss patient experience data, for example, through Type C meetings or providing opportunities for sponsors to receive written agreement with FDA on study design.

It's BIO's belief that in order to truly support patient-centric drug development, patient experience data should be considered for use throughout the entire product lifecycle including regulatory review. Such data may inform important decisions such as benefit risk assessments, labeling post market studies, and others. To encourage all stakeholders to collect patient experience data we request the FDA to more clearly indicate the regulatory decisions for which they will consider patient experience data.

BIO also requests that the FDA make clear in the draft guidance the delineation between collection of patient experience data to inform clinical studies and patient experience data collected within a clinical study meant for submission to the FDA to inform a regulatory decision. Because the level standards needed for generating patient experience data can vary across studies and will depend upon the intended use,

we request that the FDA clearly describe how the evidentiary standards may vary depending upon the intended use of the data.

DR. WOODWARD: Any final thoughts?

MS. FRIEND: Finally, we like to ask the FDA or we appreciate that the FDA has made comments regarding specific patient populations that may be difficult to collect patient experience data around. And we're hopeful that the coming guidance documents will contribute solutions to still collecting patient experience data for those populations.

Again, thank you for the opportunity to speak and we'd also like to thank the patients and patient organizations who've contributed widely to this effort as well. BIO will be submitting comments to the docket. So thank you so much.

DR. WOODWARD: Thank you, Danielle. Next, we have Elizabeth Manning of UCB Biosciences.

MS. MANNING: Hi again, Elizabeth Manning, UCB Biosciences, I'm taking a little bit different approach here. I don't have anything to disclose. Sorry. I want to highlight some of the interpersonal focus that

came out of that last discussion and show true appreciation for it. I think this is a real opportunity of a turning point for FDA as a partner with industry and for us as multi stakeholders within industry to practice the position of empathy with each other. We're trying to empathize with our patients but it's the only way we're going to succeed, is if we figure out how to relate to each other and we figure out how to combine our efforts. And if FDA can help us by facilitating those conversations, removing obstacles, letting us accelerate, and helping clear that path, I think that's a huge role that could be different and differently relayed through the guidance.

I challenge you to take the exercise tonight when you brush your teeth, use your other hand. That's how everyone feels, that's how patients feel when they get the new diagnosis, that's how we feel as we're trying to revolve -- evolve how we do our work and accelerate it. And then, I want to highlight a specific point that only came up briefly, but if you could give guidance around how gender identity and the evolution of that paradigm is, should, should not,

will, will not play a role in this conversation around patient experience where it could be impactful while sex is still critical to our clinical setting and how we can help educate the public when both of those paradigms become active in our space. Thank you.

DR. WOODWARD: Thank you. Next we have Berett Yufe (ph) from FAIR (ph). My apologies, if I misspelled or misspoke your name.

MS. YUFE: Hi, my name is Berett Yufe, and it's okay. I'm a 16 year old junior at Georgetown Day School, and I've lived with a multitude of life-threatening food allergies since infancy. And even with my parents' and my own constant vigilance, I've had many allergic reactions over the course of my life. Because the magnitude of allergy attacks increases every time one reacts, by the time I was 10 my allergy reactions were truly life threatening.

At 10 years old I suffered from an extremely bad anaphylactic reaction and almost died even with the immediate aid of epipens and hospitalization. In America someone is sent to the emergency room because of food allergy induced anaphylaxis every 3 minutes,

and my one experience affects me to this day. Nothing that I consume that night had any warning of allergens or cross contaminations and yet -- cross contamination, and yet, within an hour of eating I found myself covered in hives being pumped full of steroids and relying entirely on an oxygen tank for life. My parents and brother thought I would die at just 10 years old. Although I physically recovered, I still suffer from extreme allergy related anxiety. And for the month -- and for many months after the attack, I refused to eat, because how could I be sure that nothing was contaminated. And the answer is that I can't be sure.

There's nothing that I put in my body that is guaranteed to be a 100 percent free of the slightest cross-contamination and medically there are no preventative measures that I nor the 15 million allergic Americans can take to guarantee our safety. Epipens are only to be used as a rescue and even epipens don't always save lives. The only medical treatment that can decrease one's likelihood of death as a result of anaphylaxis is desensitization which is

not only a long obstructive process, but also has little impact on people like me who have multiple life threatening food allergies many of which are not treatable by the current desensitization program.

With staggering statistics that show 377% increase in anaphylactic reactions between just 2007 and 2016 --

DR. WOODWARD: Any final thoughts Berett?

MS. YUFE: Yeah. With the exponential growth of food allergic Americans now is the time to act before many more people's lives are taken or tarnished. We, the allergic community, are in dire need of preventative treatments and cures, because our lives and our quality of life depends on it. Thank you.

DR. WOODWARD: Thank you. Next we have Maria Osobal of FAIR. And my apologies on your name, feel free to clarify.

MS. OSOBAL: You actually did really well. It's Osobal, but you were close. In August of 2003 my husband and I rushed our toddler to the emergency room after she took a tiny bite of a peanut butter cracker. One of those very orange crackers with peanut butter

inside. She only bit off a small corner before handing it back to me with I don't like this at all face. I turned my back to her to find a trash can to throw the cracker away. And when I turned back around, Nina's (ph) lips were huge and red blotches were covering her face and neck. By the time we got to the emergency room her eyes were swollen shut and her face was unrecognizable. She was vomiting violently, red hives covered her entire body and she was wheezing. The first shot of epinephrine did nothing and for those few minutes before the doctors gave her another dose my world came to a standstill.

That day it took two shots of epinephrine to get her anaphylactic reaction under control and I have never been so grateful for a medication in all my life. Fast forward 15 years, and today my toddler is 17. We're very lucky she's enrolled in a clinical trial that offers immunotherapy treatment for a peanut allergy. But as you all know there is no FDA approved treatment for patients outside of the clinical trial setting. Meaning that the vast, vast majority of the 50 million Americans with food allergy are excluded

from treatment.

And even for those of us fortunate to be in a trial, there are enormous limitations to the outcomes currently available to patients that I think few patients -- few people are aware of. What has changed for Nina after more than a year of constant visits to the hospital, she can now tolerate 300 milligrams of peanut powder. When she started, she had an anaphylactic reaction to just 6 milligrams. So that is a big, big step. But what does that translate to into the real world, 300 milligrams is the equivalent of one peanut. The cost of getting her to be able to tolerate one peanut has included four anaphylactic reactions, two requiring multiple doses of epinephrine, ambulance rides and countless stress.

DR. WOODWARD: Any final thoughts, Maria?

MS. OSOBAL: Yes. We ask for the FDA's partnership to accelerate research to answer critical unknown questions and to help all the patients with multiple food allergies that if we continue on the current path and schedule it will be more than 20 years out before any treatment is available for them. Thank

you so much.

MS. CHALASANI: Thank you. Next we have Kathy Lash (ph) of Pharmerit International. Kathy, are you still in the room? Calling once. Calling twice. Okay, I think that concludes our open public comment session. So I'm going to turn it over to my colleague, Elektra, to provide closing remarks.

CLOSING REMARKS

DR. PAPADOPOULOS: So thank you so much for everyone to -- for staying till the very end. And I also think it's so appropriate that, you know, that we're closing the meeting with patients' voices. So it's very, very much appreciated. I just really again would like to think everyone who participated in person, on the web, and who have come from long distances, all of our panelists, very, very much appreciate it. All of the comments will be taken back, discussed, and very seriously considered.

And also really want to thank everyone here at the FDA involved in the planning of this meeting. Not only the clinical outcome assessment staff, but colleagues from other parts of the CDER, the Office of

the Center Director, Biostatistics, CDRH, CBER. This is really a cross center effort and it's very important.

I think our leadership at the highest level of all three medical products centers have been extremely supportive of these efforts. And I can just say one quote that we frequently hear from our Center Director, Dr. Woodcock is that patients are the true experts in their disease, and I think, you know, we all really, you know, that that rings true for all of us.

I can highlight some of just the key themes from the meeting, but I think this has been done very well up until now. One of the things I think we need to think very carefully about is, you know, the need to strike a balance between, you know, having too much detail, perhaps advice that might be construed as prescriptive and not enough detail. So there does need to be that balance. And we've heard different advice from different people.

But at the end of the day, I think what I did hear from everyone was examples, examples, examples, case studies that people find them very helpful. And I

think that's something that we can work on and encourage our external stakeholders to also provide examples. And not just positive examples but lessons learned. So, you know, we don't want to have a kind of a bias towards only positives, we want it to be balanced. I think the other very interesting area is, you know, this area is such a rapidly evolving field, it's a science, you know, how do we take the input, how do we go from the anecdote to, you know, to developing or selecting a measure to actually interpreting at a group level, at a population level how a treatment can be impacting patients' lives.

And it is a science, and it's an art as well as a science and it's a rapidly evolving area. And as we learned, you know, with new technology, with new methods, we need to be positioned to be able to adapt. And we don't want to lock ourselves in. So this is I think another very important key theme that we've taken away.

And I so very much appreciated Michelle Tarver's and others' comments about, you know, we have to consider that we're part of a bigger ecosystem and

we're not the only, you know, as regulators, we're not the only people who are going to be using the data, the clinical trial data. And there are so many post regulatory stakeholders. And we need to, I think, listen and work very closely together so that, you know, how -- we can be most efficient and meeting different stakeholders needs, and, you know, using core outcome measure sets where possible I think is going to be really useful going forward, so that's another area of great interest.

So I think, again, just resounding thanks to everyone for staying until the end. Please submit your comments. Docket closes December 14th. Thank you very much.

(Applause)

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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.

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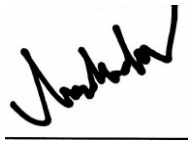

October 26, 2018

DATE

MURALIDHAREN K.V.

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