PATIENT-FOCUSED DRUG DEVELOPMENT

Methods to Identify What is Important to Patients and Select, Develop or Modify Fit-for-Purpose Clinical Outcome Assessments

Moderated by Ebony Dashiell-Aje, OND, CDER, FDA
Selena Daniels, OND, CDER, FDA
Elektra Papadopoulos, OND, CDER, FDA
Michelle Campbell, OND, CDER, FDA

Monday, October 15, 2018

9:05 a.m.

Food and Drug Administration, White Oak Campus
10903 New Hampshire Avenue, Building 31, Room 1503
(Great Room)
Silver Spring, MD 20993

Reported by: Michael Farkas
Capital Reporting Company
1250 Eye Street, NW, Suite 350
Washington, D.C. 20005

A P P E A R A N C E S

Michelle Campbell, OND, CDER, FDA

Theresa Mullin, OCD, CDER, FDA

Ebony Dashiell-Aje, OND, CDER, FDA

Dagmar Amtmann, Research Professor, University of Washington

Elizabeth (Nicki) Bush, Director and Head, Global Patient-Focused Outcomes Center of Expertise, Eli Lilly and Company

Emily Freeman, Director, Health Economics and Outcomes Research - Patient-Centered Outcomes, AbbVie

Nova Getz, Research Associate, Center for Information and Study on Clinical Research Participation

Patty Spears, Patient Research Advocate, University of North Carolina Lineberger Comprehensive Cancer Center

Diane Turner-Bowker, Director, Patient-Centered Outcomes, Adelphi Values

Selena Daniels, OND, CDER, FDA

Vanessa Arnedo, Director, Research Partnerships,

The Michael J. Fox Foundation for Parkinson's Research

Antonia Bennett, Faculty Director, Patient-Reported Outcomes Core, University of North Carolina

Bill Byrom, Vice President of Product Strategy and Innovation, CRF Bracket

Sonya Eremenco, Associate Director, Patient-Reported Outcome Consortium, Critical Path Institute

Barbara Stussman, Survey Statistician, National Center for Complementary and Integrative Health, National Institutes of Health

Tara Symonds

Elektra Papadopoulos, OND, CDER, FDA

Billy Dunn, OND, CDER, FDA

Martin Ho, Office of Surveillance and Biometrics (OSB), CDRH, FDA

Telba Irony, Office of Biostatistics and Epidemiology (OBE), CBER, FDA

Laura Lee Johnson, Office of Translational Science (OTS), CDER, FDA

Paul Kluetz, Oncology Center of Excellence, FDA
Larissa Lapteva, Office of Tissues and Advanced Therapies (OTAT), CBER, FDA
Michelle Tarver, OCD, CDER, FDA
Robyn Carson, Head, Patient-Centered Outcomes Research, Allergan
Alicyn Campbell, Global Head, Patient-Centered Outcomes Research for Oncology, Genentech
Stephen Joel Coons, Executive Director, Patient-Reported Outcome Consortium, Critical Path Institute
Phyllis Foxworth, Advocacy Vice President, Depression and Bipolar Support Alliance
Nancy Kline Leidy, Senior Vice President, Scientific Affairs and Patient-Centered Outcomes Research, Evidera
Kevin Weinfurt, Professor and Vice Chair for Research, Department of Population Health Sciences, Duke University School of Medicine

C O N T E N T S

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P R O C E E D I N G S

DR. CAMPBELL: Good morning. My name is Michelle Campbell, and I'm from the clinical outcome assessment staff in the Office of New Drugs and the Center for Drug Evaluation and Research. I'd like to welcome everyone to our public meeting. This is the second meeting in a series of meetings we'll be conducting as we work towards developing a series of patient-focused drug development guidances.

Now let me first say by saying, wow, we have a great capacity today of people who came. And we know that there's still more people coming in through registration and through security. We also have many more who are joining us on the webcast. We welcome them as well, and we thank you for being a part of this meeting today.

In our discussion over the next few days we will be continuing our conversation we began in December in 2017s public meeting. And we will focus on methods to elicit relevant information from patients and other stakeholders, best practices of these

methods, and how to select, develop or modify fit-for-purpose clinical outcome assessments.

Throughout today and tomorrow we want to hear from you on the approaches and considerations proposed in the discussion documents. If you've not gotten a chance to read the discussion documents, it is okay. We'll be going over the key concepts during our presentations today and tomorrow.

I do want to mention that in addition to this meeting a docket will remain open until December 14, 2018. You will also be hearing that multiple times today and tomorrow. To which the public may submit general or detailed comments or examples regarding specific aspects of the discussion documents or topics raised in the two-day meeting.

We do have a full agenda for both days of the meeting. And for us to keep the conversation flowing, our moderators may need to jump in and ask you to provide detailed comments to the dockets or discuss with colleagues during the breaks.

Allow me to quickly go through the agenda. Theresa Mullin, our associate director of strategic

initiatives for CDER will be getting us started this morning with some opening remarks.

We will then have a presentation on what is included in the discussion document of Guidance 2, followed by panel discussions on more specific topics. These panel sessions include session one, Methods to Identify What is Important to Patients, and session two, Emerging Best Practices on Methods to Identify What is Important to Patients.

In the afternoon, we will transition to discuss Guidance 3. We will start on a presentation of an overview of what is in the Guidance 3 discussion document, and then have two panels on initial thoughts of the discussion document.

The first panel will be an FDA cross-center panel discussion, looking at clinical outcome assessment use to support patient-focused outcome measurement throughout the medical product lifecycle. The second afternoon panel is on the roadmap to clinical outcome assessment selection or development in clinical trials.

Tomorrow we will continue our panel session on

Guidance 3. And we will be discussing considerations on selection and use of clinical outcome assessments in special populations, methods for determining and interpreting within patient meaningful change scores and clinical outcome assessments, emerging technologies to support fit-for-purpose clinical outcome assessments, and finally, identifying key themes and next steps.

It should be a thought-provoking next two days. Throughout the day the audience will have several opportunities to ask questions and provide their views. With our large number of webcast attendees, we will not be able to take your comments or questions during the meeting. We encourage you to submit your comments to the public docket. And we will also take back all of your comments that you list in the comment box of the webcast to review.

Tomorrow afternoon we'll provide time for public comment. If you wish to sign up to speak during open public comment period, please do so tomorrow at the registration table. We have 45 minutes allotted for open public comment and will be able to hold up to

25 speakers, although we do hope you're able to ask your questions during the question and answer period in each session.

A few housekeeping items: For today, we will have a lunch hour break at 12:30 and a 15-minute break at 11:00 and 3:15. But feel free to step out and stand and stretch as needed. There are food and beverage available to purchase at the kiosk outside in the lobby. It can get crowded at lunch, so we do encourage you to preorder. Bathrooms are down the hallway in the lobby and on the left. The WiFi password can be found in the front desk.

And finally, in addition to the live webcast of this workshop, we also have FDA Studios joining us this morning. The FDA is in the process of developing videos for a new series on key patient initiatives. FDA Studios is shooting footage of this workshop that they hope to use as a B roll for this series. It will not include audio.

I will now turn the meeting over to Theresa Mullin for opening remarks. Thank you.

DR. MULLIN: Thank you, Michelle. If whoever

controls the slides could -- do I control the slides? I do. All right. Well, all right. So good morning everyone here in the room and on our webcast. I'm going to spend a little bit of time just giving you a very high-level overview of these four guidances and how we got to developing these as part of our larger effort to advance patient-focused drug development. And in these opening remarks I want to cover just three basic areas.

First, just describing FDA's, in the broadest sense possible, our context of use for patient-focused drug development. Why we're -- these guidances are so important, why the quality of this information is so important, and that to make it reliable for regulatory decision making and, indeed, hopefully other decision making downstream of FDA's process.

What we've learned from our patient-focused drug development initiatives, which we first piloted starting under, in actually fiscal year for us 2013, so October of 2012 and onward. And that marked the beginning of the fifth authorization of the prescription drug user fee act, which is when we first

made a commitment to try this patient-focused drug development initiative and the approaches that we undertook.

And then, thirdly, talk about this guidance work that we're doing now under both PDUFA 6 commitments, and also they dovetail pretty well with requirements under 21st Century Cure, Section 3002. So first is context of use. And this may look very familiar to many of you, but at the end of the day FDA has many jobs, but one of our most, one that we consider to be one of our most important in the medical product centers is our assessment of drugs, benefits, or medical products -- I'm a very drug centric, I'm in the center for drugs, right, so I think drugs. But my colleagues from CDER and CDRH are here, so it applies. We all think this way in terms of our medical product assessment.

But this is a really important job that we have and responsibility to the American public, which is to do this benefit-risk assessment, and it's based on science. We often talk about science-based decisions. The reality is, it's based on science and

based on our laws and regulations.

And those decisions that FDA makes can be challenged in court and litigated and in many, in some cases they are. And so for us, there's a legal standard here that we cannot be arbitrary and capricious. We have to be consistent in our decision making, applying consistent policy. Otherwise it's not fair to, to the regulated industry and the sponsors who are trying to bring their products forward.

And so our decisions effectively become like FDA's case law. And each decision has to take account of what decisions we've made in the past. If we're going to deviate from policies that are explicitly outlined or implied by past decisions, we have to be very clear about why. Why have the circumstances changed? And so at the same time we make decisions in the face of a great deal of unknown and uncertainty.

You know, the data that -- as you all know, the data that you have at the end of a clinical development program is just giving you beginnings of an idea of how that's going to work in the indicated population. You don’t know what else will go on. And

yet a decision has to be made. So we've taken the approach of at least trying to be very structured in our thinking through the basis on which we're making those decisions so that we can be consistent and explicit and clear.

And so here's the framing that we use. It's just notional framing that we're using. And we do have a version where this is sort of how we are structuring some of our -- the content of reviews as well.

The most important thing to look at in terms of benefit and risk and what's the acceptable weighing of benefit and risk may be the therapeutic context to begin with. What is the severity of this condition? What's the degree of unmet medical need? This -- these considerations come up in every case, whether it's a new drug, a product that's over the counter, a product that's generic.

In every case it's a consideration of how much is this needed, and what would happen if this product were off the market. Would patients have an unmet need at that point, and how serious is the condition. So that context is by disease, and it may even vary a bit

by subpopulation who have that disease. But it's very important in our consideration of the data that's then presented by a sponsor or the information that we have available to us from the sponsor or other sources on the benefit of the product. So how meaning, and how meaningful is that benefit. How compelling is the evidence that the benefit is there and the risks that appear to be associated with the use of this product. Can the risks be managed such that the benefits outweigh the risks.

Very basic, but that is kind of the basic kinds of considerations that come up every time. And this patient-focused drug development initiative was begun in PDUFA five. Basically Congress directed FDA to begin having meetings with public stakeholders at the same time that we were negotiating user fee reauthorization with industry.

And so once a month while we were having negotiations with industry we also met with patients and consumes and other advocates. And they indicated that they wanted us to list to them more.

We weren’t sure how we were going to approach

that, but we absolutely thought this is critical, and we have to involve and get their input into our decision making, with the recognition that they're uniquely positioned to inform the therapeutic context. I mean, who better than the patient knows what it's like to live with that condition and the degree to which existing therapies are going to treat their condition.

And this was a source of critical information that we didn't systematically tap into. We had the patient representative programs where we would involve telephone maybe in advisory committee or other decisions about a particular drug product. And of course that requires a full conflict of interest screening that has to occur in order for that relationship to happen, which can reduce the number of people and the timing, and it creates some constraints.

So this initiative was going to approach it by getting input from the whole population who have the disease and not get into a matter of a particular drug product. It allowed us to proceed with these meetings and actually get a much more comprehensive perspectives

on what it's like to live with the disease.

So this is the set of diseases. We are committed to do at least 20. We -- at the end of the day review divisions found this very helpful. They asked us to do a few more with -- we have to compete a lot for this room. I don't know if you can imagine, but one of the constraints is getting booking this Great Room as a factor for us.

But we had 25 meetings over the course of those years, and there you can see the very wide range of the diseases that were included. In every case we basically ask these questions pretty much verbatim, these and others. But we have two sessions typically, and when people do the externally led, they typically follow the same pattern. It seems to work pretty well.

So probing the burden of disease by asking all the symptoms you've experienced because of your condition. Which one to three of those has the most significant impact on your life? Are there things you can't do that were important to you now because of your condition? Has it changed over time? What worries you the most, questions of that sort.

And then we have an afternoon where a subsequent session on what people are doing to treat their condition currently or treat its symptoms. And how does that work for them. Is it effective? And what are the most significant downsides of their current treatment? What would they look for in something that they might call an ideal treatment?

And the information that we obtained is just very powerful. These reports are referred to by our, were referred to by our reviewers when they have questions or, or they need background related to those disease. Other reports are being generated by external groups. And I've heard, at least anecdotally from some companies that they are also using those reports early on to try to get a sense of what was heard.

We've tried to reflect just what we've heard, not paraphrasing it or anything to be very faithful to the language and the ways that patients have expressed their views about what it's like. And we've come to the realization certainly, and we've just started about it this way, which is that patients are experts, okay.

This is a -- now I'm talking about drug

development is an enterprise full of experts, right? Most people have half a dozen initials after their name to show their expertise. And but patients are truly experts in what it's like to live with their condition. And it's a critical source of expertise that has to be tapped into on a regular basis in a standard kind of way.

And we -- also our clinicians realized that a lot of the things patients were talking about, which you might characterize as their chief complaints, which is how a clinician might ask them -- you know, why have you come to see me today in the clinic -- were not even being factored into drug development programs because of this lack of systematic attention to this important source of information.

And what we were hearing from patients who are parents with a child with a degenerative progressive disease is just stopping progression or slowing progression would be, in their minds, almost constitute ideal.

They also wanted to -- given that they have two jobs and they have people they take care of and so

on, still want to be as active as possible. And so people were also asking us, "Well, what's next FDA? These meetings are great, but what are you going to do now?" You know, and we knew we had this very useful qualitative report, but that at the end of the day we needed to take it further.

We also really realized how valuable it was to have workshops and have patients and others come and talk to us before we put pen to paper. And that's really why we committed to these workshops as well as producing these guidance documents because we know we, we're going to hear things we would not otherwise get to hear. And the documents we produce and the decisions we make will be better for it.

So here's one of our -- you could say the agenda here -- what, in trying to answer this question of what next, we go back and think about that benefit risk assessment that we need to do. And in addition to that very powerful helpful narrative and qualitative information that we can get through a patient-focused drug development-type meeting, which is, really informs our decision making, to inform it even further, it

would be great to get measures and tools that could systematically capture measures of whether the therapy under investigation is actually having an impact on these things that patients said mattered the most.

Both, is it affecting the disease? Is it less burdensome? And having data that we can actually have as part of the basis of our decision making about this product. And that would take some more work. And it would take some more work upfront, and we knew that. And we were hearing that it would be useful to have more clear laid out guidance. Especially if a larger swath of people were going to start to want to get involved in this work.

If patient groups wanted to get involved in this work, a document that would only be comprehensible to an academic researcher or to somebody who's already, you know, got a doctorate in this area, if you will, is going to really reduce the opportunities. So we, we wanted to basically do a series of guidances that would be as accessible as possible, as plain and clear as possible about what would need to be done to collect this information in a way that’s going to make it

reliable for many uses, quite frankly.

But there's -- the progression that we have here is to take parties from the early qualitative work all the way through to bringing this into your clinical trials and having this measures that you can use in trials that can be a basis for assessing benefit and risk as one of the goals we're aspiring to achieve.

Now, the names of these documents, the first one is the only one that's just out there already. We're working on the others. We're actually doing it more quickly than we had committed to do in the user-fee commitments where we said we'd do at least one a year. We're trying to progress this more quickly so we can get it into people's hands.

We're also aligning what we committed to in the language we used in the user-fee commitment letter with what the statute says. So under 21st Century Cure, Section 3002, Congress tells us what they want. And, of course, we have to make sure we're doing what Congress wants. And we're combining that with what we committed to do, and they align very well, but the language is a little bit different in a few places.

In any case, that first guidance on approaching comprehensive and representative input, approaches to collecting comprehensive and representative input from patients and other stakeholders on burden and disease of diseases and current treatment. None of these guidances has a short name. We often call it Guidance 1. We just -- it's like shorthand for us is Guidance 1, okay.

And Guidance 2 and 3 are really not any shorter. So this one -- the two we're going to talk about getting ready for today, we have the discussion documents out there now, but the guidances are not out yet. But Guidance 2, Processes in Methodological Approaches to Developing the Holistic Set of Measures. So what are the -- of all that qualitative rich context that we get distilling from that, though a set that reflect both the burden of disease and the burden of treatment and other critical aspects if there are others.

For example, physical functioning, if that's relevant. What's that distilled down set of what's most important to patients. And that’s under today's

discussion to get ready for that one, for that one.

And then the next was Guidance 3. And that would be how do you then approach identifying and developed measures for an identified set of impacts that you might be able to collect in clinical trials. And here, again, were looking for a set that actually would move and reflect any change or delta that you'd experience because of the new therapy that you're investigating.

And then that fourth guidance will cover a number of things, including methods and technologies for clinical outcome assessment. And here, in addition to any other issues we need to, we see we need to cover and bring into that, and may need to be updated from our 2009 guidance will also be covering technologies that can be used for collection, capture, storage, and analysis for the patient's perspective.

Of course, this is an area that's probably going to be very dynamic. And so the challenge will be a guidance that can remain robust and relevant, even as the technology keeps changing. But those are the four.

And there are a few other areas that we're

developing guidance to meet the statutory requirements. But we have a very full agenda today, as you can see. And we're very excited that we have all of you here and on the net, the webcast to help us miss -- to catch anything we may have missed, to refine and make this Guidance 2 and 3 as useful and usable as possible.

And with that, my last slide -- we have four areas that we're looking at. We have four aims that we've identified in CDER certainly that we want to go after to try to make patient-focused drug development a kind of standard practice. And the guidance really helps to support three of the four.

And the first is ensuring the confidence and the reliability and accuracy of this information. If we're going to get our decision makers to use it, they have to be confident that it's going to be reliable. And you know, we're coming from a perspective, a traditional perspective. This is not, I think, the perspective that we have in FDA today.

But I think that not that long ago you could hear people say, "Well why should we listen to telephone, they're, they're just going to, it's just a

subjective opinion that they have." You know, like everybody else's opinion is not subjective.

But, you know, and so we -- yes, it is subjective, actually. But how do we -- and so are a lot of other views. But how do we make that reliable nonetheless? How do we make it representative nonetheless and actually increase the objectivity of it? And so that it's reliable, it's good evidence, and we can use it in our decision making all the way through.

At the same time, when we're doing that, the guidances should help reduce the uncertainty of our sponsors, because this is an area, a relatively new area to be including. It would be a new area of investment. It will be moving into an area where they haven’t been established in doing these kinds of things before.

There's some uncertainty, some business risk, perhaps. And so how do these guidances help assure people that they know what to do, and they know what FDA's going to do when they bring this stuff in, and they try to work with it.

And we think that this, these things will actually help reduce and increase the adoption of these guidances in this approach. And we're talking about it in every venue we could think of. We're building it into our internal and external -- not just our external guidance, but also in our internal workings at FDA.

And there's a fourth area that we're hoping to get into soon, which is trying to support a sustained inclusion of these measures by a grant program that we're undertaking. And looking at that we'll be moving forward with in RFA, we think this winter we hope, to try to help support development of a minimum course set of clinical outcome assessments, you know, measures that for a disease area.

And we'll be piloting that to see how it goes. But we really do want to make this as accessible and straightforward for patients and for industry and other decision makers as we can.

So thank you for coming today. And I'll turn it over now to Ebony, who's going to give the overview of goals of the -- well, nope. Yes, Overview and Goals of Patient-Focused Drug Development Guidance 2, a

shorter name.

DR. DASHIELL-AJE: Good morning, everyone. My name is Ebony Dashiell-Aje. And I am in the Office of New Drugs in the Center for Drug Evaluation and Research here at FDA. I'm going to now briefly orient us to the general content that's covered in Guidance 2.

And then I will then also serve as a moderator for our first panel session so that we can dive into the discussion surrounding the content and what might need to be added, the things that we've done well, and things we can improve on.

So as you are aware, you know, we held our first PFDD Guidance public meeting last December and successfully published the draft guidance, which focuses on -- draft Guidance 1, which focuses on collecting comprehensive and representative input this summer.

And the purpose of Guidance 1 was to present sampling methods for collecting information on the patient experience that is representative of the intended population to inform the development and evaluation of medical products throughout the medical

product lifecycle.

Specifically, Guidance 1 answered major questions surrounding the target population. So whom do you get your information from and why. And how do you collect the information from them. We also discussed relationship between potential research questions and methods when deciding from whom to get input.

But Guidance 2 will focus on the actual methods to elicit relevant information from patients. In particular, how their disease affects their daily lives. What they find most troublesome, and the challenges, problems, and burdens of the treatments for the disease.

Some of these issues were introduced in Guidance 1, but will be covered in greater depth in Guidance 2 and have been outlined in the discussion document that we'll be focusing on today.

Now the discussion document for the Guidance 2 workshop presents more in-depth information about methods for eliciting information from patients and other stakeholders beyond just caregivers.

Specifically, gathering information about what aspects of symptoms, impacts of their disease, and other issues are important to patients. We cover qualitative methods, so like interviews, focus groups, consensus panels, and observations on how to elicit this information from patients.

We also talk about common pitfalls in collecting information from patient's that can lead to results that are inadequately or incompletely identify what is important to patients. For instance, we talk about potential barriers for patients that are created by inclusion and exclusion criteria.

We also talk about how to ensure that study methodology doesn’t impact the representativeness of the target population. And how to make sure that you're capturing enough information from subpopulations of interest. We also talk about advantages and disadvantages of the different methodologies.

And then finally, in the Guidance 2 discussion document we go into greater depth into these methods by talking about the operationalization of the methods. So we present operational details including development

of interview guides, selection of types of survey questions, and considerations for collecting demographics, and survey information, which are provided in detail in the appendices.

So we have the discussion document. Then we have the separate document, appendices, which are very helpful. You should read them, and provide comments on those, too, in the docket. Okay.

So for ease of navigation of the discussion document, the content is organized into three separate parts. The first part is methods to identify what is important to patients. Then we have approaches to asking the right questions, both in qualitative and quantitative research settings. And then best practices in how to do qualitative and quantitative research.

So that’s the operationalization piece. So here are the dockets that I talked about in a little bit more detail about what's under each one.

So first let's talk about the first column. Methods to Identify What is Important to Patients. So when discussing methods to identify what is important

to patients we ask the main question about what types of research methods can be used to identify what is important to patients and provide -- we also provide recommendations on the use of qualitative, quantitative, and mixed methods to collect robust and meaningful patient experience data.

It helps describe the disease and treatment burden, as well as benefits and risks in the management of the patient's disease. Concepts that are covered include how to collect relevant concepts that are important to patients, how to frame the questions to ask about treatment burden and disease. We discuss considerations for researchers for framing research questions and objectives related to disease and treatment burden, benefits, and risks.

In disease management we talk about advantages and disadvantages of the different methodologies in capturing this data, and considerations for selecting the appropriate methods for your specific needs in your studies.

When we talk about qualitative and quantitative methods, for the key messages for

qualitative research methods are identifying the appropriate participants to talk to. So patients with the condition of interest, in particular, determining a sufficient number of participants to talk to. The use of an experienced and well-trained facilitator during qualitative research, interviews, moderators to lead interviews or discussions. The use of semi-structured interview or discussion guides with well-designed questions to get better insights from participants, as well as the facilitators choice of words in these guides and how that can affect the participants' input or behavior.

We also talk about the use of balanced mixed -- - a balanced mix of open-ended and structured or predetermined probing questions in qualitative research.

With regard to quantitative research methods, the key messages that we cover are identifying the appropriate participants to survey. Patients with conditions of interest, determining a sufficient number of participants to survey for your study in designing a survey with specific well-designed and well-understood

questions and adequate response options in that survey.

So with regard to asking the right questions, we go into greater depth by explaining some strategies for avoiding inappropriate framing of questions in both qualitative and quantitative studies. Selecting or developing questions for surveys, as well as talking to and surveying special patient populations and different cultures and considerations that you have to take into account when you're designing those types of studies.

The last docket, we go into detail about best practices and how to do qualitative and quantitative research. So we talk about designing and implementing qualitative and quantitative studies in depth. How to design relevant study materials for both qualitative and quantitative studies, and then choosing settings for qualitative and quantitative studies. So whether it's an observational setting, screening or exit interviews or surveys, those types of things are the types of topics that we discuss in terms of operationalization.

So that is a brief overview in a nutshell of what we cover in Guidance 2. I decided to keep this

discussion brief because I wanted to open it up to a more in-depth panel discussion about the comments, the content of the document.

So at this time I'm going to transition into the actual panel session. And I'd like to welcome my panelists for panel one to come to the table and have your seat. We have a very dynamic panel today. Looking forward to a wonderful discussion regarding the content of Guidance 2.

And I'm going to focus on the first docket for panel session one. Our discussion will be surrounding the actual methods that are used to identify what is important to patients.

So before we get into the questions and discussion, I'd like my panelists to introduce themselves to the audience. So starting from my left, if you can just go down the line and state your name, title, and affiliation.

DR. AMTMANN: Good morning. My name is Dagmar Amtmann, and I am a health outcomes researcher with training in statistics and measurement. And I'm a research professor at the University of Washington in

Seattle.

MS. BUSH: Hi, I'm Nicki Bush. I lead the Patient-Focused Outcome Center of Expertise at Eli Lilly and Company.

DR. FREEMAN: Hi, I'm Emily Freeman. I'm in Patient-Centered Outcomes at AbbVie.

MS. GETZ: Hi, I'm Nova Getz, and I am a research associate at the Center for Information and Study on Clinical Research Participation. And we do a lot of like patient engagement sort of stuff.

MS. SPEARS: And my name is Patty Spears, and I'm a research patient advocate, 19-year breast cancer survivor at UNC Lineberger.

DR. TURNER-BOWKER: Good morning, everyone. I'm Diane Turner-Bowker, and I'm a Director of Patient-Centered Outcomes at Adelphi Values.

DR. DASHIELL-AJE: Thank you, all, for joining us. So today for this particular panel, focusing on the methods to identify what is important to patients, the objective is to just discuss different methods, qualitative, quantitative, mixed methods, or other technologies that can be used to generate patient-

experience data.

We want to have the panelists discuss from their opinion how we have covered this content within the Guidance 2 discussion document, and how well we've explored factors and approaches to ensure that the best methods are selected and used to gather input from a sufficiently representative range of respondents in studies.

So to open up our discussion, we know that the purpose of this guidance was to identify methods for eliciting representative information about what aspects of symptoms, impacts of disease, and other issues are important to patients and their caregivers. So I'd like to pose a very general question to the panel about what level of methodological detail is appropriate for this guidance, and whether or not we have sufficiently covered that detail in the current document.

So to begin the discussion I'd like to pose that question to Patty.

MS. SPEARS: So I'm coming from the patient perspective looking at this. But, you know, looking at the document I thought it was very nicely laid out.

But I thought one of the things that was missing is that every patient is different, like Theresa was saying. That, you know, you really have to get a lot of different input at different times. But there are different levels of input as well.

And one of the sections that wasn't really addressed clearly to me was the mixed methods. Instead of just using one method, rather use a survey or an interview or a focus group, I think you need to use several different methods sometimes to get different types of information.

And you might start it like a patient advisory group that's really well knowledgeable to help you guide what you ask in your interviews, what you ask in your focus group. And use that information to kind of maybe go out for a broader survey to general, you know, general patients that are just, you know, in clinics in the country type of thing.

But I think it's a level thing that you need to get at all different levels to really inform what you're going to get back to inform further. So I've done that on some projects that I've been on, and I

think it works pretty well. Because then you can get a really in-depth, but broad, sense of what the patient is experiencing as far as burden of the disease and treatments.

DR. DASHIELL-AJE: Thank you, Patty. And Diane, do you have anything to add?

DR. TURNER-BOWKER: Sure. I would agree with what Patty has said. And I also think that the document is laid out nicely in terms of having a bit more general information in the main document and more in the appendices. I'd say that we could do even more of that. And that the beginning could have a bit more in terms of strategies, which is kind of what Patty's getting at.

And then I have a specific comment with regards to social networks. Throughout the document there were terms, different terms used to describe social media. So we see social network, social media networks, social media research. And I think we can do a little bit of clarification there in terms of the terminology.

For example, some folks might look at social

network and think friends and family, you know, not social media. And but more importantly social media, if you were to look at page, I think it's 10 through 12 of the discussion document, in Table 3 where qualitative methods are mentioned, social network is listed as a qualitative method.

And I really don't see social network as a qualitative method, but more so as a source of data for which we can use to conduct qualitative and quantitative research. For example, you can use that data source to conduct interviews, focus groups, whether they're done online or done in person or in another form.

And also we conduct survey research, and you can also conduct historical content analysis of historical records using that data source. So I think that the discussion document can kind of reframe this a bit. And there's a nice definition in the glossary. I think that's a nice point to map to for that purpose.

DR. DASHIELL-AJE: All right. Nicki, do you have anything to add?

MS. BUSH: Just a little bit. So I agree with

most of what's been said. I do really appreciate that right now as it stands there's a lot of focus paid to paying attention to defining a question or objective for the study. Because everything really needs to fall from that. And sometimes we skip over that piece and right to, oh, we're doing qualitative, let's do this. Or we're doing quantitative, let's do this.

And it really is a reminder to step back and see what's really the objective of what we're trying to do, what's the question we're trying to answer. And I think that's a good guide for the level of detail we would want in a guidance. I'd hate for an unintended consequence of a regulatory guidance to be the stifling of innovation in the field, right?

So being prescriptive about all of the details doesn't allow us to move forward. And we heard earlier about keeping the guidance robust and relevant. And I think a good way to do that might be to focus around the strategic piece as Diane was saying. And defining the research question and some methods, but then leaving some of the nuts and bolts and the how to as reference, either to good practice or best practice

documents or the appendices that may be easier to update as the field moves forward, especially thinking about social media.

And also thinking about how the FDA are going to use the data. Not all patient-experience data are the same, and the end use of the data, as well as the research question would be helpful.

And I do appreciate the detail that's in the document now. I think linking some of the research questions and objectives to some of the methods that are also discussed would be helpful to see how they interact, and done in a way that can be helpful to all the stakeholders, so industry and patient advocates as well.

DR. DASHIELL-AJE: Thank you so much for those thoughtful points. Emily, do you have anything?

DR. FREEMAN: Yes, thank you. I cannot agree more with what Nicki has said. I think the research questions should drive the methodologies. And that's something that's not completely obvious from the guidance.

The other piece that I think is missing is,

and its reference to observational research, but ethnography is a great methodology that can really get at understanding the lived experience of the patient and really understanding the burden of disease and burden of treatment options that exist for patients as well. So it would be helpful to potentially include ethnography under the qualitative section.

And secondly, one of the key challenges that we may face as researchers, as scientific researchers is to differentiate ourselves with qualitative research and market research. So further distinguishing that in the guidance would be very helpful from a sponsor's perspective to clearly lay out the differences between qualitative health research and market research as well.

DR. DASHIELL-AJE: Thank you so much.

DR. FREEMAN: And finally, one final comment. I understand that patient preference is out of scope for this particular document. However, under the benefit risk section, one of the key features to understand from a patient perspective is the tradeoffs patients are going to make regarding benefits and risk.

And that is a method that could be used to gain the patient perspective in that section.

DR. DASHIELL-AJE: Okay. Thank you so much. And you're correct. Patient preference studies were out of scope for this particular guidance, but that's a great point. And if you have any additional recommendations for how you would like us to integrate it within the scope of this guidance, you can submit that to the public docket by December 14.

DR. FREEMAN: We are working on that.

DR. DASHIELL-AJE: Okay, perfect. All right. And, Dagmar, do you have any additional?

DR. AMTMANN: Sure. I like how the document is laid out. And I like the level of detail. In particular, I really like more detail in the appendices.

DR. DASHIELL-AJE: Mm-hmm.

DR. AMTMANN: What I would like to see is the, having the appendices be the leading document where in the main document you line out -- you outline the strategies, the, kind of the bigger picture approaches and methods, and you leave the more specific details

for the appendices where you can incorporate new technologies, new methodologies, new developments. So your strategies and approaches stay the same, but the specifics and the details that we're talking about may change more often.

DR. DASHIELL-AJE: Okay. Do you have any additional information to add regarding the quantitative methodology that we discussed?

DR. AMTMANN: In quantitative methodology I was, I was thinking about how the whole section on survey questions is at the item level. So I was just wanting to pose a question whether there is a place for a questionnaire or a multi-item instrument there. Because this is not at all touched upon or acknowledged.

And I can think of, you know, standardized ways or using multiple items to measure burden of disease or, you know, interference of treatment. So I don't know whether this is required that there, we would have an individual questions or if there is a place for something that would utilize a multi-item instrument.

And if there is a place for a multi-item instrument, that would be a way to increase reliability, which also is not listed in that section. And then it would require some guidance on how to do that, what the role of these multi-item instruments would be, what the scoring would be, just kind of treating it as what is in Guidance 3 with developing instruments rather than just specific questions.

There was -- I don't know if I can find it right now, but in one of the, one of the tables there was an example of items, which had mismatched the item question -- the question with the response options. And I don’t -- I'll look for it. But basically the question asked, how frequently -- yes, thank you. This is in the appendices.

So the question asks under verbal, how often have you had pain during the past week, and the responses are not at all, a little, quite a bit, and all the time. So if you're asking how often you would respect -- you would expect frequencies as response options, while the response options here are of intensity. So if we're saying how often, then I would

say, never, rarely, often, sometimes, or something along those lines.

If we want to know how much, then the response options would be not at all, a little, quite a bit, all the time. So it might be really interest -- really useful to users of the guidance to understand the preferred response options and what they actually measure, so that we don’t end up with these mismatched items, which really confuse patients.

DR. DASHIELL-AJE: Okay. That's great. Are there any additional comments from the panelists regarding the level of methodological detail that we've covered, whether it's appropriate or not?

MS. GETZ: I just wanted to add that it might be helpful to also better clarify like appropriate ways that sponsors can get involved with patient engagement sort of initiatives, and like to what extent they can be engaged in different conversations with patients to really extract that patient experience data.

For example, if we're talking about mixed method, mixed methodology, maybe multi-stakeholder kind of conversations and stuff like that, I don't think,

wouldn’t fall out of the scope of this document and might actually be very helpful.

Also, speaking to, I think it was Nicki's point, about there maybe being a little bit more clarification around different things. I know right now the document's set up with like disadvantages and advantages of different methods, but perhaps also including some sort of advice about when different things might be the most helpful could also go a long way.

DR. DASHIELL-AJE: Okay. All right. So we've had a lot of different perspectives on the level of methodological detail. Overall it seems that, you know, we've covered a lot in this discussion document. But there are a few areas that we could use some elaboration, specifically surrounding strategies that should be used, clarification on terminology linking the different methods to the types of questions that should be asked.

Adding some breadth to the qualitative methodology, for instance, adding some more detail about ethnographic research and its place, especially

within the regulatory context, differentiation between qualitative health research and market research, and how to tell sponsors or other stakeholders how to engage patients to gather this input, to be more prescriptive regarding that.

And then also with regard to the quantitative methodology, although we have sections giving examples of the types of survey questions that might be asked, it would be useful for the users to know what the preferred response options would be based on what you're trying to measure.

And then, of course, the end-use of the data, you know, making sure that we just link throughout what the usage would be for the different type of data that can be collected through the different methods. Did I cover that well?

(No audible response.)

DR. DASHIELL-AJE: Okay.

DR. TURNER-BOWKER: Ebony, I'd like to --

DR. DASHIELL-AJE: Oh, yes.

DR. TURNER-BOWKER: -- reiterate what Nova just said about the timing issue. And I think the more

time you spend up front really figuring out what the patient experience is, the better your output is going to be in the end.

DR. DASHIELL-AJE: Mm-hmm.

DR. TURNER-BOWKER: And so really do this early in the process and not wait till the last minute like I've seen it done before. I think that's a really important point.

DR. DASHIELL-AJE: Great point. All right. So now we're going to move onto our next set of questions. And this set of questions surrounds social media sources and whether or not we need a verification of patient identity, as well as the other types of data that can be useful. For instance, data from social networks, accelerometry, and room surveillance to elicit information from patients and stakeholders.

So with the first question, when -- that I want to pose to the panel is one might collecting information from social media sources, like collecting representative information on important symptoms, burdens, and related issues, meet the goals of Guidance 2. And how do we determine the adequacy of data from

social media sources. I'd like to start off with Patty.

MS. SPEARS: Yeah. So, so, I actually am a social media person. I'm on Twitter. And there's a lot of disease-related hashtags and conversations that go on. And I really listen to them, and I think it's really interesting to listen to how symptoms affect daily living you can really find on social media. And it's very nuanced.

But I think it would be very hard to quantify or rely on it as validated data, but you can tell from the patient's that post things like that how it's affecting their daily living. Whether they can ride a bike on Xeloda because their, the bottoms of their feet are sloughing off, things like that.

So you can find these nuances. But I also want to count to that in kind of a caution as well, that even me as an advocate on social media, I don't bare all on social media. It's out there forever.

And I really worry these days about some of the negativity on social media. And so you really have to be careful what you put out there for what you're

going to get back as well. So I think, you know, there's a lot to gain in nuance, but I think there's a cautionary tale there as well.

DR. DASHIELL-AJE: So in your opinion, Patty, how might social media be most useful in terms of informing what is important to patients? How can it be used within a practical context within a study?

MS. SPEARS: So I think it might open up some, I think, that daily living part. Because I actually read like a blog on somebody on Xeloda, and I found out a lot more from reading that blog than I would read in a side effect sheet, right?

DR. DASHIELL-AJE: Mm-hmm.

MS. SPEARS: So, you know, and I can read a quote for you from somebody on social media, a young woman going through lymphoma treatment at the end. And this just gives you the nuance of how they experience the side effects and what it does to them.

And she starts by saying, "My sweet baby didn’t want to -- want mommy today. I know I look really different this week. Large orange circles where my, where my eye sockets used to be. More hair loss,

slight weight loss. My body smells weirdly chemical. I know it's temporary, but this hurts more than everything combined."

And I think that's where you get it. Like, you know, that's where the essence of burden is for this disease. And that weirdly chemical thing is just so true. I don't think I've been bit by a mosquito since chemo. So I think that, you know, it, it's just something that you just don't think about.

DR. DASHIELL-AJE: Right.

MS. SPEARS: And so those nuances of the different treatments are just really, I think that's where you can get --

DR. DASHIELL-AJE: Okay. Great example.

MS. SPEARS: -- just an idea of what to ask in the end.

DR. DASHIELL-AJE: Right. Great example. Diane, do you have anything to add?

DR. TURNER-BOWKER: Yes. I think that the, you know, data that comes from the source can be hard to verify and subject people who come to these, these places on social network sources, there's a self-

selection, you know, bias, right.

And so I think one of the -- to me, one of the best uses of these data is to use it as a first source of information potentially, to learn as much as we might be able to initially about this target patient population, or the patient population more broadly. And to use that information to help drive the kind of information that might go into an interview guide, for example, or a discussion guide for a focus group. I've done some of that work before, and it's worked very nicely.

So I think it's that there's a lot, like you said, Patty, I think there's value to this data, but we sort of need to treat it properly. We have to think about what we're working with, think about how reliable or unreliable that data source might be, and then position it properly in our intended use, again, getting back to strategy.

DR. DASHIELL-AJE: Great. Emily?

DR. FREEMAN: Yeah. To follow up what Patty said, it's -- if I think about what kinds of patient experience data we can collect, one docket, in fact,

the first docket that Theresa showed was around benefit risk. And one of the ideal ways we could use this data is to look into a linguistic analysis of how patients describe their adverse events. And make things like risk management, so think about REMs. How can we make it more patient friendly?

Because patients do not communicate in languages like doctors do. They communicate in, in a way that's most meaningful and beneficial to them. And so I think we need to do a much better job of the way we communicate our adverse events and into our risk management plan.

So I think that’s a really good way because patients do go on Twitter. And they do talk about their symptoms and side effects.

The second way is to think about how can we triangulate social media data with other sources. So it could be a first pass of data. It also could be -- it could represent symptoms and burdens that a patient might not discuss in a setting that they're comfortable in. So it's really around social networks, who they feel comfortable talking to, things like this.

DR. DASHIELL-AJE: Great. Thank you. Dagmar, do you have anything to add?

DR. AMTMANN: Is it on?

DR. DASHIELL-AJE: It is on.

DR. AMTMANN: Okay. I've used social media to inform the language of the items for the instruments and found it very useful. Looking at how patients describe what words they use to, to put together questions that are meaningful to patients that aren't using medical lingo that patients can relate to is very important. And I, I find the social media to be very useful for that.

The other part that we've use social media for was to recruit for studies. And I think we're going to talk about those, those uses a little more in the next item.

DR. DASHIELL-AJE: Mm-hmm, yes, definitely. Anyone else have other things to add? Nicki?

MS. BUSH: Yeah. So, I, I think with the social media piece it's helpful also to distinguish between social media data as a source of data that we might think of as great literature that can be used,

and I agree with Emily, as far as triangulation.

At this point, probably not the sole data source. I don't want to put words in your mouth, but more supportive, but then -- and to distinguish that from a method around social media that might be used to perspectively collect data, whether that be concept elicitation, exploration. Because they really are quite separate.

And I know, I know this is sort of outside the scope, but the ethical considerations to around whether patients know they'll be included in any kind of research study without being consented into a research setting really has to come into play. And a lot will change in this area over the coming years. But that distinction we call sort of social listening of scouring for what's already there versus social media as a proactive way of collecting data with more intent.

DR. DASHIELL-AJE: Now that's a great point. So we talked about patient verification a lot. You all have mentioned it in your comments. So let's just go right into there. How important is patient verification if social media is the data collection

method used to elicit information from patients and other stakeholders? Let's start off with, let's see, Patty.

MS. SPEARS: So verification is very, very, very important. I actually started social media back when I was diagnosed in '99. There was a list server and message board at iVillage that had a lot of breast cancer patients on it. And it was very helpful going through treatment kind of as a support system. And I actually met quite a few women from that list. When I did a clinical trial in Seattle, I connected with a woman out there that was on the list and we had dinner, you know, every night I went, every time I went to Seattle.

But there was an imposter that actually came online, too. So, and they were called out because they were posting stuff that people knew were not normal to patients. And so finally they admitted they were impostering. Which why, why somebody would pretend they had cancer, we didn't know why, what the motivation was. And that was way back in the day.

And I think now, still, it still happens, and

I'm pretty sure it happens. But I also -- since our call discussing this and, and this meeting I actually had a new follower. Tom Cruise followed me. So I have to look it up. Mostly MDs, patient advocates, you know. I'm like oh my gosh. So I looked it up and, of course, 300 followers. So that's red flag. It's not Tom Cruise.

But, you know, I, I thought that was just so appropriate for this meeting. And we had talked about, you know, misrepresentation, which I think you really have to take seriously in this day and age.

DR. DASHIELL-AJE: Mm-hmm. Emily?

DR. FREEMAN: I, I cannot agree more with what Patty has said. I started using social media to understand patients' experiences back in 1993, started really understanding what women with endometriosis go through.

And one of the challenges that you face is that people, for whatever reason, may come on a user board and try and ask questions, or spread false information. That's the other challenge that we have. Especially on Facebook and Twitter, you can have these

little bots that like to spread misinformation. And that's really critical.

The other piece from a regulatory decision making perspective is that if we're going to use this data for patient experience data collection, will we have to verify the diagnosis of the patient, or will it be self-reported diagnosis, and what would be acceptable to the agency. That's a -- that would be a critical challenge.

But really it's a very rich source of data when used appropriately, but we really have to be careful about people with not so nice consequences coming on these chat boards.

DR. DASHIELL-AJE: Thank you so much. A quick administrative note. So apparently it's hard to hear in the back. So if you all could just really put your mouth into the mic. Ready? Go ahead practice in your Darth Vader voice. Hello. I'm just kidding. So if you could just make sure that your mouth is very close, then that would be helpful. Okay? And if you all still have trouble hearing, then just let us know, and we'll try to remedy that. Okay.

Nova, did you have anything else to add regarding patient verification or just the use of social media data?

MS. GETZ: Yeah. So kind of going off of what Emily was saying about, you know, verifying the patient's sort of experience, like whether they actually have the condition, and also -- what was that last bit about with patients kind of maybe -- oh, spreading false information, I think it's really, really important to verify that this actually, these experiences are actually what patients are experiencing, not just going off of social media.

But then taking what you learn on social media and social media and then perhaps having a focus group. And then including people from patient advocacy groups who can really speak to the broader patient community and then kind of verify whether or not what's heard is really true or if those are anomalies and, yeah.

DR. DASHIELL-AJE: Thank you. And, Diane, do you have anything to add around patient verification?

DR. TURNER-BOWKER: Well, I have a similar message that I shared before, which is -- and I don't

think it can be said enough, I guess. And it's a general statement. But I think the discussion document should make sure that we have some language up front about having awareness of the source of the data, the methods that are used to collect the data, you know, the scientific method. That that's applied in an approach to make sure that we feel comfortable with the data we have available to us, and help us determine then how to use that data.

I think if we're thinking -- it's kind of simple terms, but if we think about things that way, it can help us to be cautious about the way that we use data that might not be verified.

And when Emily was speaking I also thought about something else. You know, when a lot of folks are on social media, they're searching for information as well. They're experiencing, maybe, a new condition, or have a new diagnosis. They have, you know, symptoms that are unexplained. They're asking questions like, is this normal.

So I think -- and a lot of folks, remember, have multiple conditions. So there could be

experiences that people have and they talk an awful lot about, but might be driven by a coexisting condition. So those are the kind of things, I think, we have to think about, just following up on what Emily said as we kind of take this data, make sense of it, and think about what to do, you know, with it.

DR. DASHIELL-AJE: Great. So before we move on and talk about other data, I just wanted to quickly summarize some of the points that we talked about. Oh, Nicki, you ...

DR. AMTMANN: Yeah. I just wanted to add that I've been using social medial to recruit patients for focus groups and interviews and for studies. And from what I've seen, it's absolutely essential to verify a diagnosis.

There are people out there who just are professional patients. They will tell you they have every condition under the sun and try to participate more than once. It's been really eye opening. And unfortunately I had the same experience with the panel companies as well.

DR. DASHIELL-AJE: Mm-hmm.

DR. AMTMANN: So it's verify the diagnosis if you are going to use the information for regulatory decision making. I think it's essential that we know who is providing the information.

MS. BUSH: And just sort of building on that in a small point. Patients don’t always know their exact diagnosis either. When we set out to do a study, there's a reason we narrow down that patient population to mirror our target patient population. And I’ve never heard in everyday language a patient say, oh I have moderate to severe plaque psoriasis, right? I mean no one talks that way --

DR. DASHIELL-AJE: Exactly.

MS. BUSH: -- except for commercials. And so when we're -- there's -- so that introduces a lot of noise, then, into the data that you would get because you're getting this super-heterogeneous population in a wide range of severity when your target patient population might be very, very narrow. And so that's not going to give us an exact picture of what we would be looking for. MS. BUSH: And it makes it less efficient and, you know, perhaps.

DR. DASHIELL-AJE: Most definitely. Great point. Nova?

MS. GETZ: To that point, I think it's important to maybe provide guidance on how to ask patients what their diagnosed with. Because sometimes leaving things more open-ended can be helpful to make sure that they're providing a real candid response rather than, oh, they know the exclusion criteria. Or the inclusion criteria is the specific disease of this like, you know, these experiences and symptoms. So letting them just come to that on their own, I think. And providing methodology on that would be good.

DR. DASHIELL-AJE: That's a great point. Now, in terms of verification, Emily, you had mentioned the difference between patient verified and clinician verified. So can you speak on the importance of clinician verified versus patient or vice versa?

DR. FREEMAN: So what I meant by that was that if you're in a moderated chat room or a moderated website, such as PatientsLikeMe, for example, that the patient has actually received a diagnosis from a physician versus a patient trying to sort through what

their actual diagnosis might be.

DR. DASHIELL-AJE: Mm-hmm.

DR. FREEMAN: So that's what I meant by that is that a patient has received an actual diagnosis of, let's say, moderate to severe plaque psoriasis from their physician and not just thinking, I have severe itch, what does this mean to me. And I think that would be helpful, especially if the data's being considered for regulatory decision making.

DR. DASHIELL-AJE: Okay, perfect. So I'm going to recap responses to the first two questions because they're really linked together. So in terms of social media being a source of data that would meet the goals of eliciting information from patients, we heard from Patty that the data from social media is valuable. It's very nuanced. And you can use it in a systematic way to develop questionnaires.

But it's particularly useful when you're trying to get information about daily living, specifically with adverse events. You can use it to develop study materials. We know that social media can be a good source of data to help draft any of the study

materials, like interview guides, etcetera.

It can also be used to understand the language that's appropriate for developing questions in questionnaires. Emily had mentioned the usefulness of a linguistic analysis of social media data. So the terms and language surrounding side effects, etcetera, can be used to help support the benefit risk framework. There's also mention of triangulation of social media data with other sources of data and not just standalone.

And in terms of patient verification, it's very important. It seems like there's consensus that you need to confirm diagnosis. You need to confirm identity in order to have the data be useful, especially within the regulatory context.

So are there any additional points that I might have missed that you want to elaborate on before we move on to the next question?

(No audible response.)

DR. DASHIELL-AJE: Okay. So this final question is regarding -- on this slide, not final, final, but final here. What other data from social

networks or accelerometry, other technologies, room surveillance can be used to elicit or derive information about the patient experience in a feasible manner? So I'd like to start with Emily.

DR. FREEMAN: So to me I think this is probably one of the best examples of the excitement around patient experience data collection because you can really get at the lived experience of the patient. And with the onset of digital technologies, and digital technologies are advancing so rapidly, we could start to think about, if you think about clinical outcome assessments and specifically patient reported outcome measures, could this be validated, for example, with some of the wearable technologies.

So if a patient complains about itch, and we know that itch is a problem, what else in a patients' life is itch impacting? Could we start thinking about things like activities of daily living, sleep, work productivity, etcetera.

The next piece is, is it gets back to ethnography and looking at what that interaction between a clinician and patient or a patient and the

healthcare system looks like. And think about could we understand cultural variations in a patient's experience. Could we understand better the impact of the existing treatment options by collecting additional kinds of data from social networks, digital health?

Room surveillance I found to be an interesting one because I interpreted that as ethnography, but that got interpreted as, for example, if you're in a sleep room, or if you had sleep data, etcetera. So some of the language to me is interesting. As a social scientist I interpreted it one way. But I think in the guidances it means something else.

But I think the best opportunity for this kind of data, for regulatory decision making is really to focus on how can it tell the lived experience of the patient, and what would be the expectations of this kind of data if we were to submit it for regulatory decision making.

And I would go a step further. It may be a little out of the scope, but if we're collecting this data and it's obviously important to the patient, how then do we communicate something like wearable data or

social network data to patients so that it really gets at that lived experience that a patient's going through with their disease.

DR. DASHIELL-AJE: Great points. And I wanted to comment on the nomenclature, so room surveillance and what that really means. You know, the relevance of room surveillance in terms of digital monitoring centers, that’s applicable.

But then also as you mentioned, we do want to make sure that everyone knows that we're open to observational methods as well, video observation, ethnographic methodologies, those types of things. So it includes both in that term. Maybe we could clarify that better.

DR. FREEMAN: That would be helpful. And I think, you know, just being flexible with any approach that you can come up with, as long as it's rigorous and transparent in the research methodologies --

DR. DASHIELL-AJE: Mm-hmm.

DR. FREEMAN: -- would be a helpful addition to the guidance.

DR. DASHIELL-AJE: Great. Wonderful. Dagmar,

do you have anything to add?

DR. AMTMANN: Sure. I think this is the area where it's really important to not box ourselves into the currently existing technology. So leaving the door open to the technologies coming down the pike and which may be today are not acceptable source of information, but will likely be tomorrow. There are a lot of patient-generated digital data devices out there. And there are -- you know, starting with Fitbits and apps and lots of data.

So getting some broad, broad-brush guidance on what data are acceptable for regulatory decision making, how do you know? How do you support the use of those data? What makes those data be okay to be used in that process, providing guidance in that aspect and being -- providing the general strategies rather than talking about the specific technologies about which we know now. And then maybe building on the appendices where we can add to more information about the new technologies coming on.

DR. DASHIELL-AJE: That’s a great point.

MS. BUSH: Yeah. I think that transparency

piece is key. And what would be helpful in a guidance is not necessarily detailed around the type of data, but what FDA would expect to see as far as evidence that it's reliable and meaningful and interpretable.

So, again, going back to what's the research question and can you demonstrate clearly why this source of data collection or this source of data is applicable and makes sense.

You know, data are like chocolate and wine, right? You want quality over quantity. And when you get a lot of data from accelerometry, but it's not going to be meaningful or, or good if we don't base it on a research question and collect it in a way that makes sense and in a way that we can communicate it.

So I couldn't agree with Dagmar more around that transparency piece. And I think in a guidance that's what is really useful is what does transparency look like as opposed to what, what types of data are acceptable. So that we know coming to the table these are the types of evidence that we should be providing proactively.

DR. DASHIELL-AJE: Great points. Any other --

any other panelists?

DR. FREEMAN: Yeah, to follow up with what Nicki and Dagmar were saying, that would be critical, critical to include in the guidances is what would maybe be the evidentiary standards that we would need to meet to have this data accepted.

DR. DASHIELL-AJE: Okay.

DR. TURNER-BOWKER: Yes. And I think we need to keep in mind as well that even though some of these methods may be exciting to use, for some patients they may be burdensome in some ways. So I think we have to be mindful of the fact that for some therapeutic areas this might be the only way to get important data on a patient population. But in other patient populations there could be a variety of other methods that might be used just as well and not invasive or bothersome or burdensome to patients.

If you think about, you know, my elderly parents wearing a device on a regular basis for three weeks or whatever, that might be very concerning to them. They might feel that’s invading their life, their daily ritual.

So I think we do have to keep that in mind as well and be -- you know, the question is, feasible manner. You know, we have to have some practicality and be feasible, I think, in these approaches.

DR. DASHIELL-AJE: Great points.

MS. GETZ: I just kind of wanted to add to that about burdensomeness to the patients. I think, you know, it's also really important to test whether the way that you're collecting patient data is something comfortable for the patient to use. And to that end, I think, you know, doing more user testing and advising user testing for apps and all the new technology that's coming out is really critical.

I mean, we did some user testing for an app at one point. And one lady was saying it was really hard to push through the blister packs because she had arthritis, and that was really something that we wouldn’t have learned otherwise if we hadn’t included the patient's in the development of the, the thing itself.

DR. DASHIELL-AJE: That’s a great point.

MS. SPEARS: Yeah. I think that's really

important. And when I read this at the beginning, I felt that this was a very invasive way of getting data from patients, and so it would have to be treated that way as far as transparency and ethics and everything else. Especially the room surveillance.

And like you say, every app is like -- has to be super tested because they're not going to be patients like me. They're going to be patients like my mom. And so I always say, would my mom be able to do it. Would my friends in the support group that I did. I mean most of them in breast cancer didn't know if they were ER positive or HER2 positive.

I mean that's what we're dealing with when you go out into the community. So, you know, how can that language be done and the transparency and the ethics is really important with these technologies.

DR. DASHIELL-AJE: Wonderful points. So some common things that we're, that we're seeing with this, the usefulness of other types of data, so social networks, accelerometry, room surveillance, is that they can be useful in terms of capturing the lived experience outside of clinic.

And we need to be careful not to box ourselves into the existing technologies and have a mechanism for, through appendices or some other source of live, living documents to be able to speak to current technology, but without having to focus on that within the, the guidance document.

But broader, you all are saying that it would be helpful for us to provide some general strategies as well as what is acceptable within the regulatory context for this type of data, how it will be used, and what's acceptable to support the use of this type of data within the study context.

And then another point that was brought up that’s very important is patient burden. So as you select the type of method that you're going to use, you want to make sure that you're keeping in mind how burdensome it might be to patients to use that type of technology or how burdensome it might be to patients to engage in that type of data collection exercise. Because that could potentially impact the quality of the data that you, that you gather.

DR. DASHIELL-AJE: Okay.

DR. AMTMANN: Can I make one more point?

DR. DASHIELL-AJE: Sure.

DR. AMTMANN: I'm not sure if this belongs in the guidance, but if you're using both digital data, like accelerometry or any other type of data, in addition to patient-reported outcomes, how do you, how do you integrate the two, 'cause they are likely to provide different information.

If you ask somebody how active they are, and if you measure the number of steps or distance traveled, you're probably getting slightly different information.

DR. DASHIELL-AJE: Mm-hmm.

DR. AMTMANN: I don't know to what degree you can actually address that in the, in the guidance, but this is something that will be interesting to negotiate.

DR. DASHIELL-AJE: And we might not be able to cover that in detail within the scope of this guidance, but we do have the future guidances that could potentially address that. Okay. So now let's move on to -- these are our last three questions of this

session.

So I'd like to pose a question to the panel about what should be considered when estimating a reasonable feasible sample size to assure representativeness, whether it be qualitative or quantitative studies. So I'd like to first start with Diane.

DR. TURNER-BOWKER: Sure. So I think that the discussion document needs to make some specific points regarding sample size, representativeness, and saturation when we're thinking about qualitative data collection. And if you notice on the screen here, the question that's written is what constitutes a reasonable feasible sample size to assure representativeness. It's, it's not how to sample to achieve saturation.

And I point this out because we can achieve saturation in a sample that is not fully representative of the target patient population. And so we just need to be a bit careful of this and point it out in the discussion document. And also I would note that the discussion document could highlight some resources that

are available to help readers to know how to plan their sample size.

For example, I recently published an article with my colleagues at Adelphi Values, Alan Shields and Roger Lamoureux and others. And it's a very simple article. It's very short, but it provides some evidence-based guidance in the a priori estimation of sample size for concept elicitation interview studies in a drug development context.

And so we, you know, while we hope this is a useful -- we, we published it 'cause we needed it. Everybody, we felt it was a useful tool for us and hopefully for others. But it also still has its limitations, you know.

It's a source that can help people to know maybe where, where there's a good starting point when you have a homogenous target patient population. But when you have a lot of heterogeneity in your target patient population, then you have to make some adjustments to think about the subgroups and kind of build from there.

And unfortunately I don't think there are too

many -- there's not really hard and fast rules for how to do that. And so we have to think about the approach that we take to representativeness and saturation, I think, in parallel.

And I do think that there are some methods to do that. Does it mean that for a heterogenous patient population we always need to sample extensively so that we would pursue a saturation analysis for every subgroup that we have represented? Not necessarily.

I think there are some other approaches that can be taken. And maybe that's something that we would talk about later this afternoon, because I know that's a methodological conversation to be had. But I do think this is important.

And I'm not sure, to be honest with you, if there are other resources out there for estimating sample size for a focus group in this context. And maybe others can comment on that.

DR. DASHIELL-AJE: Okay. Dagmar?

DR. AMTMANN: Yeah. I would like to see a little more in the guidance on how to decide on the strategies for the most important facets or

characteristics of the patients to be included in qualitative research for the purposes of regulatory decision making. We're talking about representativeness, but I have yet to see any qualitative study that was fully representative of the patient population.

And I would much rather see the language in the guidance to talk about adequate or appropriate or, you know, sufficient degree of representativeness. People come to me all the time and say, how many people do we need for, you know, focus groups or cognitive interviews.

It -- and they are treating it as if we were testing for statistical significance. It is really important to understand that the sample size in qualitative research has a completely different purpose than the sample size in quantitative research. And the guidance observes this, that sample size for qualitative research is intended to prevent discovery failure. In other words, not include a voice or perspective that is very important in that context.

It has nothing to do with statistical

significance. As a result, we don't have very good methods for coming up with how to determine the adequate sample size that would assure that whether adequate representativeness.

So I think giving some guidelines saying start with something, like start with a minimum of ten focus groups, or start with a minimum of ten people per item would be really useful. And following that with some recommendations for how you know when you've had enough. How you know that every important perspective of your patient population has been representative, represented in your qualitative research.

DR. DASHIELL-AJE: Okay. That's a great point. So in the interest of time, I'm going to move on to question six, unless there are some burning comments that you all also have regarding this before my summary. Anything burning? Yes, Patty?

MS. SPEARS: So I think it's really important here, you know, we've gone back to strategy a lot. Always keep in mind what your research question is to kind of define what that population is. Because if you make it too broad, you're really not going to be

specific enough and relevant for the population that you're looking at.

DR. DASHIELL-AJE: Mm-hmm.

MS. SPEARS: But within the population that you're looking at you need to be really broad in that context, right? So, you know, I think that, you know, you try to do too much, you're going to get really diluted information. Because just being in the breast cancer world, it is very different to have primary breast cancer or advanced breast cancer.

And so if you're doing a study on advanced breast cancer, just ask advanced breast cancer questions and get that information because that’s very different. Their harms benefit ratio is very different. They're willing to take on a lot of harms in their treatments because the alternative is death.

Whereas, in primary breast cancer, you live a lot longer. The, the primary is cure. So you don’t want those long-term side effects. So that's very different. So when you don’t just do breast cancer focus groups, you do specific ones.

And so for every disease I think there's a

spectrum. And so depending on what you're going after, really focus on that specific population. That's where I would say.

DR. DASHIELL-AJE: That's a great point.

MS. BUSH: I think Guidance 1 did provide some very general backdrop for the sampling and the sample size. This is an area where I think that transparency around evidentiary expectations is also very key. Because just from a pragmatic point of view, you do, you complete a study, come to the agency, and then it's, well, we'd like to see 20 more patients sort of under this or who -- and so then it's back and forth.

And while qualitative research is an integrative process, it's helpful to know at the beginning what that framework is for being reviewed. And I know we'll talk about time points and collaboration with FDA and agreement.

But that early on, just the words representativeness or sample size could mean a lot of different things to a lot of different people. And so it would be helpful to know what you -- what the agency expects to see as far as what good looks like.

DR. DASHIELL-AJE: Okay. So in terms of being able to determine what sample size we need for representativeness, it looks like I'm hearing you have to consider sample size, representation, saturation, all those types of things, but understanding that representativeness is not how to sample to achieve saturation.

So keeping that in mind, we heard that, you know, there should be a process that’s outlined in the guidance that would be useful to determine what facets of the patient population would be most useful to have targets for. And have some type of process to derive the targeted dimensions. If that's outlined, that would be helpful to the user.

And then a general thing that we're seeing across the different questions that we've been answering today is having some type of evidentiary expectations that are outlined, although it doesn’t have to be super pragmatic, at least being a little bit more detailed would be helpful to the audience. Okay.

So question six, we sort of covered content in question one. So I just want to focus on structure.

Briefly from the panelists, what document structure would be most useful for this guidance? Do you think that the current layout in the structure of the guidance is appropriate, or is there another way that you feel would be more useful to the user? And I will start off with Emily.

DR. FREEMAN: So I think the current structure is useful. One addition I would recommend is to talk through some actual case studies and examples of how these various methods. Because they are, they will be new to people. How they would be used in a regulatory decision making decision. So I think case examples would be very helpful.

DR. DASHIELL-AJE: Okay. And, Nova, did you have any additions?

MS. GETZ: I think the table formats are really helpful. I did notice at one part something started going into disadvantages and advantages, but it wasn't in a table format. So just, I guess, maintaining consistency would be helpful. Yeah.

DR. DASHIELL-AJE: Okay. Anything else? Patty?

MS. SPEARS: Yes, I like the format. I love the tables as well because that's where I could really digest the information without getting bogged down in the details. And more figures like that would be really good, and maybe the strategy and kind of how you intersect some of these things as well.

DR. DASHIELL-AJE: Okay.

MS. SPEARS: I didn't see a lot of that.

DR. DASHIELL-AJE: Diane?

DR. TURNER-BOWKER: Yeah. And I would just add to that, to what Emily was saying, actually, because that was the point that I had about case studies. And when we talk about having a strategy, what does that mean? You can exemplify that in a case study. And in the case study examples it would be nice to have an example where a single data source and method yield representative information where multiple data sources and multiple methods yield representative information.

And I think just doing that, just having those case examples in the discussion document up front, it's good for the FDA as well. Because I think without

saying it overtly, you are saying you're open to a variety of different approaches that may work to achieve the goal with regards to the research objective.

So I think it says something by outlining that kind of thing up front and would kind of frame the discussion docket. I think the rest of it is very nicely laid out, as we've been talking about earlier.

MS. GETZ: Oh, an additional point I wanted to make was that maybe sprinkling in a bit more language about there being flexibility to do other things would be helpful. Also, I feel like I had one more thing, but ...

DR. DASHIELL-AJE: Well, thank you so much.

MS. BUSH: At the risk of sounding negative, I'll say what would not be useful for the guidance is to, to look like a checkbox, right. Do I have to hit every single one of these, right, in a dossier or in a briefing document. And to really, you know, to your point to really stress that flexibility and to show if you're trying to talk about representativeness, if you want to talk about sample size, if you want to talk

about concept elicitation.

These are the elements we are going to be looking for. And this is the kind of evidence we're going to be looking for is helpful as opposed to do this method, do this thing, do this. And then some teams, you know, might look at that and say, we have to do it all, or we're going at risk. And then it becomes a much more difficult and laborious conversation. Yeah.

DR. DASHIELL-AJE: Okay. Now in the interest of time, so we can open up for audience Q and A, I'm just going to do a brief summary of this, and then I'm going to ask two of our panelists to address the last question.

So it sounds like in terms of structure, you know, tables, figures, those things are welcomed, and making sure that we present things consistently throughout the document, that would be helpful. But a big point about case studies and examples, as you know with the Guidance 1 document we had some case studies and examples.

Feel free, since you all are experts, to

provide some case studies and examples. You can draft them. And anyone in the audience and on the phone as well, you can draft them and submit them to the public docket. 'Cause we are more than happy to consider any real world experience that you have. 'Cause you all are doing the work.

So if you could just think about it and potentially give us the fuel to be able to provide those examples to you. All right.

The last and final question before audience Q and A is one of the most important time points when FDA input could be maximally helpful. So I'll start off with Emily.

DR. FREEMAN: So this is a question that the bio Patient-Focused Drug Development Task Force has put a considerable amount of time into addressing. And what I would like to -- there's a couple of points I want to make.

Is number one, patient experience data should be thought about as something across the entire product life cycle. So from drug discovery through postmarketing, it's not just a one point in time, you

measure patient experience data, but it's this continuum that you think about.

And we also hear very often from the FDA early, meet early and often. And so one of the ways we've thought about it through the taskforce is to think about integrating into existing meetings. So think about a type C meeting, end of phase meeting, type B meetings, etcetera.

But I think until patient experience data gets more familiar and the guidances are finished, it's critical to get feedback very early on, on the sampling strategy, the protocol design, and the way in which the data -- we want to communicate the data will be critical from a regulatory decision making perspective from the agency.

So, so that’s -- and also written agreement regarding the protocol and the design methods and things like that will be critical.

DR. DASHIELL-AJE: Thank you. Nicki, do you have anything unique to add?

MS. BUSH: Sidebar. We'll see. So I -- the transparency early enough it makes a lot of sense. And

I think there are ways to communicate with FDA. What would be helpful to see is an expectation at type C and expectation at set meeting times that there should be a discussion around patient experience data. Because it's not always easy to get real estate early on when you have so many other things to discuss in a drug development program.

So if we can get a push and a pull, I think in three years we'll have a lot more examples of what good looks like early and what, what the content of those conversations are. So I don't know if that’s unique, but that's what I have.

DR. DASHIELL-AJE: That's wonderful. Wonderful. Thank you, all, so much for your insights. I'm now going to open the floor to audience Q and A. We have about 11 minutes left. So if you all could -- 18 minutes, oh 18 minutes. I am early. Oh, yay, wonderful. I'm looking at this timer. Okay. Well, we have 18 minutes, which is great. So if you could line up -- are we doing the passing the mic, or are we doing the lining up in the middle? Mic's in the middle, right?

Okay. So if you have a burning question that you would like to pose to the panelists, then please line up, and I will call you in order. If there are any questions specific to the agency, we ask that you rephrase them as a comment and, for our consideration, and then also you can submit it to the docket because we're here in listening mode at this time, but we are more than happy to consider your comment or question via the docket, which closes on December 14.

All right. So anyone? And you can pose your questions directly to the panelists by name.

MS. DEAL: Hello.

DR. DASHIELL-AJE: Can you hear? Is it on?

MS. DEAL: Linda Deal, Pfizer.

DR. DASHIELL-AJE: Can you go a little closer to ...

MS. DEAL: Linda Deal, Pfizer.

DR. DASHIELL-AJE: Perfect.

MS. DEAL: I'd like to make a comment. I appreciate the conversation around technology. I think it's extremely important that we not lose sight that this is patient-focused drug development. And while I

agree with the panelists that technology offers us great potential to augment and compensate for where humans may not be able to self-report or observe a concept of interest or relevance, I think it's really important. And I think we can, in the request for evidentiary standards from the agency, I think the agency can consider things that we already have heard from you.

For example, symptoms, how a patient feels. Only a human, the patient, themselves, can tell you that. A device is not able to do that. Things around functioning, difficulty with performing something, ability, level of interference, those have to be reported by, or qualified by a human being.

And so I just want to emphasize that while we're all excited about new technologies, we cannot lose sight of the whole purpose of PFDD that patients are the expert. And it should be compensatory to humanistic outcomes.

DR. DASHIELL-AJE: Great point. Next.

MS. KHAN: Hi. I'm Seemi Khan. I'm from Mitsubishi Tanabe. I'm a nephrologist by profession.

I'm not an expert on PROs, but I have worked with it because some of our dialysis patients all the time have that.

So my question is regarding the representative sample you have it up there, a question to the panel and a comment. Because what I have observed as a physician that it very much also is dependent on the venue as well. When the patients are in a setup with a lot of healthcare providers, their perception or their answers to their health is slightly maybe more organized than in a patient focus group, and then let alone on the social media.

So what I have seen over the evolution over the last couple of years, what's been happening more and more social groups, and whether it's a pharma or somebody else, a lot of people in the room are non-medical or are non-healthcare provider. So any word or any sentence coming out of patients' mouth is very emotional to them.

And the perception and how they perceive and convey it further, it changes because some of these patient groups happen in the companies in pharma, and I

was at AbbVie before. When you come back and people are just trying to debrief, you would be surprised how the perceptions are different for different people and their level of interactions previous with the patient.

And let alone now, a lot of companies, like in independent organizations have been coming to existence who are doing these patient-focused survey. And one of the panelists said that, and rightly said there are just like the key opinion leaders are professional, now you are generating a patient, professional patients.

So I was just wondering that any advice on that.

DR. DASHIELL-AJE: Could you rephrase the question a little bit so that they ...

MS. KHAN: So my question is, in your experience, have you noticed, or does it mean anything that the venue and the existence of other people in the room have an impact on the organization of the question by the -- or the answer by the patient in themselves.

DR. DASHIELL-AJE: Thank you. Emily?

DR. FREEMAN: So, yes. The answer's obviously yes. And so I think that’s one of the strengths of the

method of ethnography. Because it acknowledges these power dynamics that exist amongst patient organizations, amongst the actual setting, the research setting that happens.

In fact, if you look at some of the patient ad boards or patient groups that are currently being studied, I would argue that it's only about 5 percent of the actual patient populations that actually live with the disease. Because they have been vocal, and have they actually been able to stand up and talk for themselves.

So I think that's critical. So I think that's one of the strengths that ethnography can bring to this discussion is setting the context for collecting the data, how it was collected, under what circumstances, and who was in the room.

MS. KHAN: So just a quick comment. I mean as a physician, I must say that I'm very biased because in the different settings I have seen that. But I think as a collective, as a community, we should think about just organizing in a routine clinical practice as well, I mean, to just give these question and to collect as

much as data as we can. And then also have it another setting and to at some point just do, have a comparison.

MS. SPEARS: So I'd like to say, so that's why I kind of supported the mixed method type of thing, because I think you are going to get different information. Whether you ask in a group setting, sometimes somebody will mention something that somebody didn't think of and say, "Oh, yes, I experienced that, too." But it's a group dynamic that you need to control.

And you can have your thought leaders at the top and your organizations and things like that. But you know, that's just a very limited, like you said, it's very limited what they tell you. But you can drill down and then go out to a broader really, really -- I think you always have to go to a broad patient population.

But by the time you get out there, you need to ask the questions in ways people understand them and can do them. But in a practice setting would be idea, because then you would be getting, you know, the

patients, like every patient that comes in, which would be ideal setting. But before you get there, you'd really need to know what to ask and what to get.

But taking it all together, I think you inform better than just one or the other. That's why I don't think one is going to actually do the trick. I think it's going to be a mixed method.

DR. DASHIELL-AJE: Okay.

MS. BRAVERMAN: Thank you. This is Julia Braverman from Celgene. I have actually two questions. The first one is several times during this, today's discussion you mentioned data that would be acceptable for decision making for agency. May you comment on how exactly you use qualitative data and how it can support the decision process?

And my second question, also related to qualitative research, again, several times you mentioned exit interviews that are interviews that are done like exit, after clinical trials. But in the modern treatment sometimes it's -- there's no definitive end of treatment. For example, when we're talking about, you know, one shot CARTI treatment or

long-term maintenance treatment. So sometimes it looks like it makes sense to conduct interviews, qualitative research during the clinical trial.

The question is, does it pose any additional challenges from regulator perspective, how you'd perceive this data, and if it makes sense to add it in a guidance special place for this? Thank you.

DR. DASHIELL-AJE: Thank you. So I want the panelists to speak from the perspective of a, of a user, you know, from your industries perspective on what feedback you've received from the agency. Because, as I mentioned, the agency is in listening mode right now. So we won't be able to answer exactly how qualitative is going to be used.

But if you guys can speak from your experience how qualitative research can be used to support regulatory decision making for your submissions or the research that you do, as well as how exit interviews or exit surveys and the timing of them could pose -- could be useful, and then potential challenges that you encounter. Nova?

MS. GETZ: I think at one point you asked how

we use qualitative data. At CISCRP we do a lot of patient advisory board meetings where we have, you know, a group of patients talk about usually the protocol for a clinical trial. And those are changes that the companies who are conducting the trial can usually go back and make before, including patients.

So I mean sometimes it can be like turnaround where it's relatively quick, and you are including the patient voice consistently through your work. That's one way. That's my experience personally.

DR. DASHIELL-AJE: Diane?

DR. TURNER-BOWKER: Yes. And in -- I work in a company that develops and evaluates patient-reported outcome measures for use in clinical trials, and so in that case we use data that comes from patients, from experts in the literature, to help us to identify the key signs, symptoms, and impacts of a condition to help us to develop those measures.

MS. BUSH: So in addition, I mean, to all of those things, demonstration of unmet treatment need, unmet medical need, internal decision making can be helpful, triangulating or supporting data that we get

from other sources, the existing data or literature. And then exit interviews are, you know, they're logistical issues. I don't think it needs to be at the exit, right.

So I mean at different time points it makes sense to -- depending on the question you're trying to answer. Is it very procedural? What does the patient experience in a clinical trial, and how can we make clinical trials better? Or is it to interpret any of the endpoints in a more qualitative way, meaningful improvement, or change in symptoms. So I think, again, it depends on the research question, yeah.

DR. DASHIELL-AJE: All right. Thank you. Next?

MS. HALLING: Katarina Halling from AstraZeneca. Thank you, very much for a great discussion. I have a comment sparkling off of, of Linda's comment related to new technologies and patient-focused drug development. It seems to me like we're coming a pretty long way now. And with this new push from the guidance that we're discussing here now, we will explore patients' experience even more

consistently than we've done previously, very early on.

And it seems to me we also have an opportunity there to start talking to patients about how they would like to communicate with us and how they would like to have information from us. So I think that's a comment because FDA is in listening mode.

But, but the question is to the panel, do you have any -- have you started to more in-depth understand how patients in different patient populations would like to be monitored in a room or would like to, to use apps and, and so on.

Because I think with PRO instruments we started off developing instruments, and then we tested if patients were okay with them. I'd like to see if we can do it the other way around and get, you know, together identify what makes most sense to, to all of us.

MS. GETZ: So in our work so far, I mean, we've -- across like all the different patient advisory boards we've had, we always hear that patients really want to be involved from the beginning when a research question is being developed. Because they want to

ensure that it's really something that’s meaningful to them and their population.

So, yeah, I think that would land pretty well with patients.

DR. DASHIELL-AJE: Okay. Any other ...

MS. HALLING: I just want to give you an example from my experience. We -- in like kind of standard methodology in -- when we develop measures, we get a lot of feedback from patients. When we do not typically get feedback is at the end.

So we've started getting patients involved at the end where we say, okay, here is what we're, we've developed here, the results of our analyses. Does this make sense to you? Does this look okay?

We've also developed a guidance to clinicians on how to interpret the scores. In particular, for things where patients feel the results could be stigmatizing. So in -- from my experience being catastrophizing, patients have a very negative reaction to, to that construct.

So we put together a guidance to clinicians on what that means and how not to interpret the score in a

way that stigmatizes the patient. And then we went back to the patients and we say, okay, does this communicate what you want communicated? And have had very productive and very useful communication at the end of the study rather than just at the beginning of the study.

MS. GETZ: To piggyback off of that, I think followup is so critical to -- like going back to the patient and seeing if it actually is what they wanted to have happen. And really including them as a partner throughout the journey is critical.

DR. DASHIELL-AJE: Okay. So ...

MS. SPEARS: Yeah. And I like the idea of, you know, having a patient advisory panel that's engaged all along. So when you have ideas you can bring it in front of them, and they're already a little bit knowledgeable, and they can give you your feedback. When you go cold to someone, it's usually at the end, like how is this type of thing, and you're going for that patient that's never seen it before and what do they do with it. And those are two different things.

And so you really need two different patient

populations to get that input from.

DR. DASHIELL-AJE: All right. So last question. Gentleman?

MR. FELDMAN: Hi, I'm David Feldman at the National Kidney Foundation. I'd like to comment on the brief discussion that we heard about benefit and risk. I think that guidance on this topic would be extremely helpful and important. I think that, especially with specific questions on, you know, how to ask these -- get information on this topic. Because I don't think that this is so clearcut, to get information from patients.

And I say this because I remember at one of our ELPFDD meetings a mother of a pediatric patient said that she really doesn't want to have to answer this type of question. And she hopes very much that her son would never have to answer a question like that.

So, number one, I'd like to see guidance on this with specific questions. And I'd also really love to hear your comments, the panel, on this. Thank you.

DR. DASHIELL-AJE: One more minute. Anyone

want to take a stab at that?

DR. FREEMAN: So that was my comments in the guidance is that you have a benefit risk section in the current methods to guidance, right? But it's not as simple as a benefit risk. It's these tradeoffs that patients have to make because the severity of their disease, their symptoms that are most problematic, etcetera. And I think that's the critical component to benefit risk.

And also, if you think about the risk management of the disease itself, is it something that a patient can manage. And you need to get that information from the patient and the caregivers themselves and from the healthcare system.

So I think that you raise it in the guidance, but you need more explicit information on that tradeoffs that patients have to make regarding their therapies and their symptoms, etcetera.

MS. SPEARS: And I tend to use language matters. I think it's really harms and benefits, not risk and benefits. It's risk of benefit or risk of harms. You have risks both ways. But, you know,

probabilities both ways, but, you know, risk seems to mean it's not necessarily going to happen or not. Maybe it might happen, but I prefer ...

DR. FREEMAN: To play off that, Patty, one term that I have seen used in this space is uncertainty.

MS. SPEARS: Yes.

DR. FREEMAN: And uncertainty is ultimately the -- 'cause you're uncertain if a benefit or a risk is going to happen. And it's something that, because benefit risk makes it seem like it's going to happen, versus you're uncertain what could potentially happen. So I know in the benefit risk discussion, kind of that world, benefit, risk, and uncertainty was a category that the FDA used back in, I think, 2014 at a workshop. But that's another potential language that we could think about.

DR. DASHIELL-AJE: Wonderful. Thank you, all, so much. I thank our panelists for their wonderful contributions to the discussion. If there are any remaining comments that you think about that you would like us to know about, you feel free to submit via the

docket by December 14.

And same thing with the audience. Thank you so much for your participation in this panel session. We're going to now enter a break for about 15 minutes. So if you all can return here in your seats by 11:15, see you then.

(Applause.)

DR. DANIELS: We're a little bit behind. So I don’t want to break into your guys' lunch. So if you guys can make your way to your seats, that would be great.

So I'm hoping everyone is enjoying the workshop so far. We've heard some great discussion in the first panel regarding the different types of methods to elicit what's important to patients, to capture the patient experience, specifically the burden of disease, as well as treatment and benefits and risks of treatment in their disease management.

And so we're going to shift gears just a tad bit, just to move on how to operationalize a study after you select that particular research method in order to generate robust data on patient experience in

a feasible manner. The focus will be on best practices or model of best practice to use or operationalize the method of interest.

And Ebony did a fantastic job setting up the stage with a brief overview of Guidance 2. So I have a hard act to follow, I must say. But it also makes my life easier, just to move right on into the panel discussion. However, I will flash up one slide. I promise, just one slide, just to orient us on the topic of today's panel session.

And as Ebony noted, in addition to the methods and the common pitfalls, that Guidance 2 focuses on operationalization. What is meant by operationalization includes how to sort of design and implement those studies, as well as the associated relevant study materials.

And so this slide in a nutshell actually shows just a small blip of some of the numerous tasks that people will be involved with when conducting a study. And what we want to target in on today is whether the Guidance 2 discussion document sufficiently presents information about best practices for operationalizing a

study that is assessing patient experience in a manner that is rigorous, but reasonably can be implemented.

And so I must say we have a great set of panelists today's session which brings a range of viewpoints that I am interested to hear, and I'm sure the audience is interested to hear as well. We have prospectus from a patient organization, industry, contract research organizations and academia.

And at this time I'm going to have them introduce themselves. And I'm going to start from my left side, and we'll move right down the line. And if you can just speak directly into the mic, 'cause I know we have some hard hearing in the back, and also we have 300 individuals on the web that would love to hear your guys' voice.

MS. ARNEDO: I'm Vanessa Arnedo, a Director of Research Partnerships at the Michael J. Fox Foundation for Parkinson's Research.

DR. BENNETT: I'm Antonia Bennett at the University of North Carolina, and I also direct our Patient-Reported Outcomes Core.

DR. BYROM: Hi, I'm Bill Byrom from CRF

Bracket. We're a vendor of patient-reported outcome solutions in clinical trials.

MS. EREMENCO: Hello, I'm Sonya Eremenco, Associate Director of the Patient-Reported Outcome Consortium at the Critical Path Institute.

MS. STUSSMAN: Hi, I'm Barbara Stussman. I work at the National Institutes of Health. Primarily my experience is in qualitative research, and I wanted to point out that I do not have any regulatory experience. So I'm just here with my experience at NIH.

DR. SYMONDS: Hi, I'm Tara Symonds from Clinical Outcomes Solutions, Strategic Lead of Clinical Outcomes Assessments.

DR. DANIELS: And we did have one more panelist, David Reasner, but unfortunately he's had some travel issues. So he will not be able to make it for this session. And so we're sad, but we're hoping that we can sort of maybe make up for some of his input with the other panelists as well.

And so let's begin with the first discussion question, the objective, again, is to discuss best

practices. I'm not going to belabor that. But the first question is what level of detail do you think is appropriate for this guidance with regard to how to operationalize studies using different types of methods? And are there any other best practices that should be included in the document?

And since this is all about collecting patient experience, I think it would be only fair to left Vanessa start to get what input she's heard from patients with regard to participating in different types of studies and what level of information would be appropriate for patient organizations and to operationalize studies to collect patient experience data.

MS. ARNEDO: Sure. So in terms of best practices, I think it's important to be explicit. But I think we've touched on in previous discussions today the variability in patient experience between patients. But I think what is also very important to incorporate is the acknowledgement of the patient journey throughout the course of disease. And that the patient experience, even at the individual level, is variable

over time and can fluctuate, depending on where in the patient journey that a patient is.

And so I think this really speaks to some of the best practices of incorporating this idea of patient experience and collecting data and engaging the patient community early and often. Because without being able to do this early and often I think it's, it's easy to not be mindful of incorporating the patient journey.

So I do think it would be very helpful to be explicit in terms of the best practices for how to actually operationalize this.

DR. DANIELS: Mm-hmm. Thank you. And so I'm going to move on to the specific methods in terms of operationalization, beginning with qualitative methods. And so, Tara, what are your thoughts on the level of detail needed for operationalization of qualitative studies?

DR. SYMONDS: Yeah. So I'm, I'm going to probably disagree with some of the panel's early discussion just, just now. Because what I felt when I read the, the guidance, it felt like I had the

ingredients with which to do good qualitative research, but no real recipe or guidance in how to then actually implement it. And that's probably because it depends, right, on the research question under evaluation.

And so that does come -- that, that makes it difficult for you to make recommendations of how to do -- you know, if you're doing concept elicitation or cognitive debrief, or you're doing patient experience, what, what qualitative approaches should you take to that.

And so what I don’t want, though, is I was around in 2006 when we had a similar situation as this, and we talked about the draft PRO Guidance. And that was -- a lot of people came up to me and were talking about a lot of excitement because people were like, aha, we now know how we're going to get PROs into the label.

However, those of who's lived that for the last 12 years know that there's more than 51 shades of gray, okay. It's black and white, but there are -- it depends. Well, try this or, you know, so I felt what I was hoping for here, we've got four guidances, five

guidances coming out that we could get into a bit more of the weeds.

And I absolutely agree with the panel before that that needs to go into an appendix, some of the guidance. And the FDA have been saying to us today, give us examples, send us case studies. I absolutely -- it does need case studies. There's only three case studies or publications that are cited, and that's for exit interviews. And that's the new kid on the block.

We've been doing other qualitative research, concept elicitation, content confirmation studies, four years, but we don't have any guidance on that. And I think that's where, where we perhaps need some more guidance in the appendices. And the FDA's seen many, many, many sponsors coming with information.

So I've done 20 years. Let's say I've done 20 measures. But the FDA must have seen the multiples of that, okay. So they must have an understanding of what's worked in the past and what doesn't work so well for them.

And so I think the FDA needs to be brave and state some things. Because today there are things that

they feel are the right way of doing things. That may change in 12 months, in 18 months, but let's face it, we've been talking about the use of social media also for a very long time. And we're not seeing that being embraced 'cause it's got to be evidentiary led, and I agree with that.

So I think the appendices should -- there should be an appendix. And if you're capturing patient experience data, then you might want to use these different approaches. If you're, if you're looking at labeling or, you know, regulatory piece, we're still at the use of individual patient interviews face to face at this point. Because we're not comfortable at the -- or share -- or publications where they feel a good job has been done to allow people who are reviewing this some kind of way of working, working out what to use and what not to use.

So for instance, with cognitive debriefing, would you do that over a telephone? Their best practice might tell them that it's actually better to do it face to face, because talking about questions on a questionnaire and they don’t have it in front of them

makes it challenging. So they could recommend or suggest, you know, if you're thinking of doing this, today we feel that this might be the best approach. So, so just some thought.

DR. DANIELS: So I'm hearing more detail, but can you sort of, I guess, elaborate in terms of your experience what lessons you've actually learned that might be not included right now in the discussion document that we might want to consider in Guidance 2 in terms of qualitative methods?

DR. SYMONDS: So around the sample size, and I had a professor years ago who said, "Well, you can interview ten patients and you've usually got saturation." How many people have done patient interviews, and yes, you get saturation quite early. And I get the representativeness piece, but do we have to do 50?

Could you say, you know, as a starting point 20 to 30 would be a good starting point? 'Cause that will generally give you representativeness. That will generally give you enough to work out whether you've got saturation.

Because Dr. Mullin started off saying that patient groups are looking to these to help them direct patient experience research. And I think it's that level of details, little help that they need. And if you don’t want to provide that, then provide best practice papers or, you know, that you can reference and give.

So like the example around the cognitive debrief, I would recommend doing it face to face. That doesn’t always -- it's not always ideal. And if you can't do that, then you have to make sure they have the questionnaire in front of them. So that kind of detail, I think, some people in the audience are looking for 'cause they’ve not done this and lived this quite as much as we have.

So interview guides, you’ve got, you’ve fully open, you’ve fully structured, and you’ve semi-structured interview guides. We know that generally semi-structured interview guides are probably the best way to start.

Structured is too structured. Open is too open. So I think there are things that you can step up

and say, today, this is what we feel is a good practice.

Coding, there was something in the coding section, and I don't know if I misread it when I was jetlagged this morning. But it basically said, you could do coding, but you don't have to do it. 'Cause, you know, you don't really have -- we don't mind. And I was like, really, I'm not sure about that. Because if it was for labeling intent, you'd absolutely anterior them to do coding.

So maybe you were talking about patient experience data there specifically. But in a regulatory context, absolutely you'd want to have the coding. So I think you need to make it clear what does it take -- what, you know, are you building conceptual model for patient experience data, or is this label intent? If it's label intent, then you might want to consider these things versus these things.

Individual interviews, yes, primary source data. And then social media is secondary supportive data, you know. 'Cause they work as well, so.

DR. DANIELS: No, that's helpful, thank you.

Sonya. Did you have anything additional to add in regards to qualitative methods?

MS. EREMENCO: Yes, I do. And I want to echo what Tara was saying and what the panel earlier was saying about the need for more detail around the sample size. I just want to quote something that was actually stated in Guidance 3, which I think belongs in Guidance 2, which is that generally the number of patients is not as critical as the interview quality and the patient diversity included in the sample in relation to intended clinical trial population characteristics.

And I was really surprised that that was not in Guidance 2 because I think that really helps to kind of illustrate that the -- that it's not just about the numbers, that it is about the quality, and it is about who is in the sample that you're interviewing. But I absolutely agree, we need to have some kind of guidelines.

Because I've seen studies that we've done in the PRO consortium where we've interviewed 50-something patients for concept elicitation. And the concern with that is you don't, you don't want to go back to those

patients for later phases of the research. And if you really only needed 30, we've just lost 20 patients that we could have used for cognitive interviews or for the quantitative study. And I think with more and more research in rare diseases we can't afford to waste those patients early on. Like we really need to be strategic about, about how we're selecting patients.

So that's one thing on saturation. I won't repeat the quote, but there's actually a really definition of concept saturation in Guidance 3, line 732, 736 that I want to see in Guidance 2. Because, again, that's part of the key decision point of do you have enough, enough interviews or enough data collected. So those are two points.

And then a couple things around best practices. I saw mentioned in a couple places in Guidance 2 that you could do cognitive interviews, cognitive debriefing in a focus group. I know that this is possible to do. I would not recommend that. I don't think that's a good practice, and I don't think it should be stated in the guidance as, as -- 'cause it comes across as a recommendation, and I think that is

giving the wrong impression.

And then in terms of conducting interviews and focus groups, I would really recommend including some language around using technology to facilitate the face to face. Maybe face to face in person isn't possible. But you could do videoconferencing. You could do a video focus group so you could get the benefits of the face to face without having the burden of travel.

Because, again, thinking about some of the populations, you know, parents of small children, they're not going to be able to travel to do a focus group. But maybe the focus group is the better venue for that research.

And then I just wanted to touch on something that was said earlier where the panel was talking about how social media isn't a method. And I want to say that patient-focused direct development meetings are also not a method. They're in table 3, and I think that's going to create a lot of confusion. Because not only are they listed in table 3 as a possible method, but they're also listed as having the same advantages and disadvantages as focus groups, but they're

completely different. They are not focus groups. I won't go into the details of why not, but they're really not.

And so I think it's risky to put that in the guidance and have people think, oh, if I just use, you know, one of these voice of the patient transcripts, that’s going to give me the same information that I would get from a focus group, and it's, it's not. So I'll stop there. Thank you.

DR. DANIELS: No, no, that was a very, very good insight. Barbara, so give me -- you haven’t answered -- you may have answers to take with this background since you're coming from the NIH. What are your thoughts on the level of detail needed for operationalization of qualitative methods for this guidance?

MS. STUSSMAN: So, yeah, so I agree that more detail in general is, is better. There were a few places in the guidance where I actually thought though that it was detailed to the point of sort of boxing in the researcher or suggesting that there's only one way to do something.

Building on what Tara said, I think the discussion about choosing to code or not code data is more confusing than helpful. This is a very complex nuanced idea that's difficult to explain in a couple of pages. In fact, there's like textbooks about this.

So, in my experience it's very unusual not to code data. It would only apply to when you have small amounts of data. Um, I almost think that taking that out of the guidance might make sense. Because I think it could cause confusion.

Another place with the qualitative software, there was mention that it must allow for integrating video into the software. And this also was a good idea in general, but I don't think it should be a requirement.

There are situations where I've done interviews in the hospital setting, and it's really not feasible to do video. And, you know, we do audio instead. So just a few places where I think it might have been overly specific.

Another example is the suggestion that there's a specific credential required for analyzing

qualitative data. And I would say experience is more important than a particular credential. And qualitative researchers come from all different disciplines. So, again, I thought that was sort of implying that there was one particular qualification for doing qualitative research.

In terms of best practices for areas that I think are not included that we could expand on, in terms of qualitative data analysis, one thing that I've found very helpful is to do a thorough readthrough of transcripts before beginning analysis. I didn't see this in the guidance.

Another is a talking of double coding so that you can assure reliability. I didn't see in the guidance where there was talk about this. But this is an important feature to have multiple people coding the data so that you can look at reliability rates and also have consensus meetings to talk about any differences and come to consensus.

Another thing that I wanted to mention is that I think in terms of displaying or representing qualitative data, the use of quotations is really

important, patient quotations. I didn't see that in the guidance.

In my experience working with patients, it's really the best way to really convey the patient perspective is to pick a poignant quote and to really emphasize your point. I mean you can -- also obviously graphs and tables are really important. But I think the use of quotations can be -- can convey in a way that you can't do with graphs and tables.

And then one more thing I wanted to mention under this question is there was a graph, and I think it was in the appendix, that showed the steps of qualitative data analysis, compiling and organizing the data, describing and classifying the data, interpreting the data, and representing the data. And the graph had these in boxes sequentially. And because these are much more iterative steps, I think that was a bit misleading.

So I would suggest adding some maybe arrows or displaying it in a more circular fashion to just emphasize the iterative nature of it.

DR. DANIELS: Thank you. That's some great

feedback. Do we have any other panelist who wants to provide any additional input on qualitative methods before we move on to the next method?

(No audible response.)

DR. DANIELS: Okay. So on to quantitative methods, which may mostly be related to survey research. I know Vanessa, since the Michael J. Fox Foundation has been involved with online surveys, what level of detail do you think is needed for operationalization of survey studies?

MS. ARNEDO: Sorry. So as background, the Michael J. Fox Foundation has a study called Fox Insight, which is an online study to evaluate the lived experience of Parkinson's disease in a longitudinal manner. Most of the surveys are standardized surveys, but we also have several partnerships with other research organizations to design a newer survey methodology as well, so a few pilots ongoing.

And I would say that as a group that sort of started to design this from the beginning, I think having to, a lot of panelists points, some case studies of what survey methodology and what examples of surveys

were acceptable from the FDA's perspectives, as well as other groups who have done this successfully, I think for us would have been incredibly valuable. And I would venture to guess would be valuable for others.

So I think having specific case studies, likely in an appendix or on a website would most likely be valuable for the community.

DR. DANIELS: And are there any other, I guess, best practices or lessons learned from the Michael J. Fox Foundation in terms of this online survey that might be helpful for us to maybe consider to include in the guidance?

MS. ARNEDO: Sure, so the obvious benefits of having an online virtual study in terms of allowing for a representative population are that you can have individuals that may be in geographically remote areas who may not traditionally have been involved in patient-reported outcome research previously be able to engage in this platform.

On the flip side of that, going back to my comment about the patient journey, especially when you're talking about a chronic progressive disease, the

use of technology and the user interface, or the patient experience of being able to use that technology will change throughout your patient journey. Again, especially if you're thinking about someone as they're progressing with Parkinson's disease and as their patient journey is changing. The ability to use this technology and complete rigorous surveys may change over time and fluctuate.

And so it is something that I think is important to be mindful of, is thinking about the patient journey and how that technology could be best leveraged at any point in the journey of disease. And it's something that I think we continue to try to tailor based on the different subtypes of the patient community.

DR. DANIELS: Nice. And I'm looking at Sonya or Tara if there's anything additional to add in relation to survey research or analyses.

MS. EREMENCO: Yes, I do have a couple things to add. And I actually did want to clarify one of my earlier comments, 'cause I realize I may not have said everything I meant to say. But when I was talking

about patient-focused drug development meetings, I wanted to say that it's a source of data. It's not a methodology. So I think it's a good source of data, but I don't think it can be treated as a methodology.

In terms of the level of detail related to the quantitative research and the survey aspect, I felt like it was not as much as the qualitative sections. And so there were some areas where I thought more might be needed. But one of the things that really kind of struck me was the use of the term observational study, and the fact that it's defined in such a specific way in the qualitative section. And then it doesn’t make sense to use that same term in the quantitative section in my opinion.

I think that for the quantitative section we should be talking about non-interventional studies to really make it clear that we're not talking about an -- 'cause I know it doesn’t make sense to think the type of observation that we mean in the qualitative, but just because that's been introduced in the early part of the guidance, I think it's going to create confusion. And I noticed a place where the wrong

appendix was referenced because of that.

So I think it's really important. And I noticed in Guidance 3, observational is not used at all. It's non-interventional. So that's one way I think we could help distinguish those two types of studies.

And there's some discussions around electronic modes and mixed modes, and I really wanted to make sure that under the disadvantages of electronic modes we make it clear that there's issues around access to technology. It's not just technology literacy. There's real differences in access that leads to differences and socioeconomic representation of the sample, and that's a really important issue.

There's discussion of mixed modes in Appendix 4. And I think that's useful, but I think it doesn't explain enough about why there might be a benefit to use mixed modes in these type of studies. Because in Guidance 3, you go into a lot of the risks of mixed modes. So I think there's a, there's kind of a conflicting message that needs to be clarified.

And I think that, you know, there are -- there

is thought that mixed modes can allow you to increase the response rate and the sample size because people are completing the mode that they want to complete, that they're allowing for preference.

And then my last comment is referring to the Appendix 6, Interviewer Administration in Quantitative Studies. This is deficiency a possibility. This is a -- this can be used. But I don't think referencing the practices under the qualitative interviewer administration makes sense.

I think there's a lot of differences -- not necessarily differences, but there's a different focus that the interviewer needs to use in a quantitative survey. They're not trying to probe for information. They're just reading the questions and recording the answers. So it's a very different context. And I think that section -- that needs its own section. I don't think it needs to refer back to the qualitative section.

DR. DANIELS: Thank you. Tara, I don't know if you have anything to add, but I want to give you the opportunity if you do.

DR. SYMONDS: Not really. I have something to the mixed methods when we move to that.

DR. DANIELS: Okay, thank you. So moving on to non-traditional methods, which may include, but is not limited to digital health technology and social media networks. I know we have a couple of individuals who are -- have a lot of expertise in this. So I'm going to go to Bill first in terms of his thoughts on the level of detail needed to operationalize the use of digital health technology.

DR. BYROM: Thank you. And I think, you know, there's a number of newer approaches that are showing promise in the types of ways we can collect data, to understand more about disease impacts, to understand more about the symptoms and the treatment impacts as well. And these are facilitated by technology.

And a couple of these that I think are particularly interesting, and we're seeing a growing interest and growing usage of are large scale or, I'll use the right term, Sonya, non-interventional studies, to learn more about the symptoms, the disease, and the treatment impacts. And then also the use of mobile

sensors to measure objective measures and provide insights, again, about the disease and the treatment.

And I think on that, on that last topic, just to pick up on a point, I think it was Linda's point in the audience earlier. About, you know, making sure that we're actually measuring the right things, and we're using these technologies in the right ways.

A nice example, I think, of where something like a mobile sensor is useful in this kind of research is, which was reported recently, was the use of an accelerometer to measure activity and sleep in patients receiving chemotherapy. And, you know, it was to understand the burden of the chemotherapy as they went through the different cycles of disease.

And it seemed that, you know, it was actually a very insightful picture that was being provided about their activity and sleep patterns in particular as they experienced the side effect profile, I guess, of the chemotherapy treatment.

And that’s a way of collecting it, which is relatively passive. It doesn’t require them to answer questions every day when they're perhaps feeling

unwell. But it's a nice way to collect some insightful data during that difficult period to measure the treatment impact.

But just to go onto it in terms of what would be useful in the guidance, I think there's a few areas. And as I thought about this, I thought perhaps more about these large scale non-interventional studies. The kind of studies that we've seen recently with things like Apple ResearchKit as a platform, you know, where we can recruit very large cohorts of patients, ask them to record things to do with their symptoms, their disease impact, their treatment impact over a period of time and use that data to make these insights.

And I think there's a few areas which I think would be useful in terms of more information. The first is around bias and generalizability of the data. So that first session that we heard, you know, Ebony described, used the term sufficiently representative range of respondents.

And I think to your point earlier, Sonya, about the survey methodology, if we're using something

like Apple ResearchKit, are we biasing our sample because we're only including patients with an Apple device?

If we look at Tweet Maps, so you look at the -- where the geographical location of Tweets, and you split them out by the different apps they're using, whether using an Android app or an Apple app, you often see that in a city the Apple usage is focused on the more affluent areas.

And so, you know, is that going to bias or give us some problems when it comes to generalizability of those results. So I think more focus on how to get around that or what considerations we should have around making sure our sample is generalizable is important.

The second is around dealing with missing data and inherit in these kinds of studies is missing data. Two examples, the Empower app, which, Vanessa, you probably have come across, which is the Apple ResearchKit out for the Parkinson's that's being used. A very interesting app because it incorporated performance outcomes, as well as patient-reported

outcomes. Less than ten percent of patients completed five days or more of values using that app.

Another example, which was more positive, was an app called Cloudy with a Chance of Pain. This was looking at the response of the relationship between climate and pain in patients suffering rheumatoid arthritis and other things. They found that 30 percent of patients provided at least half the data required. And this was for daily completion over six months. So that was a much more impressive set of data, I suppose.

But the question is, how much data do we need. How much -- because we're collecting more frequently and over much larger samples, can we get away with more missing data and just some guidance really around what the, what the rules should be around that would be useful.

And then I think the third area, again inherent in these types of designs, which we touched on in the previous session as well, is around identity verification and diagnosis confirmation. And so, you know, if I, I can download an Apple ResearchKit app today and start entering some data. And, in fact, one

of the findings of the Cloudy with a Chance of Pain was that there were 25 percent of users who downloaded the app and used it for a couple of days, and then never touched it again.

And they described these types of users as tourists. And I suspect many of us in this room might fit into that category. And I have to confess that I have been a tourist for a number of these apps because I'm just very interested in what they look like and what they're measuring. But I don't have the disease, but there's nothing to stop me from downloading it and collecting data.

So, again, how do we verify that we've got a patient with that disease condition who is entering the data in that app? And actually if we've got 8,000 patients, which was the sample size of the Cloudy with a Chance of Pain, does it matter if ten percent of those patients actually aren't true patients? Will it affect my results? So I think those are the kinds of things that I'm interested in seeing more in, in the guidance.

DR. DANIELS: Thank you. Antonia, do you have

anything additional to add to what Bill has already stated?

DR. BENNETT: Thank you. I think in the, in Guidance 2 there's no text about, about digital health technology. There's just a reference to the appendix. But I think as an example of what's been mentioned earlier about using the guidance to lay out strategy and overall approach, I think this could be very valuable.

I think some comments about, to the reader about defining very carefully, you know, what are you measuring with your piece of mobile technology? Like can you define that construct that you're measuring? Why are you measuring it? How do you think it's going to be valuable to your overall goals?

And then in the, in the appendix I think it would be helpful to add some additional issues. And I don't think -- I think the challenge will be that we can't make this specific to every different type of health technology, digital health technology, but I think there are some broad categories that we want to encourage people to really think about very carefully

as they plan their project.

In some work that I've done with collecting data using activity trackers, we were able to make it very easy for the patients. They would come into clinic during chemotherapy visit. We would put the tracker on their wrist and say, "Please wear it for three weeks, and come back at your next chemo visit. We'll come and find you in clinic, and we'll upload the data from your device at that point." So they didn't have to do anything except wear it for three weeks.

On the other hand, that put a lot of burden on the site staff. And when you roll out one of these studies, you're going to owe a lot of people a fruit basket. 'Cause it's a big ask. It really starts to make, you know, patient-facing interviews, patient surveys, focus groups, it makes them look straightforward, reliable. You're not, you know, beholden to the quirks of a particular app to get your data collection to work.

And so I'd like to see the appendix really lay out some of the broad considerations. And, you know, battery life is such an important issue with wearables.

Issues with the third-party vendor, we had a very good experience working with Garmin, but then one weekend Apple updated their operating system. And so Garmin programmers spent the whole weekend updating the Garmin app. And so then by Monday we were back in business.

But it's very interesting how I think there was the Apple update and then the changes in the regulations for how -- for European data. And so the cookies requirement and the acknowledgement of the new privacy policy just cascaded a series of hiccups throughout the multi-site study.

And, and then I think another issue that should be addressed is -- in addition to the data flow, I think clarifying FDA's requirements for the type of data that is, or for the level of data audit or audit trail that is required for data at this, at this stage of identifying patient, the patient experience and patient goals.

Because we're -- this isn't clinical trial data. This isn't PRO or COA development yet. We're sort of another step removed from that, but do you still -- does FDA still require the same level of data

verifiability. And if they do, that really narrows the, the eligible devices and pieces of technology.

DR. DANIELS: Is that all, Antonia?

DR. BENNETT: Yes.

DR. DANIELS: Yeah. And so I know in guidance when we touched a little bit on data monitoring and audit trail, but maybe we need to reconsider maybe adding a little bit more information in Guidance 2. So thank you, that's helpful.

I want to reach out to any of the other panelists while we're still on these non-traditional methods. Do you guys have anything additional to add before we go onto mixed methods?

(No audible response.)

DR. DANIELS: All right. I take silence as a no. And so last, our last method, but not least, is mixed methods. And this is related to the use of the combination of methods that we've discussed. And so what level of detail for this method is appropriate for this guidance.

And while the panelists are thinking about this, I'll break the question down a little bit more.

Currently the discussion document describes each method separately. And then from mixed methods refer back to that respective method that will be used within the combination of those methods.

And so do you think this is sufficient, or do we need more detail in how to operationalize the combination of these methods. So, for example, if we're using digital health technology with an online survey, should that be spelled out more? And so I'll see if there's any takers.

DR. SYMONDS: I've put my light on.

DR. DANIELS: All right. Go ahead, Tara.

DR. SYMONDS: Yeah. So mixed methods, I think, you know, they come into their own really with rare diseases particularly because it's hard to access those individuals. And often, as Sonya said, you need to get -- maximize the information you can get from these individuals. So I think giving some ideas of how mixing methods has helped in the past, you know, best practice.

So for instance, you know, you can ask patients what is the impact, what is the patient

experience on an online survey. They type that in. You give them some -- that could be the primary endpoint ClinRo or a PRO. They filled that in.

You can then incorporate, get a selection of those individuals to then talk to you on the telephone. So then really talk about, well, you said this and you gave these answers. What does that mean to you? If you move a little bit on these items, what does that mean to you.

So you can really start to get both quantitative and qualitative data 'cause you've given the questionnaire out. So you're getting some actual data of burden quantitatively, but you're getting this rich qualitative data through an online survey, through telephones, from, you know, the small pool that you're working with.

And there are other examples as well where, you know, you might have a patient have an app with a diary. And they're logging their symptoms. But you could also have them because now we can video ourselves, right?

Video, so it's like a journal where they can

explain, well, I've just answered these questions this way because this is what that meant to me today. So they -- and I've used that, and that's very powerful. And also very powerful within a company because, you know, people want to see the patient real experience.

And so I think mixing methods like that of getting the quantitative -- you know, you can innovate around how to bring these methods together to really maximize the story that you're getting from a patient. So some examples would be good.

DR. DANIELS: Yeah. I'm hearing more details needed and maybe sort of extrapolating in regards into the mixed methods instead of just moving back to the simple method. Are there any other comments from the panel in regards to mixed methods?

(No audible response.)

DR. DANIELS: All right. So moving on to discussion question number two. So how much detail about study materials, which could include protocol on the actual structure data collection and analysis would be useful in the guidance? And if it's not useful in the guidance, would it be useful in another form? And

I've already -- I think we've already heard some other places, like websites, where the needs can be referred to.

So I'll open this up to all panelists, since this is like study materials, it isn't just consistent to one particular method. It could be common across all methods. I won't break it down by that. So I'll let each panelist speak to, to study materials and how much information about that.

MS. EREMENCO: So I did have some thoughts on this. I thought for the most part that the information on the qualitative section was very detailed and very good. And there were a couple areas, though, where I thought there maybe was too much detail, or what was being suggested might be problematic.

In one example, in Appendix 1 in the study protocol, I was a little concerned with kind of recommending that you have to list the geographic locations of the sites and the number of discussions or interviews. And I understand why you need to kind of have -- you might need to state how many you were targeting to do. But anything of that detail in a

protocol, if it's changed, is going to trigger a protocol amendment that’s going to take time and cost.

So I think there needs to be a balance of the types of information that are necessary in protocol, and the types of information that might be part of your recruitment strategy. Your targets may not necessarily need to be in the protocol 'cause of those downstream effects.

In Appendix 2 I think it was really useful to have the information about the parent and child interviews and some of the best practices around that. And I think there's a little bit more that needs to be done related to the dyad interviews and how to make sure a parent is not interrupting a child or talking over the child. And so that -- I think that was stated maybe somewhere else in that appendix. But I think there's a table that goes through the different types of interviews in a pediatric study in there is something that I think would really be useful.

And then in the observational qualitative studies I was wondering if we needed to talk about consent there. And I think that that's one of those

kind of gray areas where if you're video recording someone, do you need to get their consent. If it was just observational and you weren't recording, maybe you wouldn't. But I think there's a, there's a concern about -- at least that needs to be, I think, touched on.

And then last point, in the quantitative section, Appendix 4, I think more detail is needed on the analysis plan expectations. It might be that it seems like that's an obvious thing that we don't need to spell out, but I saw that there was much more detail in the qualitative section around the analysis plan, which found -- which I found surprising because I think in a lot of cases most qualitative research don't maybe create that formal of a plan.

But for the quantitative section we really need a detailed plan, and we need to set that out. So I think more detail there is needed.

DR. DANIELS: Is there any other panelists that would like to speak about any detail on study materials?

MS. STUSSMAN: I can speak on this. I wanted

to echo what Tara said earlier, that I think including an interviewing script and a focus group guide would be really helpful. Especially showing the types of open-ended questions that work well in these situations and showing the instructions that are given to interviewees and the ground rules that you would use with focus groups and that kind of thing could be really helpful.

Another area that I thought maybe the guidance could touch on is the challenge of conducting qualitative interviews in various settings, such hospitals or long-term care facilities. Just based on my experience doing interviews at the clinical center at NIH, there's a lot of logistics involved in terms of trying to minimize distractions and interruptions.

For example, putting the sign on the door and talking to the staff about not interrupting. And oftentimes there'll be a family member present, and so like explaining to the family member the importance of not interjecting and answering for the patient.

Another area that I thought you might want to consider talking about is, I know the guidance talks about burden of disease and burden of treatment, but

working with -- especially MECFS patients I found that there's a lot of discussion around burden of disease management. So it's a little different than the burden of the disease itself. It's not really related to the specific functioning or symptoms, but related to the amount of pacing and lifestyle modifications that are made in order to prevent backsliding or in order to prevent additional exacerbations.

So to me this is a little bit different. I thought it might be something that you might want to focus on.

DR. DANIELS: Is there any additional comments from the panel?

DR. SYMONDS: Yeah. I just think that, you know, the more structure we can have around some of this. So like the consult guidelines, the reporting guidelines of the clinical trials as a consult PRO Guidance that was developed for PRO data specifically. And I think, you know, if we could have something like that or a reference to, you know, best practices of what to include would be, I think, welcome from a lot of people.

DR. DANIELS: Thank you. All right. So let's move on to question three. Question three is what other special populations beyond pediatric, cognitively impaired, and rare diseases should be identified for Guidance 2? And are there any other factors considered when eliciting information from special populations or different cultures?

And I think it would be fitting for Vanessa to maybe give the perspective of a patient organization on what other populations should we consider to be identified in this guidance, if you can provide us some of your feedback on that.

MS. ARNEDO: I think one aspect that has not yet been mentioned that I think is applicable to many disease states, again, especially when thinking about chronic progressive diseases or even some of these other categories is the important of engaging care partners in some of these questions and particularly for thinking about successfully collecting data from a representative patient population. A priori being very explicit that the engagement of care partners to be able to do that successfully is likely critical to be

able to do that.

And so I think at some place in the guidance discussing how to do this with care partners, I think, could be valuable again, for many disease states and special populations.

DR. DANIELS: Are there -- I guess I'm going to follow up a question with you, Vanessa. Are there any, I guess, specific groups -- I know you work with a lot of progressive chronic diseases. Do you think that needs to be drawn out a little bit more, or what are your thoughts?

MS. ARNEDO: Yeah. I think so. Again, especially for diseases that are progressive, I think we know that patients and their care partners really begin to work hand in hand as they're engaging in research. And that is in more traditional clinical research settings, but even, as I said, in our experience using facts insight and being able to have patients engage with technology, often depending on where they are in their state of progression.

They may need their care partners to support them and be able to use that technology, to be able to

contribute data on their patient experience. And so, again, we've actually been a little bit more mindful about designing that technology to be able to support the care partners to help us collect that patient experience data in the best way for the patients and for their care partners.

So, again, I think being specific about that for many of these types of diseases where this would be applicable would be helpful.

DR. DANIELS: Thank you. Barbara, do you have anything additional to add? As I know you've been engaged with a diverse patient population.

MS. STUSSMAN: Yeah. Well, what I wanted to add is related to qualitative research. One of the things that we've had to deal with is accommodating people with attention deficits. So this is not the same as cognitive impairment.

These are people who can, you know, very able to answer for themselves, but that become cognitively fatigued quickly. So that we've done things such as put less people in the focus groups so that they're, you know, it doesn't create as much, as many opinions

that a person has to focus on, or shortening the length of the interview, conducting interviews in multiple stages. So different things in order to just accommodate people who may become fatigued, cognitively fatigued easily, but still are the best person to answer on their own behalf.

DR. DANIELS: Thank you. And, Sonya, with your experience with language translation and culture adaptation, are there any other factors to consider when doing multinational studies or eliciting information from different cultures?

MS. EREMENCO: Yes. I, you know, what I wanted to say was I think the guidance does a really nice job in Appendix 5 of talking about translation methods for quantitative studies. And I wanted to see something, not along the same lines, but something mentioned in Appendix 2B in the qualitative section about how we can elicit concepts and information from other cultures.

This can be done through direct patient interviews. This can be done through clinician input. And if there are interviews, there will need to be

translation of interview guide, you know, translation of the patient responses. So it does add a little bit more complexity to the study.

And I know that that time and cost are probably big reasons why it's not done as a general practice. But I think if we really want to develop -- you know, if we're using, if we're doing this in an instrument development context and we really want to develop an instrument that’s going to be used cross-culturally and that’s relevant cross-culturally, we want to find out at the earliest stage possible if the concepts are actually applicable across different cultures.

And, you know, we're all in kind of our own cultural bubble. So we just kind of assume everyone feels the same way. But I think that's a really important thing. So I think it needs to be couched, though, in a way that it's not perceived as a mandate that you have to do these kind of cross-cultural concept elicitation interviews, but that it's something that encourages to be considered.

DR. DANIELS: Thank you. And Bill or Antonia,

are there any factors when using digital health technology in certain patient populations that we should probably consider or include in Guidance 2?

DR. BYROM: Well, I -- as I was thinking about this, I guess I thought about what we tend to do in terms of looking at usability for technologies when we use them in clinical trials, and I guess it applies to any other type of clinical research. And I think there are certain characteristics that might be present in patient populations that we need to assess usability around.

So and there's kind of -- for me there's probably four main characteristics. One is patients who are technology inexperienced or naïve, so might have difficulties using a certain type of technology. The other, which we have on the, on the questionnaire is the cognitively impaired. But I'm really interested about the point about attention deficit as well. That's an interesting one I hadn't thought of.

The other is around dexterity. So some patients, perhaps the elderly or perhaps those with rheumatoid arthritis may find, you know, fine motor

movements difficult. And so operating a small device they might find shaky.

And then, finally, the visually impaired. So I kind of think as you think about a particular patient group, perhaps you need to consider whether any of those characteristics might be represented in some of those patients. And therefore, you know, the usability of your device should be really tested in those groups.

DR. DANIELS: I don't know if Antonia or any of the other panelists would want to comment.

DR. BENNETT: I think for any type of data collection, whether it's going to be patient interviews or focus groups or asking patients to fill out surveys online or be participating in digital health data collection, I think it's, I think it may be worth mentioning in the guidance that people who are on the planning team, especially if they're not patient advocates or others who have had a considerable amount of direct experience with the patient population, to keep a really open mind about what patients can and can't do.

I think just as often as we discover in

usability testing that there's a particular issue that creates a lot of challenges, I think just as often we discover that, you know, a certain group of patients is much more capable of participating in a particular way that we might not have, that we might not have thought.

And then also thinking about how to tailor your data collection so that it's accessible. You know, if you're interviewing men with metastatic prostate cancer, and they're too fatigued to talk with you for 30 minutes, how do you turn your interview guide into a ten-minute interview. And can you really just be very focused.

DR. DANIELS: Any other panelists or ...

DR. SYMONDS: Yeah. Can I just -- one that’s been running through my mind is that, you know, with cross-cultural stuff, you know, teams -- when you're an industry, teams will be like what do you mean it's going to take six to eight weeks and thousands of dollars. Why can't we just, you know, translate it?

And then with the digital health usability, what do you mean we've got to do usability. You know, let's just roll it out. But what you need to be

putting in this far as them working in that environment is to say, well, we're not mandating this. I agree, right. We're doing this, we're suggesting this because it's going to give you more precision.

This is about measurement and measurement science, and I'm not seeing that so much in the guidance. And that, you know, then we can share that with our clinical teams and say this, therefore, will affect your power if you are, you know, developing a measure that has some error in it because you've done really bad translations or you've not implemented an electronic device very well.

So I think that message somewhere in there might be quite useful.

DR. DANIELS: Thank you. And so, you guys, we're in the final stretch. I hope everyone's still attentive at this point. There are two more questions. And you've seen these questions before. However, we wanted to give this panel an opportunity to sort of provide their thoughts on what would be a useful format or layout for Guidance 2 in addition to what we've already heard from the previous panel.

I just want to give a reminder to our panelists that Guidance 2 is focused on types of study that are targeting patient experience. And so this may be taking place to support an unmet need or maybe informing clinical trial endpoints or even your clinical outcome assessments.

So with that in mind, is there anything, I guess, that you want to state that in addition to what you've heard from the last panel on the structure on the Guidance 2?

(No audible response.)

DR. DANIELS: Are we text heavy? Do you want to see more visuals? I heard case examples already. And you might not have anything else to include, but if you want to just nod and confirm that that's the right approach to do, that would be okay.

DR. SYMONDS: Yes.

DR. DANIELS: Yeah. Okay, so that's what I'm hearing. What about time points? What are the most important time points that you think that you can seek input in terms of these patient experience studies, mind you of what we call them?

DR. SYMONDS: I'll jump in, shall I? Why not? So I was pleased to hear Emily say there's some initiatives still ongoing to try and work out how best to communicate with the FDA and the CRA staff specifically, because this is something we talked about in 2013 at a key issues panel that we put together through Duke-Margolis.

And this was one of the things that was risen -- arose was how do we get timely feedback. You know, come to us early and often, but it takes a lot of effort 'cause you have to go through the division. It can -- you know, takes weeks, months to get a meeting. And sometimes you just want to ask a simple question.

And I don't have an answer, unfortunately, of how to do that, 'cause I get the environment with which you're working in. But it's almost like we need a bat phone where we, we've got a hot question and we need to pick up the phone and phone, you know, Michelle or Elektra, you know, Selena and say, I've got this question, but then of course then you're constrained 'cause you can't give one person an answer about something.

But maybe an email address where you can throw in generic questions and you can compile, say, from the last two months. These are the kinds of questions we got. These -- we can only say this. I mean I had a question around the device. Were there qualifying measures now? I wasn't aware of that. I wasn't -- I'm not sure how that works with CDER and CBER. So I had this question, but where do I send that. And how do I ask a simple question like that.

'Cause my, you know, as a consultant, that's what my clients are asking me. And so I think maybe some form like that or ability to just throw some questions in, and sometimes you can't answer them 'cause they're too specific.

But we need to work out a better way. 'Cause you can go type C. You can go type B. You can go pre IND. You can go end of phase of two. But they take time, and sometimes it's not quick enough because we need to make decisions to move our clinical trials on, the clinical development process on.

DR. DANIELS: And I know David's not here, but on my conversations with him he did mention critical

path innovation meeting, CPIMs, might be another avenue that could be useful to sort of touch bases with the agency and to see what we're thinking and sort of lead them in terms of their strategy, in terms of their patient experience studies. So that may be a potential way as well.

And so I don't know if there's any additional comments from the panelists on time points. And it doesn't seem like there is. So I mean this concludes the preset discussion questions. So I would like to open up the floor now to audience Q and A. And there's no need to raise your hands. There's mics in the middle of the aisle.

If you could just state your name and affiliation before asking the question. And just a reminder that FDA, we're in listening mode. So if you do have any questions, if you could phrase them as comments, that would be helpful.

MS. WILSON: Great. Thank you. Hillary Wilson with Boehringer Ingelheim. First of all I just want to commend the agency for making so much progress on the patient-focused drug development guidance in

such a short timeframe. I think you guys have done a tremendous job. And I also want to thank both panels.

I have a comment for the agency to consider. I think both panels have touched on a desire for a little bit more clarity around the evidentiary standards, and maybe more of a framework for how the agency intends to use some of the data.

And as you consider that, and develop, you know, these draft two and three guidances, I'd like you to consider how these evidentiary standards might vary based on two different axes. The first is the research question that's being asked, you know, what the patient experience exercise is designed to address.

And then the second is around what phase in the medical part development lifecycle there is. You know, will the evidentiary standards be the same if you were at a CPIM meeting and maybe a pharmaceutical company wasn't even -- had to have a particular asset in mind, but they're getting in a new disease area. Maybe they've had some patient input either from a patient stakeholder group directly or they've had a couple patient advisory board meetings.

So would the same requirement be around like sample size or representativeness in that context as say would be when you're selecting your endpoints for a pivotal trial.

Similarly around the type of question that you're answering -- or you're asking. And if you're trying to get patient input on what their experience is with existing treatments or what their unmet needs are, would the same standard be for, say you're doing, using a digital technology for this.

Would you require the same evidence of reliability and validity for those digital technologies when you're asking questions around experience with existing treatments or unmet needs as you would for a clinical outcome assessment in a pivotal trial that’s going to be collected on a digital device. Thanks.

DR. DANIELS: Thank you. And we'll take that into consideration.

DR. AMTMANN: Hi, Dagmar Amtmann, University of Washington. I have a comment and a question. A comment about special populations that there is no mention of people with sensory impairments in the

guidance. And I know we have a whole session on special populations, but I would like to point out that there is no reason why a person with diabetes or COPD couldn't have -- couldn't be hard of hearing or, you know, have a vision impairment.

Then we are not talking about physical impairments that may limit peoples' access to a computer. So I would really like to see that incorporated into the guidance.

'Cause what happens in real life is that we exclude those people from participating in clinical trials, and I just think that's just plain wrong. I mean people can participate if we make an effort to make the technology accessible to them and, you know, we don't assume that oh, you know, somebody who is deaf could never participate in a focus group or could never provide data.

This is not reflected in the section where we're talking about advantages and disadvantages of different qualitative approaches. So maybe focus groups are not the best mode for people who have communication disorders. You know, I don't know,

online or paper survey is not very good for somebody who can't see very well.

So I just wanted to, you know, incorporate at every step of the way and mention these considerations as people are designing their studies. And I would like for people to be more included, 'cause they have just as valid perspective as everybody else.

DR. DANIELS: Yeah, that’s an excellent point.

DR. AMTMANN: So and then my question is, and I'd be interested in the panel's thoughts about is about how to operationalize a response rate when we post questions or requests for feedback to like social media or in environments where we have no idea how many people saw that or how many of those people would activity have been eligible to respond.

And so we're often under pressure to provide response rate, but really we often are just at a complete loss to figure, you know, how to figure out how many of the people who could have been responding and would have been appropriate respondents actually responded.

I don't know if any particular -- like if I

had a solution, I'd propose it. I just -- I would like maybe for the guidance to recognize that there are some circumstances where a response rate may not be possible. Or if you think that under those circumstances we can come up with a response rate, it would be really nice to get some guidance of how to do that.

DR. DANIELS: Yeah. So definitely we're going to take that down as more detail and response rate. I don't know if the panelists have any experience in terms of how to operationalize a response rate. And it seems like we may not. So this is something definitely that we'll take into consideration to include in the guidance.

DR. BYROM: Could I make a comment on that. I can't answer your question. But the point you made prior to that and the point that the lady before you made about the research question and how much evidentiary information you need to support the methodology that you've used, I think is really interesting.

And, you know, Sonya, I think you mentioned,

you know, mixed modes. So if we think about technology, if we're doing a phase three trial and we're collecting patient-reported outcomes, we'd probably feel a little uncomfortable mixing modes. But if we're collecting disease information to inform module of development, well why not.

And if we have patients who are visually impaired, why aren't we using a voice assistant, for example, to read out the information and collect their responses as one of the modes that we might present to the patients as well as, you know, web and app and whatever else we might choose.

So I think going back to the, almost that first comment, it would be useful to understand a little bit more about the levels of evidence needed for those different types of applications. We don't want to, we don't want to necessarily apply the phase three clinical trial standard to everything that we do. 'Cause I think that would be very restrictive.

DR. DANIELS: Duly noted. So we have three more people, and I think I'm going to cut it off at the third person in the back, just for time sake. Go

ahead.

MS. LASCH: Hi, I'm Kathy Lasch from Pharmerit International. I was recently in Tokyo and at ISPOR Asia Pacific. And one of the things that struck me is that they want patient-focused drug development, and they want the patient voice throughout the process. But it was said often by different regulatory and HTA agency representatives that they didn't just want to use the western model. Which I thought was very interesting, especially when you're talking about cross-cultural circumstances and when to include patients from other cultures, other countries.

Often we develop something in the United States, we do the wonderful little process, and we assume that they, that it's understood, the questions are understood by the other cultures.

The other question I have -- well that's a comment. But the other question I have -- and I have many, but I would bore you to death. But one of the other -- the question I have is if an instrument was developed at first in Asia, in an Asian country, can then it be taken to the US FDA, you know, cross-

culturally validated, used in the US, and passed through a regulatory approval process?

DR. DANIELS: So I'm going to actually, I think we're going to table that for the next section, for Guidance 3, because I think that's more relevant for clinical outcome assessments versus just for patient experience, if that's okay.

MS. LASCH: It's definitely okay, but I don’t quite agree with that.

DR. DANIELS:

MS. LASCH: But that's okay.

DR. DANIELS: Okay.

MS. BENJAMIN: Hi, Katy Benjamin from AbbVie. So this is more of a comment than a question. One of the things that I think you might want to include in the guidance in the section working with rare disease populations is you have to be cognizant of the fact that these people, A, oftentimes have progressive conditions. But in terms of that, they take a long time to be diagnosed.

And so when you are doing a study, especially something that's outside of the clinical context,

you're probably going to be including patients with a very wide range of disease-specific status. And also with a very wide range of treatment experiences. Because oftentimes they go through several different types of diagnoses and treatments before they even get to the right one.

And so when you are doing these kinds of studies I think it's going to be a good idea to get much more context than you normally would about where these patients are in their patient journey in order to really understand the data that you're getting.

DR. DANIELS: That's a very good point. And our last question or comment?

MR. JAGEDSHIRE: Otto Jagedshire [ph]. Actually, the question/comment, I think it's both has to do with what the next, or the lady prior to this lady stated. And actually it's kind of a continuation, but more, as a more practical application with regard to PED, or patient experience data studies that result in finding its way to the label. And particularly how, let's say, labels in different countries, including the US would be affected by maybe studies that have result

in different results.

So I guess the question is, what would be your recommendation, or panel's recommendations on how to handle situations like those?

DR. DANIELS: And are you asking them what would be their recommendation in terms of how to do these studies so the data can be included in the label or ...

MR. JAGEDSHIRE: Well, correct. Or the differences. If you have, for example, a patient experience study conducted in China and then one in the US, and maybe you have differences in the response, how would then the respective labels of products that end up being approved be impacted in different geographies?

DR. DANIELS: So I'm not sure if they can talk about labeling, but I don't know if any of the panelists have any experience in terms of how you sort of have one survey that’s been used in one nationality and try to sort of translate it to another nationality. Or if you’ve seen any differences between the two and how to simultaneously make it into one version.

DR. SYMONDS: So it's -- I saw a lot of when I

was in industry that you'd have a US study, you'd have a European study, you'd have positive results in the US study and often it failed in the EU. Now was that because of the translation issues, the cultural issues, taking -- 'cause normally you take a US-based measure and translate it. It's a bit of a bugbear of mine where, okay, there's a French measure, but it wasn't developed in US, so we can't use it.

Or, you know, that was from my own company, not the FDA to just say, okay.

DR. DANIELS: Okay.

DR. SYMONDS: But, you know, so is it, is it the cultural thing or is it different clinical trial practice. But unfortunately you're running a clinical study program that has to use exertive measures that are standard across because you're running global trials.

And so you end up with -- you will end up with different labels because you have different comforts with what to put in a label. So often we do see more put into the EU label. I personally think that's because there's less damage that can be done because

you can't have a direct consumer advertising in Europe, whereas here in the US you can.

So you have to, you know, I, I feel that that's why potentially it's more challenging to get things into the label, whatever that might be, because it could be open to more use out in the big wide world. But, yeah, I don't -- you know, normally in global trials we're using the same measure. We're not taking a different measure. And so you would anticipate similar results.

DR. DANIELS: All right. So this actually ends the discussion on Guidance 2. Can we give a round of applause for our panelists for this session, as well as last panel session.

(Applause.)

DR. DANIELS: I believe we've heard some great feedback that the FDA will take into consideration for Guidance 2. But with that, I want to recap some of the things that I've heard across the two sessions before we break out for lunch.

In regards to the level of detail on methods, we're hearing that more detail is needed on appropriate

ways to engage patients and other stakeholders, as well as the strategy itself in terms of how you're supposed to use each method. More detail on sample size representation and saturation in qualitative methods, particularly the differences for sample size to achieve representativeness versus saturation. Also maybe providing detail on the minimum number of patients maybe that is needed for each particular method.

More detail may be needed on mixed methods, including the practical use of this approach, and also how to use several different methods. Qualitative methods may not be described comprehensively. Some methods were missing, ethnography for example is one of the examples that was given.

Discuss the potential utility of market research and the differences in relation to qualitative methods. More detail on the tradeoffs in terms of how patients may -- in terms of the risk of benefit or the risk of harm. Revising how social media networks are presented.

And this method may not be completely fit in the qualitative method docket, but may be actually a

source to get an early read on patient experience to help inform future research or maybe study materials. Or maybe even be used to triangulate with other research methods.

We've heard that patient verification is important with the use of social media, as well as digital health technology in this session. As well as that the source of methods used to collect the data is important as well.

I've heard that we need more information, other methods, and how it should be considered to add to the patient experience to help explore the lived experience and maybe tie it back to the research question. Also exercising flexibility around the methods that are used, as long as it's rigorous and transparent.

We've heard that we need more information evidentiary standards and how to use with each methods and what's the susceptibility of each methods from the agency in terms of the level of detail on operationalization. We've heard to emphasize that the steps for data analysis and qualitative studies is

probably essentially iterative and not sequential.

Maybe revisit how we approach coding or not coding qualitative data, as that seemed to be a little confusing as written in the guidance from our panelists. More detail on cultural factors on qualitative methods. Maybe emphasize how the methods used can sort of make the data more precise.

Emphasize experience of the qualitative research versus the researcher with credentials. We've heard from this panel maybe more detail operationalization on response rate, more details on generalized mobility of data, specifically related to any digital health technology used. And maybe include some digital health technology in the main document and not having it just as an appendix.

Maybe discussing more missing data in terms of the respective method. And identity verification with technology. As far as other best practices on operationalization, we've heard that maybe to emphasize using transcripts, like reading them all the way through to get a little bit more detail in terms of how we would analyze the data.

Discuss the importance of double coding of qualitative data to ensure reliability. Discuss the importance of use of participant quotations to represent qualitative data in the patient's own words. Acknowledgement of the patient's journey.

As far as level of detail and study materials, provide examples of qualitative interviewing script and focus group guide and appendices. Add challenges of conducting qualitative research in various settings, such as hospitals and long-term care facilities.

Consider adding burden of disease management. Information on reporting. We've heard that there needs to be a balance of information and study materials, particularly with the protocol and maybe including something about patient consent.

As far as other special populations and culture factors and emphasizing the use of care partners. Maybe a section on individuals with attention deficits and how to leverage technology remotely. Sensory impairments we've heard from the audience. And maybe also maybe focusing in terms of technology naïve individuals or maybe individuals with

dexterity conditions, as well as visually impaired, which that would fall in with sensory impairments.

As far as the Guidance 2 format, we've heard figures and tables are always good. Linking the methods to research questions. More case studies or examples, avoiding a checklist, but sprinkling flexibility here and there. Time points for FDA engagement. Patient experience data should be thought across throughout the product lifecycle and early.

We've heard more type C meetings maybe where we can bring in patient experience data or maybe type B meetings such as in a phase two meetings or type C meetings. And then also maybe having more clarity around the pathways to receive advice in the terms of looking at these patient experience studies.

So I want to encourage everyone to comment on the discussion document. The public docket does close on December 14 of 2018. I think Ebony sort of drove that in our minds, but heres a slide right here to show you how you can do that. Reading slides and a webcast will be posted within two weeks of the meetings. And transcripts will be posed in a month.

And so that concludes this session on Guidance 2. Thank you. And lunch will be from 12:30 to 1:30. And after lunch we'll begin -- full, one full hour. Okay, for an hour from now. So I don't know what time it is right now, 12:40. So 1:40, and after lunch we'll begin Guidance 3. And the next session will start, I guess, at 1:40. So we'll ask everyone to come back so we can begin promptly. And, again, thank you for all your participation and your attention. And have a great lunch.

(Applause.)

DR. PAPADOPOULOS: ...in the Office of New Drugs and CDER. And for the next day and a half we're going to be talking about Guidance Number 3. And so in the morning we heard a lot of very helpful discussion on how we go about collecting useful patient input and information to determine, you know, what is really important to patients and caregivers.

And for the next day and a half or so, we will be discussing how we use this information to really measure what matters most to patients in medical product development. And so I'm going to be covering

an overview of the methods to select, develop, or modify clinical outcome assessments to be fit-for-purpose.

So I'm going to start with a background. I'm going to define some key terms and outline some general principles. And then I'm going to go into some of the key topics that we're going to be discussing over the next day and a half in panel sessions in much more detail.

So before we discuss methods, it's always useful to take a step back and remember what is our goal with outcome assessment. And it's generally to determine whether a medical product has been shown to provide clinical benefit to patients.

Clinical benefit is defined as a positive, clinically meaningful effect of an intervention on how a patient feels, functions, or survives. And we use clinical outcome assessments. Ultimately how we describe this clinical benefit to patients and providers and other stakeholders, is determined by the concept of interest or the outcome that was measured.

So there are different ways of classifying

clinical outcomes based on how they are collected. Clinical outcomes can be collected, of course from the perspective of the patient. And here we -- this is the preferred method for collecting symptoms, for example, pain and fatigue. They can be collected from the perspective of a clinician. And generally we use these when clinical judgement is needed.

It can be from a non-clinician observer, such as a parent or caregiver of young children or someone who has cognitive impairment. And they can also be performance-based. And this is based on a task that a patient performs that's relative to their functioning.

And in addition, we can also use digital health technologies, such as activity monitors to assess clinical outcomes. In 2009, the FDA published final guidance defining good measurement principles to consider for patient-reported outcome or PRO measures intended to provide evidence of clinical benefit.

While this guidance does not cover other types of COAs, these general measurement principles are widely considered to be applicable to all types of COAs. Importantly, while the guidance describes best

practices, we also recognize that alternative approaches may be needed to meet the practical demands of medical product development.

Now Guidance Number 3, when final, is expected to replace the current 2009 PRO Guidance. It'll comprise a main document describing good measurement principles relevant to all COAs. It will also include attachments describing unique issues related to the individual COA types. And we expect this guidance to retain and build upon the good measurement principles that are in the current 2009 Guidance.

So Guidance 3 will emphasize four general principles. One, all COAs should be fit-for-purpose. Two, there are certain good measurement principles relevant to all COA types. Three, alternative methods and approaches to those described in the guidance may be applicable based on the circumstances. And finally, FDA encourages leveraging existing COAs where appropriate.

So central to the evaluation of any tool or outcome measure is the concept of fitness for purpose. And for medical product development tools, fit-for-

purpose is a conclusion that the level of validation associated with that tool is sufficient to support its context of use. Of course, this is a generic definition. And so how do we then operationalize this definition for clinical outcome assessments.

For COAs we need to consider three main areas when evaluating whether a tool is fit-for-purpose. One, is the COA appropriate for its intended use? Is it appropriate for the study design, the patient population, and other factors? Two, does it validly and reliably measure a concept that is clinically relevant and important to patients.

And finally, we ask can the scores produced by that measure be communicated in labeling in a way that is accurate, interpretable and not misleading, provided, of course, that the COAs appropriately applied. Why is it important to use fit-for-purpose COAs? The use of an adequately developed or tested instrument introduces risk, whether the instrument is used off the shelf, modified, or developed de novo.

And lack of a thoughtful approach to measurement may lead to lack of a patient-centered

instrument where the tool doesn't assess what is important to patients. It can lead to content validity problems or misleading content, such that the tool doesn't accurately assess the target concept in that population. And this may compromise our ability to accurately describe the clinical benefit.

And finally, it can lead to poor ability to detect change, which, of course, may compromise the ability to detect a treatment effect when one exists. And ultimately the concern is it might lead to failed clinical trials.

Given the importance of fit-for-purpose COAs, FDA has developed tools to help guide our stakeholders through this process. One of the tools that we developed is called the Roadmap to Patient-Focused Outcome Measurement in Clinical Trials.

We developed this roadmap to help people systematically think through the important considerations when selecting a fit-for-purpose COA. Essentially, there are three main components of issues that we feel are important to consider. Number one is understanding the disease or condition. Number two,

conceptualizing clinical benefit. And number three is selecting or developing an outcome measure to be fit-for-purpose.

Now, having some understanding of the disease or condition is really fundamental to setting up a measurement strategy. And it includes understanding the natural history, patient subpopulations as we heard this morning, where patients are on their journey is an important factor to consider.

We should also consider the healthcare environment and what therapies are available to patients. And also very importantly, as we discussed this morning, is input from the patients and the caregivers themselves.

Now column two is really where the rubber meets the road in medical product development. And it relies on some understanding of the intended clinical benefit of a medical product. The first part is identifying the concept of interest for meaningful product development. And so this is the clinical benefit in terms of how patients are feeling and functioning.

And when we're identifying our concept, we want, of course, the concept to be important to patients, but we also want it to be clinically relevant and something that can actually show a change with an intervention.

The second part is, of course, defining the context of use. And this includes description of the disease or condition, any patient populations, subpopulations, the clinical trial design, for example, the endpoint in which the measure will be used, and factors like the endpoint positioning. Will it be used to assess a primary efficacy endpoint and a registration trial or will it be used in exploratory context. So all of these are important when we're thinking about the context of use.

And it's only when we've considered these elements can we then really meaningfully select or develop an outcome assessment. We can go about selecting the type of COA based on what we want to measure and in whom. One point I wanted to make is that, you know, we talk a lot about patient-centered outcomes.

And importantly I think we need to remember that the term patient-centered outcomes, which refers to, which refers to outcomes that are important to patients is not equivalent to patient-reported outcome. And so we have a number of tools that we can draw on to measure what is important, either measure or reflect what is important to patients and the particular context of use. So that's just an important distinction.

Then, we can also search for a COA for the context of use. And I'm going to go through these, the later two steps a little bit more in a framework that I'm about to show. And so this framework is really to be used with the roadmap. And it provides, again, a more detailed method or approach to describing, selecting, modifying, or developing COAs.

So why did we feel the need to develop this framework? Well, we acknowledge that with the many thousands of diseases and potential drugs in need of development, I should say drugs and other medical products in need of development, it's impossible to have instruments that have been fully developed and

tested specifically for each disease in context of use.

And so we often look to use existing COAs. And a decision that we grapple with frequently is whether an existing tool is fit-for-purpose as is for a context of use. Whether it could be modified for a new context of use, and whether a tool should be developed from scratch. In other words, there is nothing that we can employ that's existing.

So typically once we identify the concept and the context of use, we'll go to the published literature and other sources and also seek stakeholder input to see what existing tools might be fit-for-purpose.

And some common questions that we ask are, did the development include patient or caregiver input? Does it assess well-defined concepts that are important to patients and could be modified with an intervention? Does it have the appropriate measurement properties for the context of use, or could it be modified to be fit-for-purpose? And these are challenging questions.

So this slide shows some potential applications of an existing instrument. Of course, it

could be in the original context of the original development and evaluation, but it can also be in a new context, such as in a new population or subpopulation, a new trial design, new indication, or a new intended use, such as, you know, it could be more of a diagnostic, and now we seek to use it as an outcome assessment.

And there are other cases where we may have questionnaires used in a clinical setting to collect patient information that just don't meet the standards of drug development. So we need to consider all of these things.

Okay. So this is the proposed framework. And it's going to be hard to read on the slide. So I'll break it down later. But I wanted to show the entire figure, which is composed of two main parts. The top part is the decision framework. And the bottom describes the steps to instrument development.

So here's the top portion of the figure from the previous slide. And I'd just like to take a few minutes to walk through this. And, as I mentioned before, we always need to start with the -- identifying

the context of use and the concept of interest. And that's shown on the upper left corner.

And then next we look to see whether there is an existing COA that might be fit-for-purpose. If we find an existing COA that has been demonstrated to be fit-for-purpose to assess the concept we're interested in, as well as in the same context of use. It can be used without any additional work. Again, that's provided that it is fit-for-purpose. And that is shown on the top right-hand side.

If it can't be used as is for a new context of use, it may need to be modified. And so in this case we would, of course, seek stakeholder input in the modification process. And then we would want to confirm the measurement properties of that tool using the steps of instrument development.

So then, again, if we -- so I actually should go back a step. If an existing tool can be used as is for a new context of use, then we would want to confirm the measurement properties in that new population, say. And if they aren't, they have been confirmed, then we can use it as is. And if not, then we would want to

modify the tool for a new context of use. And, again, following the steps to instrument development.

And sometimes we don't find a suitable tool, or we might find something, but to -- we're unable to modify that. Or the modification would be such a major modification that it would really necessitate starting over. And so in that case we would then want to go through de novo instrument development.

So here we see the bottom portion of the diagram, and this will be familiar to many people in the audience, because it's derived from the wheel and spokes figure that's in the final PRO Guidance. And it shows the steps to demonstrating validity, reliability, and ability to detect change, which, again, are important to any COA type.

Now, I'd like to emphasize that instrument development is iterative. It involves both qualitative and quantitative components, and when we modify an instrument, generally the level of modification and the nature of that modification will determine what evidence is needed from these steps.

This is a copy of the wheel and spokes figure.

This is in the 2009 PRO Guidance. And this figure, while useful, of course, was developed for PRO instrument development rather than COA instrument development more broadly. And it might also be more relevant for de novo development than for leveraging existing tools.

And so given these considerations, one question we have is whether the new framework that I described might be a suitable replacement for this wheel and spokes in upcoming guidance.

Okay. So now I'm going to be discussing some other key topics. And to set the stage for tomorrow's panel discussion, I'd like to cover some of the challenges and opportunities of COA development in special populations, including pediatrics and rare disease population.

So I'll start with children. And in children there are particular considerations when it comes to clinical outcome assessment. And these include the child's cognitive and linguistic development, their ability to recall their experiences, and to reliably and validly self-report, and also their willingness,

their actual willingness to self-report or perform a task.

We also need to consider the child's ability and motivation to complete study assessments according to instructions and the complexity of the measurement concept and the assessment methods.

And finally, there's also potential for differences in disease manifestations by age groups. So these are all very important considerations for pediatrics. And so, you know, in pediatrics, as with all COA development, it's important to consider the roadmap.

And if the impact of a disease or condition on how patients feel or function, for example, if it differs across the age span, we may need to use different COAs. And then also if we're modifying an existing COA, say we're using a COA in a new age group, we should also involve the target population in that modification process.

Also we should consider whether a certain type of COA can be validly and reliably completed in young children or those with cognitive impairment. And so,

for example, an observer-based outcome assessment may be needed instead of self-report in these populations.

And importantly FDA is open to considering alternative methods and approaches in this setting to meet the challenges of measurement. Now, in rare diseases we also see a lot of the same challenges because, of course, rare diseases will frequently affect people across the lifespan.

And here we see some challenges related to, perhaps, incomplete understanding of the disease, such as its natural history or important subsets. Of course, by definition there are small patient populations that we can include in our instrument development, as well as clinical trials. And we heard some about that this morning.

There are cognitive and linguistic differences and developmental differences and several other considerations similar to that in pediatrics. But also there's limited availability of disease experts. And there's wide geographic dispersion of patients. And so we have to carefully consider, you know, the cultural and linguistic validation of any clinical outcome

assessment that we use.

So what are some of the recommendations to help approach some of these challenges? Well, of course, we should use fit-for-purpose clinical outcome assessments in natural history studies that will inform clinical benefit in future drug development. And so this is very important consideration.

We should also carefully consider the measurement strategy, leveraging existing COAs where appropriate. Measurement property is also critical because any noise in an instrument can interfere with our ability to pick up a treatment effect, in particular, when there are small populations.

So we recommend consulting with the FDA with patients and other experts early in medical product development. And I'd also like to stress that pretty competitive collaboration is also extremely important in rare diseases as with other diseases, and that the FDA's open to considering multiple approaches.

Another area that we often struggle with is how to interpret clinically meaningful change in a measure score. And that, again, will be another topic

for the panel discussion tomorrow. So why is this important? Well, it's imperative for understanding whether a medical product has provided clinical benefit or, perhaps, harm. And we know that statistical significance alone doesn’t indicate whether an individual has experienced a meaningful clinical benefit.

And so I’ve shown some of the specific methods on this slide, including anchor-based methods, which we see quite commonly, again, and distribution, cumulative distribution displays. Again, we see that quite commonly.

Cognitive interviews are very useful. We can ask patients or caregivers whether the differences among response options are important. Study exit interviews might be employed. In addition, surveys and perhaps, and there are also other emerging methods. But typically we use multiple methods in combination. And this provides us with greater confidence in that we have a meaningful change threshold.

Tomorrow afternoon we also have a session on digital health technology. Again, this is an emerging

area of research, and we are continually learning about how we can leverage this technology in clinical trials.

So first I wanted to say that this term, digital health technology is a very broad term and includes categories such as mobile health, health information technology, wearable devices, telehealth, telemedicine, and personalized medicine. So it's quite broad.

For the purposes of this workshop we're using this in the sense, in the context of clinical trials to capture clinical outcomes. So, for example, mobility, sleep, falls, and just wanted to say a few additional words about the technology. It can be used to collect -- it can rely on either active or passive patient participation. So an example of active participation is where a patient is asked to perform a task. So it could be, say, a memory test. And in that case it's basically a performance outcome assessment.

Digital health technology also very commonly, as we've heard about this morning, is used for passive data collection, such as through wearable activity monitors. But importantly, I think, you know, the

value of this and why I think this area is so important is that it can provide us with a window into patients' lives that may not be accessible any other way. And it can also provide us very useful complementary information to patient-reported outcomes or other types of outcomes.

So, again, digital health technology is being assessed in many venues and actively discussed in many venues, both within the agency and outside the FDA. And why is that? Well, it affords many potential opportunities. And some of these are shown here in this slide.

We can assess patient functioning in a real world setting. It could streamline clinical investigations, including areas, such as rare diseases, pediatrics, and sleep. And it can capture offsite and remote data directly from study participants. And this allows us to access patients in distant locations and potentially enable broader participation and inclusion in clinical trials. And there are other potential opportunities, I'm sure, that are expressed here.

There are also many elements that need to be

factored in when planning for digital health technology. So, you know, importantly is how do we select the appropriate tool for the concept and the context of use. So what performance characteristics in the specific technology are we looking for? And are they appropriate for that patient population? What aspect are we measuring?

So maybe we're interested in mobility. Well, are we looking at walking speed, walking distance, you know, what are we exactly, what's the most appropriate aspect that will give us meaningful information in a particular population?

Another consideration is how do we develop the endpoint and the analysis plan? So what data are we aggregating, and how are we analyzing the data in a meaningful way? Because, as you can imagine, we can get massive amounts of data from using this technology. And we want to be able to analyze it in a meaningful way so that we can interpret the results.

Also we need to think about compliance so that we avoid missing data. So is the patient, is the patient willing to wear a sensor? Are they going to

forget to wear a sensor? Those are things we need to consider. And among other factors, such as safety, comfort of wearing a, say a wearable device, and privacy concerns. And I'm sure there are others.

So in closing, I hope I've reinforced that any COA should be fit-for-purpose in medical product development. And FDA has developed tools to help stakeholders select and use fit-for-purpose COAs, which include the roadmap for patient-focused outcome assessment, and a proposed framework for decision making for COA selection, modification or development.

And finally, I want to stress that the agency recognizes that multiple approaches to clinical outcome assessment and instrument development may be appropriate.

Okay. Thank you for your attention. And now we're going to transition to our FDA panel discussion. So I'd like the panelists to -- I'd like to invite you to the table, and we can get started. So if everyone on our panel could please introduce yourselves. We'll start with Michelle.

DR. TARVER: Good afternoon. I'm Michelle

Targer. I'm the Director of Patient Science and Engagement at the Center for Devices and Radiological Health.

DR. HO: Good afternoon. My name is Martin Ho. I am Associate Director for Quantitative Innovations at Center for Devices and Radiological Health.

DR. IRONY: Hi, my name is Telba Irony. And I'm a Deputy Office Director at the Office of Biostatistics and Epidemiology at the Center for Biologics.

DR. JOHNSON: I'm Laura Lee Johnson. I'm the Division Director for Biometrics III in the Office of Biostatistics and the Center for Drug Evaluation and Research. I'm also our Clinical Outcome Assessment Liaison and our Rare Disease Lead for the office.

DR. KLUETZ: My name is Paul Kluetz. I'm a medical oncologist working in the Oncology Center of Excellence, and I'm leading a patient-focused drug development program as an associate director.

DR. LAPTEVA: I'm Larissa Lapteva. I'm 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.

DR. MULLIN: Hi. Theresa Mullin, Associate Director for Strategic Initiatives -- oh, there's my title -- in the Center for Drugs. And I lead the patient-focused drug development effort in CDER.

DR. PAPADOPOULOS: Thank you, all. And Dr. Billy Dunn, who is the Division Director for the Division of Neurology Products will be joining us a little bit late from another meeting.

So I'd like to just start with, you know, the general principles that we hope to emphasize in Guidance Number 3 as shown here in this slide and invite anyone on the panel to comment on whether these are the appropriate principles to emphasize if they would emphasize any other principles. And perhaps, you know, from your perspective, what are some of the activities, some of the policies or practices in your respective areas that could speak to some of these.

So I'll just open it up. Yes, Martin?

DR. HO: Thank you. I would to speak on

number one and number two. I think they are -- goes well with each other. Mostly because in devices we are -- our regulation is a bit different from drugs. And when we're talking about COAs mostly, the focus we -- would be on using them as an endpoint, which would result in labeling claims.

But in devices we not only are using them for labeling claims, but we are also using them to inform us to make the benefit risk assessments when we are conducting clinical trials or when we are evaluating clinical trials. And, therefore, definitely the COA should be fit-for-purpose and also that specific purposes should be well understood before we are committing resources to, you know, to study them or perhaps to use them in clinical trials.

And I also wanted to say that the good measurement principle is not only relevant to all COA types, but I would say that to all the measurements being used and studied in clinical trials for us so that we can learn from this experiment.

But I would say also that validity is a spectrum to me. So yes or no -- it's not yes or no,

but rather is a combination of different types of evidence that gather, and we are using them as a whole to consider for us to make our regulatory decisions. Thank you.

DR. PAPADOPOULOS: That's a great point. Yes, Laura Lee.

DR. JOHNSON: So I'll mention a little bit about number four kind of with my rare disease hat on. And it was mentioned in the morning as well. And one element that I like about much of what Elektra just presented out of these documents is to really clarify the ability to leverage the existing COAs where appropriate.

And we have gotten feedback over time where it appeared that sponsors were concerned about not -- they thought they had to create de novo. And I think we've spent considerable time trying to say, no, that's not the case.

So what I'm hoping, and I'm sure probably others agree with me, is that this will encourage use, and to steal the phrase, reduce, reuse, recycle, to think about that. And especially when you're thinking

in the rare disease realm where we do have precious few patients, and patients are your most important resource everywhere, regardless of actually the group that you're working with and the patient population.

But to be able to leverage something, especially if you're measuring a common concept, such as physical function. Others say, okay, does this really apply to my patient group. And if it does, can I get a little bit of information and move forward. And that's not always going to be the case, you know.

For example, if you're worried about ambulation and the tool is talking a lot about your upper extremities, that may not be the case. But that general principle of can we leverage what we know because we know a lot. And that reduces burden on patients and allows us to spend the energy and all the other resources in many of the other areas where it's necessary.

DR. KLUETZ: I'll make a couple points to Elektra's slides. I guess from the oncology standpoint we typically don’t have a patient-reported outcome as a primary endpoint in our clinical trials. And yet we

have patient-reported outcomes collected and assessed in most every commercial randomized clinical trial that’s submitted to the agency. And so they're important.

And it's important in our context for obvious reasons. Our diseases can be symptomatic. Our diseases have therapies that can also be symptomatic, and those that net benefit from the improvement in disease symptoms. And unfortunately the symptomatic toxicities will feed into physical function.

So we've taken a look at patient-reported outcomes within our area, and while not a primary endpoint, looking to find ways that it can discriminate between drugs. We see a lot more drugs than we have ever seen, thankfully, in the oncology setting right now. And so we have an opportunity now to have two or three drugs in the same actual space, when that's never happened before.

And so how can we help patients and providers understand and differentiate between these therapies. So we've created a framework of core outcomes, and if I could make one comment, it would be that in each

disease area it would be nice, and I believe Theresa has, is also looking to do this, to identify core outcomes that would make sense for your disease-specific area. And for us, we've looked at disease symptoms, symptomatic toxicities, and overall side effect impact in physical function and your ability to work and do your activities as important.

And with a regulatory hat we try to ensure that we are isolating the effect of the drugs. So these concepts are close to the effect of the drug, potentially less affected by non-drug influences.

So just to also mention on leveraging existing COAs, we have these concepts that we're interested in. There are many COA tools or patient-reported outcome tools available for physical function, as well as particularly symptomatic adverse events. And I think it's really important that we leverage existing tools where possible.

I think we spent a lot of time developing new PRO tools. And I think the next three to four years is going to be focused on identifying a very good research question for these tools and the analytics and

interpretation to be able to use them effectively in whatever disease area that you have.

Also to Martin's point, 'cause Martin does a lot of this, digital health, I don’t see digital health wearable devices as replacing, for instance, patient-reported outcomes. I think that they can be used in concert.

I can imagine where a wearable device, for instance, would give you great activity data that could be further complemented by a patient-reported outcome to give you an idea of the quality of that increased activity and also the meaningfulness of that. And it'll give your trial some internal validity. So you should see things going the right way. Because there is uncertainty in patient-reported outcomes, and there's also uncertainty in how new the wearable devices are.

It's a very exciting time technologically, and I think we can do them both.

DR. PAPADOPOULOS: So -- I'm sorry, go ahead Theresa.

DR. MULLIN: All right. Well, just quickly,

and I, you know, the methodological experts are to my right. But I think that to me the first statement just sounds -- it may sound so obvious, but how could you use COAs that are not fit-for-purpose? But if you think about what was said earlier today, like you have to start, Patty Spears, for example, I believe was said earlier, you know, you've got to remember to start with asking people what matters the most. Don't skip the step of finding out, listening to patients and hearing what really mattered to them.

And having done that early work, and that sort of sets the scene, I think, to me, before you go into the little flow diagram that Elektra showed. But imagine if you had that, you had talked to people about what really mattered, you had identified those things, your product actually, you think, effects that.

What if you don't have a clinical outcome -- if you don't have a COA that's actually going to measure those things, your product is not -- you're not going to have the evidence you want to present at the end of the day to the regulatory. You've done all that work. You've invested all that money, but you used a

tool that actually wasn't going to really effectively or wasn't relevant to the concerns that people told you about. It may not be valid or reliably measure that. And so, you know, you don't want to blow it in that sense.

I mean, I think in terms of investment you really want to be careful to connect what you hear early to the characteristics of that tool that you use. And not to say anything that's not consistent with what everyone has said in terms of if you can find an instrument to use that's already out there that does that, great. If you can adapt something that's already out there, great. But it's tied to those things that you heard mattered the most.

DR. LAPTEVA: Well, I would like to add that in addition to agreeing with everything that's been said before, I think we should not be losing sight that when we're talking about methodologies of clinical outcome assessment development, we should really remember to view COA development from the perspective of finding new treatments, because that's what really important to patients.

In the draft guidances we've described more or less classic psychometric approach to how to develop a scale. You have a number of items. You would select them. You would reformulate them. They're supposed to reflect on the domains of interest and concepts of interest. And then with application of the appropriate statistical methodology you would have an outcome measure through an iterative process.

And I think that this is really a proper way of doing it, and a sound methodological way. And I would like to really commend COA team and Elektra and Laurie Burke before her for advocating for this approach and really for bringing up in the quality the outcomes assessments that we see in development programs.

I also would like to say that inherently any outcome measure in drug development would be connected with the molecular pathway or pathways that a particular investigational drug or biologic is supposed to influence. And there are also realities of R and D and R and D productivity metrics where one of the initial steps in drug development would be target

identification and validation.

And we all know that oftentimes this is done through automated searches of chemical compounds and receptors and proteins, gene libraries nowadays. And as we focus more and more on the clinical meaningfulness of the patient-centered outcomes, I think what we will probably be collectively doing, and we hope to do that, would be to nudge the R and D a little bit away from the combinatorial chemistry and high throughput screening types of approaches towards the systems biology in rational drug design.

Where we could potentially influence, really target the focused places on the pathways of diseases. Where it could be targeted specific disease modifications and specific symptoms and signs that are truly important to patients. So I think this is really in the long run going to be a good thing. And hopefully will increase the number of compounds that are identified and then make it through the development process to the market.

I do have a couple of comments about the roadmap and the framework, but I think that should be

later, right?

DR. PAPADOPOULOS: Yes.

DR. LAPTEVA: Okay, thanks.

DR. PAPADOPOULOS: And after this one.

DR. TARVER: So just to make a couple of quick remarks. In the Center for Devices we've seen an exponential increase in the number of patient-reported outcome measures being included in the submissions. And we're seeing the use, not just in the effectiveness component, but also in safety and inclusion and exclusion criteria as composite endpoints.

So these measures are extremely important. And being able to measure things that are important to patients, we zoom out. What we're really trying to do is help people make good decisions about how to take care of themselves and how to make good healthcare decisions. And so what we're measuring should reflect those concepts.

So I think the fit-for-purpose concept is something we've really focused on quite a bit in our center to ensure that the measures that we are seeing are actually measuring the concepts of interest that

are important to the patient's and the providers.

And also in terms of the leveraging existing COAs, I think we all are echoing a similar sentiment, which is that we really want to make this most efficient. And in our center we have regulation that says least burdensome approach so that we get the answer that’s meaningful to the providers and to the patients.

So I think that these principles all reflect what sentiments we are saying in our centers and across the agency.

DR. IRONY: And finally I would like to comment the principles of fit-for-purpose and the leveraging the existing COAs and see how they might fit together. And I think the great idea in that is when you are leveraging an existing COA for a different condition or a different patient population. The difference might be on the clinically meaningful benefit.

Because that will basically depend on the condition you are treating, the patients in that population and what the patients prefer, and the level

of risk. So if you have more risk, let's say, in a certain treatment or for a certain patient population because the disease or the condition is riskier, you would probably require a higher benefit.

So the clinically meaningful benefit might be not the same, even if you are using the same COA. That will depend on the condition, will depend on the patient. And that's an important comment that I would like to make and emphasize, given everybody said a lot of things about the principles.

DR. PAPADOPOULOS: Thank you. And I, I guess I also wanted to highlight an example of, you know, where we've actively tried to encourage the use of existing outcomes. And this was discussed a few weeks ago at a meeting on transplantation. And this meeting was -- one of the key topics discussed there was how can we do a better job of assessing symptomatic toxicities in patients who are on immunosuppressive drugs in the transplant setting.

And so what we, what we did was we brought in other disease experts, Paul and others, and we -- and also people from the NCI, looking to see how we could

leverage a tool that the NCI developed in the cancer population that measures symptomatic toxicities in the transplant population because a lot of the toxicities are the same, fatigue and others. And it could be that we can leverage these.

And so that's very exciting. That's what we're looking to do. And, you know, of course there may need to be some more specific items unique to the transplant population and the drugs that are commonly used. But certainly there -- nobody thought there was a need to reinvent the wheel and start from scratch. So I just wanted to highlight that example.

Yes, Larissa?

DR. LAPTEVA: So I would like to also bring up an example. I speak for the Center for Biologics. And one of the products we approved recently was a product which contained autologous, meaning patient's own, cells, chondrocytes, chondrocytes constitute cartilage that is inside our joints. The chondrocytes were harvested from a patient and then expanded en vivo and then put on a membrane and then re-transplanted into the knee joint where the product is currently used for

symptomatic defects of knee cartilage.

And so when that program came to us and we were discussing a primary endpoint that would be used as fit-for-purpose and in the desired context of use, to then in the clinical trials demonstrate the primary evidence of effectiveness, there was an instrument that was developed years ago. And we looked at it and it clearly covered the important concepts that we were looking for.

It covered the symptoms, the signs, the functioning, the activities of daily living, the quality of life that was body-part related. And so we adapted that instrument, and the program ended up being a successful program.

And this is just one of many examples where we don’t necessarily worry about whether it's a new instrument or an old instrument, whether it was developed in the specific population -- we do worry whether it was developed in the population for whom it is important to really measure the concepts as we're interested in. But it doesn’t matter whether it's an existing tool or a tool that’s developed from scratch.

It's important whether it measures the concepts that are important for that disease.

DR. PAPADOPOULOS: That's true. And I think we've seen many examples where, you know, you have tools that are, primarily have been developed in the clinical setting that include items that aren't expected to be modified with a treatment. They might be -- you know, patients might have some impairment which is fixed and cannot be changed with the treatment under investigation. And so we will then want to not include those items when we're developing, when we're applying that COA because the concern there is that it might interfere with the sensitivity of the measure.

So that's one common scenario that we've seen when using existing instruments. Okay. Yes, Paul?

DR. KLUETZ: I would just also say as far as the fitness for purpose, like one of the things that we've been running into a lot in oncology is the research question. And, again, I think there's so much heterogeneity and lack of clarity on what the research question is that it can hamper the utility.

And so one example would be you may be

interested in showing that you're add-on trial design fails to decrease, or is about the same physical function as the comparative arm. So there's no meaningful difference. Or you're trying to show that there's not a lot of difference between the arms. So you can say we're adding some toxicity, but in general patients are functioning the same.

This is a pretty common thing to do in oncology because, of course with an add-on trial you're adding another therapy that has more side effects, and the side effect profile is usually a little bit worse. So if you're trying to show that there's no difference, suddenly the sensitivity of your tool becomes really important.

And so we really look now to say how, we need a sensitive tool. You're not going to ask a single question, a single item about function in that scenario. And then conversely, if you're looking to show that you have a superior function between the arms for a product, a new product, well, now in that sense, geeze, if you use an insensitive instrument, it's at your risk. And if you show a big benefit, wow, that's

even better. And in some cases a single item is even more interpretable because you have categorical changes rather than a transformed score of a small difference that you're into the clinical meaningfulness question.

So I guess my point is the research question is so critical, and that's why -- shameless plug coming up -- the 2019 Clinical Outcome Assessment Workshop for Cancer is going to be July 12, 2019. And we're going to actually put people to task and say, here's two research questions for physical function.

Number one, how does function -- describe function while the patient is taking their therapy. 'Cause patients want to know, how am I going to function while I'm taking my therapy. That's sort of a tolerability question. And then, and it implies a different population that you're going to study.

And then the second question is, you think your drug is superior to the alternative in function, how would you show a superiority that you improve function or that function at some later time is better on arm A versus arm B. That's more of an intention to treat analysis. And that's more of an efficacy

question or a net benefit question.

And so those are very different, and we'll create trials based on that. So I think we have to get a little bit more specific about our questions, and the tools may be slightly different to answer those.

DR. PAPADOPOULOS: I just, you know, this brings up a really important point about context of use. And how are you looking to use your COA. Is it a primary endpoint? Is it, you know, secondary exploratory? You know, in the case of a lot of oncology it's not the primary endpoint. It's secondary. And so, you know, there may be a little bit more willingness to tolerate risk.

But say you have a scenario where you're developing a drug for a rare disease, and there you -- and it's a primary endpoint, and there you only have one shot, okay. Then it's really to everybody's, it's everybody's risk, really, if you fail on that. So I think that’s an important consideration when we're talking about fit-for-purpose. Laura Lee?

DR. JOHNSON: Yes, building on that, you know, sometimes, and I'm going to say this in a very

colloquial way, it almost seems like folks want it to matter a little bit less early in development. So why do I have to be so rigorous early. But with my biostatistician hat on, then becomes the problem that you are getting ready for these later trials, and you've realized, oh, well now I've had to tinker with the COA, or I finally went and talked to the patient's and figured out what mattered. So now I have to change what tool I'm using.

And so now you're asking your statistical unit to design and power a trial using a tool they basically have no data on. And that is a huge risk. And shockingly, as someone said, we shouldn't necessarily have to put COA should be fit-for-purpose as number one, but shockingly we see a lot of things that come in that may be have been taking higher risks than other sponsors would be willing to take.

And but sometimes you're in a situation where you've got one shot. And so they're just, you know, there really hasn't been that opportunity otherwise. So you're doing the best that you can. But there is this consistent risk in really talking to patients

early, even before starting your molecular development of understanding where should we even be targeting. What is important to them, and how are we going to figure out how to measure it.

And this is something that is so key and can really help development. Because as Elektra mentioned earlier, you know, it cost a lot more money to fail in the trials that you want to send to regulators for registration and marketing. So it is about, as I think everybody in this room and listening online probably gets that, but feel free to go back and tell folks and remind them of that.

DR. PAPADOPOULOS: Okay. Now I'm going to transition to the roadmap. And I'll show the schematic, but the question is whether it includes the appropriate elements to help with the measurement strategy. If not, if there's anything missing, what's missing and where should it be positioned in the diagram.

And so to review, here is the diagram. First of all, I hope everybody can read it. But I just wanted to get the perspectives from the panel, you

know, how they -- what do you think about the roadmap.

DR. LAPTEVA: Well, I promised to comment about it earlier. So in the place where we're talking about reliability and the ability to detect change, I think it may be also useful to think about resistance to bias. Because not even from the perspective of a, say, an endpoint in the clinical trial, but from the perspective of the tool itself.

It may be particularly helpful for, say, instruments that are supposed to or anticipated to be administered over time, where learning as well as the knowledge that gets accumulated about how to compensate for the stable performance on the parts of the respondent whether they're doing a physical task or a cognitive task, you know, may interfere with this exactability to detect change. And this is just one example.

So I think emphasizing the resistant to bias and the particular context of use for specific instruments, at least some preliminary look should be taken when an instrument is being developed.

DR. TARVER: I think another important point

is the endpoint definition in the trial. We often see sponsors tell us that the PRO measure is the endpoint, when it's really not the endpoint. We want to know what concept are you really trying to capture, what change has to be seen in that concept in order for it to be the endpoint that we're going to be looking at in the trial.

So that, I think, is very clearly laid out in the roadmap. And I think it's very important to highlight that issue.

DR. KLUETZ: Can I just add to that. I think it's important to come up with an endpoint if you're going to statistically test it obviously. So you're going to need to have an endpoint. But it is not likely to be the only analytic test that you do on that endpoint. And, in fact, we really do want to see prespecified -- at least in oncology -- prespecified sensitivity analyses on these sorts of endpoints, especially for scales where you're picking a threshold and you're doing your best you can because you don’t exactly have that threshold.

But we really want to see what the result

looks like at different thresholds. And also, particularly for oncology there can be a missing data issue. So stressing different sorts of analyses looking at missing data.

The other issue I -- I guess I have a question for some of the other panelists. And this is probably more important for therapeutic areas where it's the primary endpoint or whether you're -- where you're trying to make a claim of treatment benefit. You know, is there ever a drawback to adding an anchor in a study?

I mean, to me it seems like it's just -- it creates one more piece of data that gives you, you know, some more certainty that you're having an effect. And then if where you have a scale where you're unclear about the meaningful difference it gives you that anchor-based method to allow you to do that in addition to distributional methods.

DR. PAPADOPOULOS: Yes.

DR. JOHNSON: So, I will answer your question with what I've been told. And I'm -- go into my target, which is we've been told sometimes is it's the

cost. And so when we've asked to add an additional anchor, now one might say, why hadn't they worked it in there in the first place. But think it was the hundreds of thousands of dollars that it is going to take them sometimes more to change their electronic data capture system to make all these other changes. But in general could you preplan it a bit more, yes.

But, and I see it's a few people nodding, like yeah. But I do think that, again, gets back to thinking about the bigger picture and the encouragement of bringing all these different parties in early. So what we don't have on here, but you eluded to, Paul, and I've gone back and forth.

And I guess we'll talk a little bit more about this when we get to Guidance 4 in the series. And that is really thinking about the endpoint analysis. And sometimes people also forget to bring in, again, those statistical colleagues and your data colleagues as if thinking about this to have an endpoint definition, but to also think about it and tie us to that trial design as well.

So I'm in 2B going through those little

bullets. The design of the endpoint definition I'm really thinking about how am I going to analyze the data and the interpretation of it. And that's something that's hard for us to write in guidance because this could be very particular to the study in front of you. But gathering all of your daily diary information, but not knowing really how we are going to bring this together and then how I can come up with great statistical techniques, but can I write it in labeling.

So early on in my career at FDA I had a division director who sat down and said, okay, just tell me how to write in the label so your grandmother understands it. I was like, well, okay. And but that's my gut check. Every time that I think about it, it's like, okay, how am I going to write it, because at the end of the day all the people on this panel, that's where we have to go. We have to make a regulatory decision, and then we have to figure out how to communicate that information. But so does everybody else in this audience as well.

DR. PAPADOPOULOS: So I have a comment on the

roadmap. And that is, I think, the digital health is conspicuously absent. And that's part of why we're here because we want to get people's input. But that's something, I think we need to consider as including digital health. Yes, Paul?

DR. KLUETZ: Can I make a, in the not reinventing the wheel vein, I think that, let's take wearables for instance, and let's take steps for instance. I don't think that the important lessons from this will be lost to wearables either. I think when you get a stream of wearable device data you're going to run into the exact same issues that we're running into with patient-reported outcomes.

We're going to have maybe very sensitive -- it could be very sensitive with very small effects. And now you're looking at a 20-step difference between two arms in a cancer trial. Is that meaningful to patients? I don't know. And so you're going to need to integrate, again, a patient-reported outcome question that says, you know, what is being -- and I see some people smiling because we're doing this right now.

We have -- we are collecting wearable device data. It can be challenging. So as I said before, I think we should look at both streams contemporaneously and try to learn from each other. This would be a great example of that there's no difference between the arms functioning thing. It will be nice to have the sensitivity of a wearable in that setting. And that might give you that ceiling that you need for some of the existing PRO measures. Then you could have the PRO physical function data to also inform the meaningfulness.

DR. PAPADOPOULOS: I think that's a great point. And I think, you know, there's been a lot of interest in use of wearables to supplement patient-reported outcomes. So for example, one project that’s going on is looking at pain as, you know, patient-reported pain as well as the activity. And the reason is that oftentimes patient's will increase their activity as they improve, even though their pain may stay constant.

And so by having both measures we can really have a fuller picture of what's going on with the

patient. And, Paul, I am -- oh, yes, please, Laura Lee?

DR. JOHNSON: And I guess this is something folks can tell us during the open session or into the docket, which is where would it go here. I mean we also -- we don't separate out other types of data collection on here. And maybe we don't need to. And so I think we need to think very carefully about where it goes. Because I do think a lot of this applies. I also worry about, kind of, false precision, but that's a different conversation at a different time.

But I do, I think we need to be cognizant of making sure that these documents appear to be very open. And as somebody put it, kept almost timeless in certain ways, but allowing that flexibility. And so that's something that we do need to hear from folks is, you know, does it go in the roadmap? Does it go somewhere else? Kind of, what should be wear in order to make everybody -- we don't want to stall development. We want to make sure that good work happens.

DR. PAPADOPOULOS: Yes, thank you.

DR. MULLIN: So one comment that I have as I look at the stage two or phase two of the roadmap, the second, B, it seems to me, I mean, and this is where -- it looks to me like this is just your basic good practice for any kind of -- I mean we're -- it's not special to patient-centered kind of work. You always have to -- and back to points Paul and others have made, you know, what's the objective of your study?

I mean there's an ICH E9 guidance still in development on the importance of the S demand or as they put it, knowing what your objectives are before you start a study. And, you know, the fact that we're now here in 2018 writing an international guidance on this suggests that sometimes people proceed without that. And it causes lots of problems.

But so I think the other thing to me is these are all clinically important to any good program, right, and definitions of endpoints. And it's certainly true, and as you're integrating the patient's perspective and through the instrumentation and your plans for your trial design driven by your objectives and so on, that that's pulled right in.

So if anything, I think we might even want to unpack that term, context of use a bit to make sure people know just kind of what are the considerations we've been talking up here not to miss it. But it seems not special just to this kind of information source.

DR. PAPADOPOULOS: Agreed. That's a great point. Okay. Any other comments on the roadmap? Then we're going to go to the next figure, the decision tree diagram. And question is does it adequately describe, you know, how to go about selecting, developing, or modifying a COA. And if not, what else should we be considering.

And then also, you know, is this something that we should replace the wheel and spokes with, or should we retain the wheel and spokes figure and modify that figure? So this is the decision tree. Can you see the decision tree well, or do you want me to go back to the other slides that I have?

(No audible response.)

DR. PAPADOPOULOS: Okay. I'm going to go back. Okay. So this is the decision tree, and then

this is the steps of development. So I'll put it on the decision tree first.

DR. KLUETZ: I have to say, I love the fact that the first thing that you run into is, is there an existing COA tool? Do you actually need to go down the road of creating another one? And it does force people to say, is it fit-for-purpose. What's my context? Is it the same exact context? I like that thought process.

I think this does really show that -- I think the COA staff has become more okay with a modification of an existing instrument. I think that’s a very critical point that I think a lot of -- could save a lot of time. And I think we should leverage what's been done in the past. So I think this is reasonable.

DR. PAPADOPOULOS: I also wanted to backtrack a little bit and just remind people that this is supposed to be used with the roadmap. So, you know, you still need to go through columns one and two, and then decide on, okay, what type of COA, is it PRO or whatever, before you can even begin to search for an existing tool. So I just wanted to remind people of

that. Okay. Any other input?

DR. LAPTEVA: I just want to make a comment that would probably continue Theresa's earlier comment about clinical trial endpoint and the endpoint positioning in the objectives. When looking at the steps for COA development, there are four steps here. And then the first one includes a number of bullets in there. And I guess you could potentially apply it to both developing a COA from scratch as well as considering an existing COA and modifying that existing COA.

And in that aspect the sub-bullet that talks about endpoint positioning, when we're talking about an originally de novo generated clinical outcomes assessment, at the same time when the context and the concepts of interest in the domains are still being identified, it may sometimes be a bit too early to actually talk about endpoint positioning in the clinical trial. It may not be too early to talk about endpoint positioning for an existing COA, but with something that is just being developed from scratch it may just be not, perhaps, the right place for that

particular sub-bullet, or maybe we should also place it somewhere towards the later stages.

Because realistically speaking when you're just trying to figure out what's important to patients, immediately thinking about positioning an endpoint in the clinical trial may be just a bit too early.

DR. PAPADOPOULOS: And that's actually a really important point, and one that I should have also made earlier. And that is, you know, this, this is a framework for things to consider. And it doesn't mean that we know all of the answers. And it just -- it's sort of a reminder to think about these things.

But oftentimes we have to move forward with incomplete information and do the best we can. So, but I think that's a really good point. And thank you for bringing that up. Okay. Michelle?

DR. TARVER: I think as I look at the framework on the next -- maybe it's the previous slide or the next slide. The important first step is to identify the context of use and the concept of interest. So I think a lot of times we see a shotgun where there's not a clear idea of what you're trying to

capture.

And by starting at that step, I really do think that it helps to set the case for what do I really need to ask patients. It's not an easy task for patients to take hundreds and hundreds of items of questions and answer them visit after visit after visit. And we're trying to get the highest quality of data to make a good decision.

So I think really starting at that point, figuring out what do I really need to ask, what do I really need to know to help make a decision about this product is critical.

I like the fact that it clearly lays out the modifiable instruments, that’s a possible pathway. Everything doesn’t have to start from scratch. We have literature. There's a lot of things we can start with to better inform clinical outcome assessment development. So I like that it opens the door. Whereas the prior wheel and spoke kind of closed the door. It eluded to the fact that maybe you have to start from scratch every time.

So I do like the openness, the flexibility

that’s reflected in this. And the fit-for-purpose that’s very clearly laid out.

DR. PAPADOPOULOS: Yes, martin?

DR. HO: Yes. I would like to second what Michelle has said. I also wanted to say that sometimes when I talk to sponsors, most of the time, even though they understand the important of pinpointing, you know, the endpoint or have a, you know, a concept as specific as possible, but sometimes they may not really firmly grip the concept of concepts.

In other words, what does it even mean to them, a concept. So I think, therefore, I think it would be extremely important that the core concept measurements or the core common sets, that kind of, you know, exercise can really help to firm up our examples of what the concept's referring to. And therefore the sponsors can have a better understanding or context as to what exactly concepts they are referring to when they are developing medical product.

DR. PAPADOPOULOS: So I have a question. One regret that I do have is we can't put it all one slide. So you have to keep moving back and forth. But the

question I have is what do you think about the layout? So this is the -- excuse me. This is the wheel and spokes, which is a circular figure. And we took it and we put it in a line. And but, however, it isn't an iterative process. So, does that raise any concern for anyone? Would you change how it's laid out?

DR. JOHNSON: I guess it -- I kind of like it this way. But I could see -- I'm interested to see what we hear on the docket because I think even when it was in the wheels and spokes and in a circle, people felt like they had to go in a very prescribed format and that also that they were done.

What I like about more of the flow diagram is they keep saying, and don’t forget you got to recheck steps two to through four. And don’t forget you got to recheck. And like I’ve gotten questions when we use the wheel and spokes. They're like, oh, but I'm skipping to this part, is that okay? And it's like, yes, it's fine, you're good.

So but, you know, some people may think they literally have to finish everything in one before they move to two, before they move in. So I don't know,

other than continuing to use the word iterative, what we can say.

DR. PAPADOPOULOS: And we also paid careful attention to this, so. We say as appropriate. So the type of evidence that you gather would depend on the modification, the extent and the nature of the modification. So it doesn't necessarily mean you have to do everything on this. Yes?

DR. KLUETZ: Can I just see from a show of hands who is either a clinician or from the clinical development group of their industry? So some, but not the majority. So one of the things that I really want to focus on over the next year or two or couple years is to make sure we pull the clinical groups in much more into this process. Because I guarantee you if I stuck this up in front of one of my clinical reviewers, they would be like, context of use, concept of interest, content validity, iterative -- what is iterative? I mean that's -- no, I'm just kidding. I think they'd probably know that.

But literally, there's a lot of terminology in there that is going to really blow clinical folks away.

So A, I would recommend that we do a very good job at marketing very good glossaries that Theresa and her group have put out in the PFDD Guidance to glossary there, the best guidance from the NIH and FDA on what is a biomarker, what is content validity, what are the different COA instruments.

And then B, really loop our clinical colleagues in. I'll do my part, but you, you know, you need to get your clinical teams together so that we can actually come up with those research questions and those endpoints.

DR. PAPADOPOULOS: Yes, Theresa.

DR. MULLIN: Elektra, I don't have the, I don't know the answer, but I can imagine that if you -- I mean, we say iterative, but I think we also want to not scare people off with this idea of endless iteration. So I think it has to be when are we close enough to the asymptote that we're good.

And so when is it good enough. And a little bit to Paul's point, and maybe it's the New Jersey perspective, I don't know. But I think I'd even like to see what this would -- if we translated it into here

are questions you need to ask yourself at each of these stages. And so the question might be, for example, what's the research question you're trying to answer? Somewhere that comes in. How good, how sensitive does that tool have to be to really be able to address the research question you're trying to -- so some of it might be we can even flip it a little bit to a different way to think about the same concepts, the same considerations.

But I think we'll want to give people a sense of, you know, I've done some iterations on this, and I'm -- it's at a good usable place now for the purposes of my study and what I found out about, you know, the patient population or something.

DR. IRONY: Let me just suggest, you know, one approach would be to come up with examples that illustrate the process. So if we could get a couple of examples as we went through the iterations in the guidance, that will be helpful, you know, it could say some that have very few iterations and some that are very, you know, took more iterations because of one issue or another one.

Another thing I would suggest, I wouldn't call steps because steps have the connotation of, you know, you're going in one direction, but maybe points or items to consider or, but steps, you know, they look like you're going up somehow.

DR. PAPADOPOULOS: Thank you. Thank you. That's extremely helpful.

DR. TARVER: I was going to say, it's not just Jersey, it's California, too. But I would say that creating a similar lexicon really does help empower everyone to know that we're talking about the same thing. I'm a clinician by training as well, and when I came to that -- before I came to the FDA, some of the terminology that's used here was just not familiar to me.

And so when you're talking about the clinical sites, when you're talking about the chief medical officers that are helping to organize and design and put these studies into action, we all have to speak the same language. And so that what comes in resonates with everyone. And so I do think that that's really a very important point, figuring out a way to translate,

create that dictionary that -- not just the glossary, but a dictionary. Because we -- action, we make these words into actions, not just words that just exist on paper. And so how do we make them actionable.

And maybe, as you all already eluded to me, the examples will help or the questions or something that makes it more tangible so that we are getting what we need to get out of it.

DR. PAPADOPOULOS: And I think getting back to Paul's point about, you know, the terminology that may not be familiar to the audience and, you know, we're trying to make it for a broader audience. So I think that's a very good point. Martin?

DR. HO: Yes. One last thing. Even though I am a statistician, and of course I would love these, you know, the statistician can also use the same set of languages. But I'm also now pitching for our regulatory affairs colleagues, since they are the one who are budgeting for these studies and lining up all these timelines and making sure that things get done.

They are extremely important for them to get them on the same page so that everybody is talking on

the same thing and move this forward. Thank you.

DR. JOHNSON: So I'm going to ask for another case study. I know there are folks out in this audience who have had to explain this to their clinical colleagues and the reg folks and figured out how to word it. So as we're thinking about case studies, let us know, how should we reword these and to those, you know, four or five simple questions. Or how is it that you all convince folks to get things funded or started earlier, etcetera?

DR. PAPADOPOULOS: And maybe you can also do some focus groups on this document understanding. But to that point, I think that if you could send examples that you would like to see, something that you've had practical experience, anything concrete that would really help us that we could potentially adopt or adapt, that would be great.

And we are joined by Billy. Welcome, Billy. We only have about five -- anything else on the figure? And then I might -- I'll just go back.

So the question, the first question I wanted to bring up is -- so the first question was this,

whether the -- so these are the principles that we aim to emphasize in Guidance 3, the guidance that's going to be replacing the PRO Guidance. And so the question, initial one, was, you know, are these appropriate principles to emphasize, and if not, are there any others, and if you could speak to some of these from your perspective. And I know you have extensive perspective. So I'll open it up to you. And not to put you on the spot, but, yes.

DR. DUNN: Yeah, I'm going to pay, right, yeah. I shouldn't have been chatting with you 'cause I didn't hear everything. I'm so sorry. I apologize to the group.

DR. MULLIN: Let's catch him up on what happened.

DR. DUNN: Yeah, I apologize to the group for being late. I was with a sponsor in an independent meeting that was co-scheduled that we didn't really have control over. Sorry about that.

Was there a particular area, Elektra, you wanted me to focus on, or do you want me just to give general comments?

DR. PAPADOPOULOS: So these are the principle, kind of the general principles that we hope to emphasize in this upcoming guidance, Guidance 3, to replace the PRO Guidance. And so the first one is around the concept of fit-for-purpose that the COA should be appropriate for the research question, the population, study design and such.

And the second one is, you know, the certain good measurement principles, validity, reliability, ability to change, that are common across all COA types and not only that, other types of outcome assessments. And that we want to emphasize flexibility alternative methods and approaches may be appropriate to those described in the guidance.

DR. DUNN: Right.

DR. PAPADOPOULOS: And then a big topic is leveraging existing COAs where appropriate. And I know that's something that we've had some really good discussions about as, you know, how do we take a COA and utilize the things that are fit-for-purpose and maybe leave behind some of the other things.

DR. DUNN: Right. Right. Without making the

people that do this work too angry in the process as we pare things away. You know, I think those topics are great. You know, some of the thinking that I was doing about this topic in discussions with you and the panel in advance, I think, you know, dovetail with this quite well. And, again, my apologies for being late.

But one of the things I really like about this guidance is that I agree that documenting the optimal approach is really the right way to go. But I think there's an awful lot of room for flexibility and judgement when you apply this, these principles. And so having a repository of something that’s optimized or idealized is very, very important.

It doesn’t necessarily mean it's going to be attained in all situations, and I don't think it will be in most times. But it's very reasonable, I think, for us to write our guidance in a way that gets that out there up front. And then we kind of know what the playing field's like. So I'm very glad to see that being emphasized.

You know, often we talk about the importance of assessing how patients function in their daily lives

in their natural environments as opposed to a lab or a clinic setting. That gets a lot of, pardon me, that gets a lot of play here. But we don't want to be too extreme about that.

You know, obviously a measure in a trial will of necessity be assessed in that trial, and that may and probably will involve structured assessment in a clinic setting. You know, such assessments take a wide variety of forms. And they can provide important and often adequate evidence of a drug's effectiveness that we can rely upon for a regulatory decision.

But the closer that we can come to the function people experience in their daily lives and their natural environment, the more informative we can be about what patients might experience on a day to day basis when being treated. And so trying to bridge that gap, not losing the practicality of conducting our trials, but trying to be as in touch with the daily experience as we can is very important.

As Elektra just mentioned, we have extensive experience and success with modification of existing scales. Sometimes that's all we can do. I really like

what we do in this space, and we do it a lot. This can be particularly important with some of the diseases that we're responsible for in neuroscience where specific tools and scales may not exist for the condition being studied, you know. And the resources of those responsible for the investigation may also be limited, perhaps in time or perhaps in resources or often both.

So leveraging existing knowledge and experience can really enhance in efficiency. And we try to do that very aggressively. We work with our sponsors. And we work very hard to accomplish that. That can tremendously enhance the efficiency of the program if we can take advantage of what's already out there.

Relevant tools from related conditions or disease independent measurements are something we emphasize a lot as well. Things that are not specific to the condition being considered, but may nevertheless be appropriate for evaluating effects in the population under study.

I think this new guidance is going to ideally

present a fairly comprehensive and optimized approach, which, as I already said, is very important to strive for. I already mentioned flexibility as well. This is very important, as various constraints may ask us to make do with something that's less than perfect. That's often the case, and that's often okay. It's very much okay to do that. We try to do the best with what we have.

A key point with regard to the roadmap, and one that I think is reflected in the roadmap that I'm assuming you presented earlier, is the staged approach outcome development. I think that's very important that you have this staged approach. And it emphasizes that the more that you can frontload your work on the understanding -- there it is right there. The more you can frontload the work on understanding the disease or condition you're considering, the more you can minimize or insulate yourself against the risk inherent and having the later stages of development be something other than optimized, as will be reflected in the guidance. So really, doing that heavy work early can really pay off when it's time for the rubber to meet

the road down the road.

I'm not so sure if we want to talk about digital health assessments. Have we gone there at all? I can leave that alone. But talking about efficacy, you know, I kind of have two laws of outcome measures that I try to, you know, convey to the staff when they arrive here at the FDA. And these are things I really believe in that makes it very easy in some ways, is that you want to assess meaningful concepts or domains. And you want to ensure that measured changes in those domains are meaningful.

If you do those two things, if you're assessing something meaningful and you're scoring it meaningfully, you're in really good shape to rely upon any change that you find persuasive between the groups. And that really covers a lot of the clinical meaningfulness basis. So that’s something we work very hard for.

And that really is relevant to the question about altering scales. That’s commonly how we modify a scale. We'll have a scale come in. It'll have 20 items, let's say, and we'll see that, you know, 15 of

those items look very appropriate, maybe a couple tweaks here or there. But five of them are clearly just not meaningful. There's something appropriate for following a symptom in clinic or a physical sign in clinic, and so we take those away.

And, again, that drives the psychometricians nuts. They wonder what have you done to the performance of my scale. But it doesn't decrease the fact that if you do detect a change, you can interpret it. And I think we've done very well there. And, again, the constraints we have upon our situations where that's all that you can do, pardon me, make that a really good effort for that particular situation. So I would really encourage people to keep that in mind.

I have a few other thoughts, but I can stop there. I've been talking for a few minutes.

DR. PAPADOPOULOS: Maybe a couple of minutes we have. We're a little bit over. But I, I really want to hear your thoughts.

DR. DUNN: Oh, you want more?

DR. PAPADOPOULOS: Yeah.

DR. DUNN: Okay. So I see a good movie lately

-- no, digital health assessments. I mentioned I wouldn't talk about those. So I know there's been some discussion about whether that's a fifth COA, a fifth type of COA or not.

You know, I don't really think so, but we may end up doing that. But I'm not too troubled by that. Call it what you want. You know, I think it's an artifact of the definition to some degree. They really aren't that far, if you think about it, from performance outcomes or observer-reported outcomes. It's just how we define who's doing the reporting in those situations.

And they can even play a role in an augment traditionally-defined clinician-reported outcomes and patient-reported outcomes. What we do, do when folks want to use these is that we pay an awful lot of attention that the devices do what they say and that we know what the output means. It's very common for these enthusiasts in this space to just say, it's going to give you an output, and it's going to work, and trust us. And we have a lot of real good experts here, both on CDER and especially with our device colleagues who

really do a great job thinking about what are these devices doing, how are they working, and is the information we're going to get from them going to be what it is advertised to be.

But I tend to have a pretty simple view of these things. As long as we get those technical aspects right, I have to tenets about applying digital health technology into trials. Let's do something more accurately or better with regard to efficacy endpoints or another endpoint that we traditionally do. Or let's allow it to measure a meaningful endpoint that weren't previously feasible or easy to assess.

So let's not just do it because it's cool and it's the new thing, and everybody wants to strap something to their wrist or their head or, you know, whatever it is. But let's do it better. Let's do something better or find things that were previously undetectable.

And so I try to make sure our discussions with our sponsors are guided in that direction to ensure that we're accomplishing something there.

Another thing that I wanted to point out, just

'cause I had made some notes to myself is the, is the real importance of precompetitive work in this space. I already spoke to the fact that we often have resource limitations for the folks who are working, particularly with small populations. But we need to succeed, we need to get there.

And I think people are really starting to buy in. People know I sing this song a lot, but people are starting to buy into the fact that when situations are under-resourced on an individual basis, the advances that we can get from pre-competitive sharing and knowledge benefit all. They'll benefit the patients, and they'll benefit the individual contributors to that data base.

So that's something that we work really, really hard on. We're highly engaged with the Critical Path Institute on multiple fronts, as well as with a number of typically smaller private consortia that are working on this as to provide maximum benefit to our incremental increases in scientific knowledge. So that's something that I just can't emphasize strongly enough as we think about developing new measures is the

fact that we can really work together pre-competitively, which the FDA will participate in, as we all know, and help ourselves get there.

I want to try a second time to stop and see what you think.

DR. PAPADOPOULOS: And, yes, with that I'd like to thank all of the panelists for a very informative session.

(Applause.)

DR. CAMPBELL: Thanks, Elektra. So we went a little over. So what we propose is maybe combining the Q and A time from this session with the next session, 'cause the next sessions also going to focus on the similar presentation. And so we'll just do Q and A all at once if that’s okay. So we'll just go ahead and take our break now, and we'll try to come back around 3:30, 3:35. Is that reasonable? 3:35. Thank you, all.

And this is going to be somewhat similar to what we just had, except this time we've brought in some of our external stakeholders. So I think it's going to be a really great complementary session that

we're about to have.

So today we have a really great panel ahead of us, and I'm going to have them first introduce themselves and then I'll set up how we're going to run this session. So Robin, can we start with you?

MS. CARSON: Sure. Good afternoon. Robin Carson, I'm head of Patient Center and Outcomes Research at Allergan.

MS. ALICYN CAMPBELL: Hi, I'm Alicyn Campbell. I'm the global head of Patient-Centered Outcomes Research for Oncology at Genentech and Roche.

MR. COONS: Stephen Coons, I am the executive director of the Patient-Reported Outcome Consortium at the Critical Path Institute.

MS. FOXWORTH: Phyllis Foxworth, I'm the advocacy vice president for the Depression and Bipolar Support Alliance.

DR. KLINE LEIDY: Good afternoon, my name is Nancy Kline Leidy. I'm the senior vice president of Scientific Affairs and Patient-Centered Research at Evidera.

DR. WEINFURT: Hi, I'm Kevin Weinfurt. I'm a

professor in the Population Sciences Department at Duke and a member of the Center for Health Measurement.

DR. CAMPBELL: Thank you. And so how I want to start this session first is really to get some instantaneous reaction from our panel, from our panelists on what they just heard from Elektra's presentation, and some of the discussion we heard from our cross-center panel.

So if we could just ask, if I could ask you guys just to give a couple minute's thoughts of what you just heard. And then we're going to segue into our questions about the roadmap and the decision tree figure. But was your initial reactions to what you heard? So we'll start with Stephen with that.

MR. COONS: Thanks a lot, Michelle. Well, I think I was very appreciative of the fact that we did have the FDA folks weigh in on this and give us their perspective, and I think that's critically important.

One of the things, and Elektra brought this up in terms of mobile devices, or mobile technology, and I -- in terms of potentially adding it to the roadmap, and I think that that is an important question. I

don't think it needs to be added to the roadmap, 'cause I think as -- I think Paul mentioned that it's really just another mechanism for collecting data and particularly clinical outcome assessment data.

And I, but I think what I've seen here in terms -- and what I've heard here, in terms of the documents that were prepared and the things that we're talking about, we're making some important steps from the original PRO Guidance and providing a lot more information that's going to be incredibly useful for all of us, all the stakeholders that are in this area.

So I guess that's it from me for now.

DR. CAMPBELL: Thank you, Stephen. Phyllis?

MS. FOXWORTH: Thank you. I, too, appreciated the FDA being here and giving their perspective, as well as having the opportunity to have read the guidance beforehand as part of my homework.

And one of the things I would say, share from the patient perspective, I think it's a great start. It's a good document. It's accessible to patients. I mean the language is accessible. I will admit that it is very overwhelming from a patient perspective, and

also very intimidating. But I like the fact that the language -- it was clear to me that the language was intended to make it accessible to someone who's not a data scientist or part of the regulatory community.

But having said that, one of the things that throughout when reading the document, as well as through the comments today, one of the things that I found missing that I would like to see is that it does a great job of explaining the what, but for me, as a patient, not necessarily the how.

And so what I mean by that is, you know, how was the patient input gathered for the, just drafting the document. One of the things that I heard in the panels this morning was the need for a patient advisory committee in developing tools. And I would just love to be able to comment, you know, into the docket on the process of how we got the patient input into the overall process of creating this in the first place.

DR. CAMPBELL: Thank you, Phyllis. Nancy?

DR. KLINE LEIDY: General comments, the document is a good start, and the panel discussion earlier today was an excellent foray into the FDA's

consideration for how we can improve upon the document as it's been drafted.

Couple of things came to my mind throughout the day, actually. The first is I agree with the comment in the previous panel that digital health seems to be a method rather than a type of outcome per se, and we really need to think about how can that method be applied in order to develop endpoints that are meaningful.

Right now I think we're restricted to steps and activity, which is an important outcome, but then how is that translated into endpoints, and could it fit into one of the other categories so that we don’t overcomplicate our lives.

The second thing that I hope this panel especially discusses is my radar are up on the use of existing measures. I think it's a great idea to use existing measures. The question is, how do you modify an existing measure and what constitutes modification and why.

As a developer of instruments, I can tell you that modifications are recommended by almost everyone,

and slight little improvements can really create problems in standardizing outcome measures. So we really need to think about the rationale for modification, the process for modification and making sure that that process is systematic. And that we actually take some of the documents and figures that are in the guidance document that we have now and truly make them applicable to the modification process so that we can really formalize that process rather than saying, oh, you can use an existing measure, just modify it.

Let's make it systematic and then make sure that the application then is standardized in a modified way so that it can be used, you know, continually in that new context of use. So let's really address the modification issue. It's extremely important.

And then I think we're going to have an opportunity to talk about what exactly does context of use mean and how do we apply that across the board, so.

DR. CAMPBELL: Thanks, Nancy. And I think, hopefully in our next part when we start talking about the roadmap we can get into some of those questions and

discussion, and our panelists can start thinking about that, about what is modification and what would it look like. I think it's a really great point. Kevin?

DR. WEINFURT: Just a quick high-level reaction. First of all, I was very grateful to be a part of this and to get a chance to review the materials. And the thing that I was struck with, both in the materials and in the discussions today so far was just the thoughtfulness that has gone into this. It's clear in reading the documents and hearing the discussions from FDA that there is an appreciation of the types of challenges that people have been facing both outside and inside FDA with respect to these issues.

And all throughout the guidances, especially Guidance 3, there are repeated commitments to thoughtfulness and flexibility, which I think is just terrific. I think some of the challenges, then, will be translating the sentiment of flexibility and thoughtfulness into more of a, what does that mean. What does that thoughtful process look like. What's an example of a reasonable argument to be made in a

particular case, so.

DR. CAMPBELL: Thank you, Kevin. And I do think that's a really important question about what does flexibility look like. And perhaps we can touch on that a little bit when we talk about what would modification look like. Robin?

MS. CARSON: Yeah, just to echo something that Kevin had stated. You know, first I just want to acknowledge both the panel's efforts and all of the efforts at the FDA that have gone into the discussion document. It's truly appreciated. It's clear you're listening to the challenges that everyone is facing in the multi-stakeholder environment.

With respect to directory actions to the panel, I think the one thing that really resonated with me is that an endpoint is an endpoint, right? And so I think if we can reiterate that to our cross-functional colleagues. It's not just the PRO people, right. What are you bugging me about now, is sometimes the reaction we get. And why is the quality here or the methods different. And I think the quality is not different. The level of rigor is not different. Sometimes the

methodology to get there and the skillset needed is different.

But if we can emphasize that, as well as better define, you know, concept versus measure versus endpoint, to get us all talking the same language and help them understand the benefits. Just so we were talking earlier, I think Tara mentioned it. It's not just about better quality endpoints, it's about better precision and an ability to detect treatment benefit.

So I think if we speak in the terms and incentivize on the aspects of trial design and clinical development that apply to a broader stakeholder group, they'll begin to feel some accountability. And we can talk more about that in the roadmap. I think there are aspects of application and implementation that we can bring in that will make them feel and identify more with the roadmap as opposed to this is just instrument development. It's something different than what I do.

DR. CAMPBELL: Thank you, Robin. And Alicyn?

MS. ALICYN CAMPBELL: Thank you. I really enjoyed the last session. I thought it was really helpful to hear the different directors at the FDA's

perspective, and I really appreciate their time.

What really resonated with me was what brought us back to why we're here, which is we really need to start with the outcome of interest and the concept of interest that’s relevant to patients. We then need to think about how that can be measured in an endpoint and we construct an endpoint to measure that concept or outcome of interest. And then we choose the right tool that will measure it in the most rigorous and reliable way.

And I really appreciated Dr. Dunn's comments that digital health is just another tool we have to measure what's most relevant to patients. And I do think it's important, then, instead of focusing on technology, we remind ourselves as measurement experts that we're here to understand what's most relevant to patients, measure that in a rigorous and reliable way. Because if we don’t as researchers, we're all doing a disservice to the patients we have the honor to serve with the work we do.

DR. CAMPBELL: Thank you, Alicyn. I thank everyone for those opening remarks. It seems to all

resonate on the themes that we continue to hear, even from this morning's session about some great advances that were seeing. We see some challenges that we may need to continue to address in our guidance documents, but it's a great start. And definitely some more examples on what is flexibility and what does that look like.

So I want to transition to our panel to our question that we've been charged with answering, which was about the roadmap that was presented. There was some lengthy discussion in our cross-center panel about this. But from your perspective, does the roadmap capture the appropriate elements and strategies to select and/or develop and/or modify back to Nancy's point for COAs for use in clinical trials. And if not, what is missing? So I'm going to pull up this slide so we can see it. It's on the screen for everyone. And I want to turn this discussion over to what are your thoughts about this? Are we heading in the right direction? Are we missing something fundamental? So I'm going to start with Kevin with this.

DR. WEINFURT: I think that one and two were

reasonably clear. It felt a bit like 3, 3B and 3C, especially 3C, I wondered how applicable those were going to be across all COA types. The language is very much taken from psychometrics. And one general theme I'll have is that there are alternative measurement models that might be appropriate for other types of measures. So we ought to perhaps look for places where we're inadvertently dictating that people use one particular type of measurement approach.

DR. CAMPBELL: Okay. We'll just work our way right up there. So, Nancy, what are your -- some thoughts you have?

DR. KLINE LEIDY: I thought the comment in the last session about be careful about the use of the word steps and how do we communicate the iterative process was a very good one. The other piece of it is I think the title of this is steps in development. So we kind of, it's development and modification. So perhaps we need to think about this as a process of readying. It's really a process that you're using to ready a measure either through the development or the modification process so that it is ready to be used in

a pivotal trial for evaluation purposes.

So we might want to think a little bit more about the title of it so that it adequately addresses the process that's being used. Yeah, I think -- other than that I think it's applied nicely from the, I mean it's a nice slight modification from the original version of this table.

DR. CAMPBELL: Okay. Phyllis?

MS. FOXWORTH: So I'm going to take a slightly different direction than the rest of my panelists here. I'll be speaking to the, addressing that question as far as the elements and does it contain all the appropriate elements, speaking as a patient representative from a patient population that lives with a progressive and a chronic condition.

And some of the things that I guess I would just like for the agency to take under consideration, just some suggestions on elements that I think are missing, especially when I look at understanding the disease or condition, the natural history.

One of the things that I think that is important is to understand the important of relapse and

the environmental factors of relapse on that condition. So, for example, is it cyclical. Someone living with a mental health condition of depression or bipolar disorder, they may find that the environmental factors of, or external factors could be the reason for the relapse. So understanding the natural history and how that affects relapse, I think is an important consideration.

Another important consideration when thinking about clinical trials, and understanding the natural history is a past experience, especially for someone who's living with a condition that has -- while there might be multiple alternative options for a therapeutic intervention, none of them are working. Well, why is that? And is there an opportunity for understanding what -- in the clinical trials what has been the past history and what bearing that has on that particular clinical trial.

Tied in with that, I would suggest looking at genetic testing. I mean just in the condition in which I represent, two-thirds of individuals will go through multiple therapeutic options before they find one that

works. Other people, a full one-third of them will never find an option that works.

And genetic testing is proving promising in being able to identify for people, especially those living with depression, there are genetic tests that can identify which classes of medications would be optimal for you. What the metabolism rate is. Those are all things that would be an important aspect from our population that I represent in the clinical trial.

The other thing that I would like to touch on around elements that I think that -- make some suggestions for elements that could be included under the patient and caregiver perspectives is under the clinical definition of benefit. And I think that if you talk to most of the peers within my community, that the clinical definition of benefit probably doesn’t resonate with them. It's probably not the same definition.

So when we're looking at clinical trials, it's extremely important that we have good definitions of what a clinical benefit is, and make sure that also we have a, that we're representing what is the patient

benefit, because as I said, they are typically, at least in my community, not the same thing.

Another area that we should be looking at is on impact of change. And I would respectfully ask that we consider whole health considerations there, that that involves, you know, not only just the whole health of the individual, but the impact of navigating the healthcare system. Because individuals, depending on their ability to navigate the healthcare system, they may have different risks and benefits and different tradeoffs that they're willing to take just based on things such as equitable accessibility to healthcare, which can be, you know, a big barrier to their determining what is the appropriate benefit and risk for them.

Moving over to the conceptualizing the clinical benefit. One of the things that I would encourage us to take a look at is under the surviving fields and functions, I think there's something really important missing there. In our community we call it thriving, and I've been cautioned that that is not the appropriate word to use for this community. That it

means something very different.

So let me just share with you what we mean by that in my community. We talk about we're not, we're not looking to just survive, we want to thrive. And to do that, I'll just give you an example walking through the fields, which is symptoms and functions, and what I mean by that.

I was talking to a woman from San Francisco just last week, and this woman lives with a mental health condition. She lives with a mood disorder. And she has an MBA and has had a position as an executive in a high level company in sales as a sales executive. She is now working in the retail environment. She works and is the top sales person at that store, and she gets, you know, her commissions based on that.

But let's take a look at the charts here. She's surviving, yes, she is. She's surviving. She feels -- if you looked at a WHO-5 wellness index or if she has a scale, you'd say she's doing great. She's marking those all off. Is she thriving? She tells me that there's nothing more than that she'd love to be go back to the position where she can use her MBA. So I

would say she's not thriving.

And I think that that's something that we need to be capturing from a patient perspective. And then again, I'm not married on language. So if thrive is, it means something different in the regulatory community, I'm, you know, perfectly, you know, happy to find a different word for that. But I think that's a very important concept that’s missing.

DR. CAMPBELL: Thank you, Phyllis, for those concepts and those good thoughts for us to take back and consider going forward. Stephen, do you have anything you'd like to add?

MR. COONS: Sure, just a couple of points that I'd like to just put out there as food for thought. In terms of the conceptualizing clinical benefit, we, I really feel that we need to think about the source of the information there rather than in three.

You know, we talk about selecting the clinical outcome assessment type, but I think when we're talking about the concepts and who should be reporting those concepts or how we should be assessing those concepts that it's really an integral part of column two. And

we can certainly talk more about that.

The other thing, and there are a couple minor things under C on column three, I don't understand why construct, validity, and reliability are in the same bullet. It's a minor point, and it's not anywhere near as important as what Kevin brought up about, you know, are we too psychometrically oriented here in terms of this issue.

The other thing relates to engage FDA early and throughout medical product development. And I know the FDA says this a lot. And I think it needs to be considered in terms of what that means and how it can be done, particularly in the INDND, BLA sort of path. Because I think there are a lot of folks that really do want to get FDA feedback on a COA tool for their trial, and they find it very hard to do. So just something to consider.

And then there was another line that’s not here, but it was a note under this that said, "Note, this roadmap can also be used to conceptualize tolerability or risk." And I certainly understand the issue of tolerability. We need to think about the

issue of symptomatic adverse events, and we should be assessing that routinely, no doubt about it.

Risk, though, is a more objective phenomenon, and that's not something that we would ask patients about specifically. We can ask them about their perceptions of risk or, as Patty was saying, the term harm may be more appropriate. And if it's getting at this issue of, you know, patients willingness to tradeoff, you know, real or hypothetical risks for real or hypothetical benefits, then that's a totally different exercise. We might use discrete choice exercises or something like that.

So I guess I'd like reconsideration of this note, this roadmap can also be used to conceptualize tolerability or risk. 'Cause it seems like it's sort of a throwaway line. And then there's no further discussion of, well, how would this roadmap be used for that.

The other issue is that along with that, safety is mentioned on page 14, that concepts related to treatment safety tolerability or burden may also be measured by COAs. And I think -- and that’s a little

problematic. And I think we don’t want to be conflating safety assessment in a clinical trial with what we're doing in terms of clinical outcome assessment for efficacy on points essentially. But I do understand how we can look at patient-reported tolerability. But safety is a much broader issue. And there is a path for collecting safety data that is traditionally done in a way that the patient isn't as involved as they should be.

And I'm very much a proponent of, along with safety, safety reporting within a clinical trial, which is usually done by the clinician, that there should be patient-reported routine and systematic assessment of patient-reported adverse events.

So those are just a few comments.

DR. CAMPBELL: Thank you. Alicyn, do you have anything you'd like to add?

MS. ALICYN CAMPBELL: Yeah, thanks, Michelle. I have four points on this topic. The first is similar to Stephen's. I think at the bottom it talks about engaging FDA early and throughout medical product development. And I'm part of a number of

precompetitive collaborations where I have the pleasure of partnering with a number of my sponsors. And clarity and timing in expectations regarding agency feedback and sponsor communication, I think it will be really important to clarify.

In my discussions with other sponsors, this is where things tend to fall down on the path for evidence inclusion and labeling. Feedback is either not received at the right time or often folks get feedback in response to type B or C packages that acceptability and inclusion will be a review issue. That's really hard for teams to digest. Because it's really challenging for them how can they derisk that along the development program.

And so I think it'll be important to be quite clear about the type of feedback and when it's received if we want to be successful.

The second comment will be around digital measures. It's similar to what was mentioned before, but since my colleagues are passionate about this, I want to make sure I'm super clear. So we really feel that digital measures, including electronically

administered performance outcomes and passive monitoring, since they're being increasingly used, we need clarity on how exactly they will be classified and evaluated in a regulatory context.

Our recommendation was similar to what I was happy to see Elektra present earlier, which is to really break the performance outcome category into standardized tasks. So those are measures where a patient is instructed to perform a specific task. And then monitoring measures where the patient's instructed to behave as normal, but in the knowledge that their activity is being monitored.

We'd also recommend further discussion about how you might determine which type of PerfO is appropriate in column three of this figure. It would be really helpful for clear articulation about how either digital PerfOs or passive monitoring tools will be evaluated by the COA framework and what their empirical evidence requirements will be.

From a reading of Guidance 3, Appendix 1, it would appear that all the information in that section would be applicable. However, explicit clarification

would be extremely helpful, as their use is expanding so that stakeholders can be prepared for agency evaluation and interactions, and the agency's also getting what they need for their evaluation.

Because I'm the oncology person, I have to comment on blinding while I'm here. For those of you who know me, you won't be surprised. While we understand the desire to remove the potential risk of assessor bias, this is neither operationally feasible, nor frequently ethical in hematological malignancies and rare diseases, for example, hemophilia A.

When treatments are being compared to active entities with different schedules and roots of administration, particularly intravenously, adding in a placebo is quite a challenge and often not appropriate. Additionally, treatment toxicities, if we were to blind, can lead to inadvertent unblinding through a lot of the social media and discussion forum that Patty and others spoke about this morning.

So our perspective is in settings where patients are receiving active treatment and the concepts being reported are quite specific, such as

symptom severity or symptom interference with daily activities, the bias should really be of minimal magnitude as to not significantly impact the results in their interpretation.

And then, finally, we really appreciated the section on observer reported outcomes, and I was really pleased to hear from Elektra's section that they'll be kind of sub-guidances on these. And we really think ObsRo is an important source of real-life experience on how patients feel and function if we really want to get at Section II, Part A. This is important empirical evidence, and we really don't want to miss out on this.

And so I think to get to that next level of success it would be helpful to have the agency clearly define what they find a reliable observer to be. 'Cause in the past when we've collected this data we haven't been as successful as we'd like to be in including it in labeling. Thank you.

DR. CAMPBELL: Thank you, Alicyn. And, Robin, do you have anything else to add?

MS. CARSON: Yes. And I think I agree with a lot of what's been said today. And I just want to

reflect on the positive, certainly with respect to the roadmap. I think the addition and emphasis on modifying existing measures and leveraging those is a wonderful addition, as well as the extension to broader COAs.

The other thing that really resonated with me coming from an ATOR [ph] background and training is that it is reflective of the multi-stakeholder view. In column one it certainly calls out the need and emphasizes patient and caregiver, but it also allows for a broader healthcare system perspective. And thinking about clinical practice as well as how access to medicines are achieved in a certain condition.

I think this is important because I think we all recognize that regulatory approval is sufficient, or is necessary, but insufficient. And, you know, what we're all trying to do is get patients medicines that will improve their lives. And so we really need to be thinking to the extent we can what's relevant in a regulatory context for patients, but beyond that as well. Are there outcomes that, you know, core outcomes -- and I know this was mentioned earlier in terms of

the RFI about looking towards core outcome sets that might be the minimum set that are applicable across both regulatory, clinical practice, and even market access.

To that end, I think there might be a value in building out what we mean by expert perspectives in column number one. So giving some examples of those other stakeholders for folks who have not used to be -- aren’t used to thinking beyond the regulatory context.

In addition, as I eluded to earlier, I think a big part of this roadmap for consideration to add could be a fourth column or perhaps sprinkled within if you're adverse to a fourth, but it stops short of identification and development. And it doesn’t talk about the implementation or application of the measure.

And that’s where things like the final endpoint definition and what's prespecified in the SAP, what analyses, what sensitivity analyses are we going to be doing? How are we ensuring that quality is preserved when we put it onto an ECOA or digital health technology? Translation and linguistic validation, all of these things tend to be thought of as extra. Oh,

they'll just happen. And there's groups that do those.

And I worry that we tend to regulate those to a more operational aspect. And they're critical to preserve the precision and quality of what we've spent years, sometimes developing in a scientifically rigorous way, especially as we go global.

So I think that's really important and could also, again, come back to that cross-functional aspect, make our stakeholders and other functions aware of how the rubber really meets the road here in the context of a clinical protocol and how they may help as well.

I would be remiss if I didn't also comment on the, you know, double-edged arrow there at the bottom in terms of engagement with FDA. I think that's a wonderful addition, and I think everyone really does recognize the value of that. But it's definitely one of our biggest barriers today.

Particularly, again, getting cross-functional buy-in and agreements that, that should be a priority. So the more that we can educate others in regulatory and, you know, statistics, and clinical, etcetera, that the discussion around COA endpoints, the development,

the validation, the interpretation are just as critical as the dosing and the trial design, I think we'll all have much more efficient discussions.

So some clarity and timelines and even just from FDA how to make our submissions more efficient for you. Do you, you know, what do you like to see, and how can we make that more efficient? Maybe there's an opportunity to increase slightly meeting times instead of additional meetings from the sponsor perspective. Additional meetings are double the work. Adding a half hour to an existing meeting would be incredibly more efficient from our perspective. It might allow us to address one or two more topics. I know that may not be feasible, but I just wanted to throw that out there.

The other place that I see, and I'm looking forward to the subsequent guidance for, I see a lot of teams struggle when they get to the end of the roadmap and they think, just, okay, well, we've got our line in the sand in terms of interpretation. How do we translate that to an endpoint? And, again, I think where that fumble tends to happen is because that is a very cross-functional exercise.

It requires statistical and PRO expertise, as well as clinical expertise, inside and outside of the company. And oftentimes it's not clear how to make that leap from a responder threshold to a responder definition, which might take into account time spent in that health state. You know, what is the right number of weeks? Is it responder or should we go continuous? And so I really look forward to that endpoint guidance, because I do believe a lot of folks are struggling with how to make that leap.

I think we've spent a lot of time in years on the aspects already illustrated here, but the endpoint definition needs a bit more time.

And lastly, the one thing I just want to mention, while it does seem that there's more interest in leveraging existing measures, I think we have to be careful that we're clear on what type of documentation is needed when we want to modify and use an off-the-shelf measure.

You know, we've mentioned here in 3C, Develop and Evaluate a COA, I would say that probably needs to be evaluate and document a COA. Because whether it's

new or modified, you need to evaluate it, and you need to document that. But how far do you go? Does precedence in labeling negate the need for additional company to do their own content validity documentation? I mean we're talking about improving drug development and overall efficiency.

So I think some clear guidance on truly the documentation needed in the modification space would lead to a lot of efficiency.

DR. CAMPBELL: Well, thank you, Robin, and I want to thank the panel for those thoughts. One resonating theme I heard was that really this column three is where there's good starting information, but we need some more things. You seem to be missing or there's maybe unclear information, or are we focusing on the wrong things.

For example, Kevin mentioning, you know, 3C seems to be a little measurement property heavy versus, you know, such things. So does anyone have any thoughts of what additional things they would like to see or clarity or is there maybe a better way of presenting this column? Stephen?

MR. COONS: Well, Michelle, I would like to just second consideration of a fourth column. And I think this idea of expanding this to not only selection or development for clinical trials, but selection, development, and implementation in clinical trials because I think that's an incredibly important point.

And as you mentioned, Robin, Guidance 4 is going to address more of the endpoint side. But there's no reason why this couldn't go that next step and talk about that and all of the other things that you mentioned. The translatability issues, and implementation on electronic data capture platforms, etcetera.

So I think there are an awful lot of things that ultimately mess up the implementation of a clinical trial that would be in that fourth column. So I second that suggestion.

DR. CAMPBELL: Kevin?

DR. WEINFURT: And I also second bringing in considerations of thinking through how the measures will be used as endpoints earlier in the process here. And I think when we talk about endpoint definition,

endpoint positioning, I think this, in the context of this here it's a, kind of an earlier rough version of it. But when you're forced to think through exactly how you'll use the numbers, one of the things that it can do is to help avoid the error of trying to solve an analytic problem with a measurement solution.

So, for example, taking presence and absence of some symptom or function and agree to which that symptom or function is happening, and trying to combine those together into the same score somehow, when you're just focusing on how should we measuring this thing right now, that usually results in something not helpful. But if it was built in, but right now the analytic guys are sitting down and figuring out what are the analytic options for this, or we've got this high-dimensional diary data, all right.

If the analytic considerations are brought in earlier, then we wouldn’t have some of the clumsy approaches that we use sometimes to try to reduce the dimensionality of the data with a measurement strategy rather than an analytic strategy.

DR. CAMPBELL: Thank you, Kevin. Phyllis?

MS. FOXWORTH: I agree with what my colleague over here to my right has said about needing another column for implementation. I think that would be extremely helpful.

But when I'm going back again and looking at the -- starting with section A, and what I see missing is, you know, I see patient-reported outcomes and on down the line, but I don't see anything that says are we measuring the right, and collecting the right outcome in the first place.

So I'd love to see something before that, that you know, was an opportunity to understand what is it that the patient wants measured? That's one of the challenges that I think we have with just a patient-reported outcome is that it's nice that a patient gets to report their outcome, but are we reporting on what is it we want measured.

So I would just love to see a bullet before that list that somehow indicated that we actually got the patient input into what it was that we wanted the COA to be measuring in the first place.

DR. CAMPBELL: Thanks, Phyllis. I actually

think that perhaps what you're saying is maybe some of the ordering in this column. Because you're kind of referring to the content and validity that we're measuring what's important to patients and we've captured that.

Perhaps the ordering needs to be changed to reflect that, which would help us guide was the best way, as also was mentioned earlier about what is the therapeutic aspect of the drug. So what are trying to target? So are those symptoms matching? Have we captured everything together? Maybe there's some reorganization that needs to be done. Is that what I'm hearing, perhaps?

MS. FOXWORTH: I think that would be helpful, yes.

DR. CAMPBELL: Okay. Stephen?

MR. COONS: Well, I think the other thing that Phyllis brings up is this issue of under D in column one, Definition of Clinical Benefit. And I think that's easily misinterpreted as what do clinicians think about the benefit? And I think often we tend to use the term treatment benefit. We think it's maybe a

little more patient friendly.

But I think that’s one of the problems right there because that, 1D is where we really are trying to determine what is important to patients. What do they want relieved. What do they -- what are they dealing with that they would like to not have to deal with in terms of this condition.

So I, I think we just need to make it clear that that's exactly what that is getting at or is attempting to get at in terms of what is important to the patient's that we would want to treat the disease and have an impact on.

DR. CAMPBELL: Okay. Do we feel good about -- I want to move on to the next figure. But I just want to make sure are we comfortable with this discussion. I think as we transition onto figure 6, which my version is not going to be as pretty as Elektra's where I did not separate them out. So it will be hard to see on the screen. I apologize.

But it is that decision tree. And one thing I'm hoping, if you can think about and reflect as well, was a statement that a lecturer made when she said that

"We envision that people will use both this decision tree together with the roadmap." And so if you could also think about that, does it make sense together, their use together? How do we make sure that's done? Things like that. So if you could touch on that as well.

As we think about this question is -- and I think I'm hoping we get into this modification discussion that everyone's hinting at. Does that decision tree really capture the process of select, develop, or modify sufficiently? And if not, what are we missing?

And then, finally, I'd really like to hear thoughts about should this diagram replace the wheel and spokes that was in the original PRO Guidance of 2009. And what are your thoughts on that. So, again, I do apologize for it being small. But what are some thoughts? I don't know who wants to start. Kevin's looking at me. So you win.

DR. WEINFURT: All right. I hate to introduce math this late in the afternoon, but there are five possible paths drawn through this, this thing. They

all start with step one in the steps of development.

Of the remaining four, they all involve two, three, and four, all right. And I think -- so first of all, I love this decision tree. And it helps to highlight the need for even more guidance and tailoring what two, three, and four mean in different parts of this.

So the middle box, for example, is about using steps two through four to confirm whether an existing COA could be used as is. On the bottom left it's using those steps to develop a brand new one. And on the bottom right it's using those considerations to modify an existing one.

So this is, this is great, but it also called out to me the need for more guidance of what flavors of two, three, and four would I need to accomplish the developing, confirming, modifying. Are there examples that we can give that would help people to understand how if I've got a measure in front of me, how I might review the considerations in two, three, and four to figure out whether it's going to be appropriate for this context of use, or which pieces would need to be

modified.

So it's great that it calls these things out. And would be even better if there was one more layer of detail than noting that these are three very different functions for which two, three, and four are being put.

DR. CAMPBELL: Thank you, Kevin. So I think I'm just going to start up with Robin and work our way down, if that is okay. And, Robin, is that okay?

(No audible response.)

DR. CAMPBELL: Okay.

MS. CARSON: Sure, no problem. In terms of whether or not this should replace the wheel and spokes, I do like this presentation a lot. And I think it will help folks really think through, sort of, the new mindset, right. Does one exist? Do we need to modify?

But there are three key things from the wheel and spokes that I think if we could weave back in that I really liked about that tool and that I emphasized when speaking with my internal colleagues.

One was the importance of matching the COA to the claim and thinking really early about that end goal

with the claim and making sure that we matched the concept and the measure to that.

Two, there was an aspect in the wheel and spokes that made it very clear that we were focused on the hypothesized conceptual framework, but that we would iterate that over time and continue to confirm it with patient input, psychometric evaluation, and still end up with a conceptual framework, which is the foundation of any measure. And so I think there's a way to bring that back. It's mentioned in step one below, but we need to weave that back into the other aspects.

And then, third, just an emphasis on the iterative nature, which I think we were all debating a little bit earlier about how to really emphasize that. In addition, one thing that I find that may not be here and often isn't top of my intro teams, and it started to come up in the last panel was thinking beyond the measure that you're focused on for the, you know, endpoint in claim to the other measures you need to evaluate it, right.

And often we think about those too late. So

we'll get to writing the trial protocol around this primary measure and realize, we don’t have an anchor question. How are we going to evaluate that measure? Or we didn’t think about a measure to evaluate construct validity, whether or not one exists, you know, not always easy. But so I think there needs to be an aspect in thinking about the broader measurement strategy to make sure that you're set up to evaluate your primary measure well.

And then in column two, in step two at the bottom, it definitely calls out the need for patient, caregiver, and expert input. But in my experience, the best measurement strategies involve them throughout. So it's not just about a defining the concepts and the items, but re-engaging them with key results and the interpretation thresholds and even conceptualizing the endpoint and beyond.

So I would make sure that is pulled through. And then, at risk of sounding like a broken record, I think the implementation aspect is missing. So whether or not we put it in the roadmap or hear, I do recognize that there are some overlaps between the two documents.

And I'll have to think through that a bit more, knowing that they're intended to be -- I should say the two tools intended to be were used together. But I do think the implementation here could be about how do you actually think through that and what are the steps to go through.

DR. CAMPBELL: Thank you. Alicyn?

MS. ALICYN CAMPBELL: Thanks, I unsurprisingly agree with a lot of Robin's feedback. She's also from the sponsor side. In particular, about the conceptual framework and just the iterative process as we gain more empirical evidence that we refine it over time.

I definitely prefer this to the wheel and spokes diagram. I think the legacy wheel and spoke figure implied that a new COA was almost always needed. And so this new decision tree really addresses this limitation by demonstrating that it is an iterative process and that modification is not only feasible, but desirable.

I was really placed to hear that feedback today. Because there's many cases where we can modify and reuse COAs and provide the requested empirical

evidence. For example, in oncology when measuring symptomatic adverse events across tumor types, and due to our development timelines and cost and the need to get life-prolonging treatment to patients quickly, we frequently lack the time for de novo instrument development.

And so I really like the way this shows that modification is not only desirable, it's feasible. And I think for all researchers it clearly spells out the steps.

Additionally, the only other feedback I would have is I think it'd be helpful to clarify in section two that not every step listed is required when using a measure without modification in a new indication. I think some clarity around what steps are for new COAs versus existing will be helpful for researchers moving forward.

DR. CAMPBELL: Stephen?

MR. COONS: Yes. I think that's an incredibly important point, Alicyn. And I think that one of the suggestions I have is that you have to give up on getting this on one page. And ...

DR. CAMPBELL: We could make the document, you know, legal size, right, paper, make it longer.

MR. COONS: Yeah. Right. Right. No, I think because the other reason is, certainly the flowchart deserves its own page, but I think the steps have to be expanded, and it gets to what Alicyn was saying. I don't think this is enough.

This essentially -- it says Steps of COA Development. So it still emphasizes the de novo instrument development. And I think you need to walk the talk, you know. And you need. It needs to have at least a couple more of these that actually talk about the stages that you would go through for using it as is. You know, what is the evidence?

Because up at the top here, you go across, and yes, there is an existing measure. Yes, there -- it is being used in that specific context of use. And then it says, "Use the existing COA, no additional work needed." Is it as simple as that? I mean aren't you expecting to see an evidence dossier. But, indeed, it does do what it's intended to do.

So I think that needs -- there needs to be

clarity there. But I also think that having essentially an iterative or cumulative -- I think of it more as cumulative, 'cause it is linear in terms of these -- there are things that need to be done before you can actually do the next step. So I think there is something to be said.

I, I like, I prefer this to the wheel and spokes for a number of reasons, but that’s one of them. But I do think you really need to consider, and I think it needs to be for the levels of modification, have these steps, but also it really would help. And I know there are going to be appendices on PerfO assessments and ClinRo assessments. There's already a draft for the ObsRO assessments.

But I still think it would be helpful to have a plan like this, of steps for performance outcome measures and for the other measures that actually talk more explicitly about the steps you need to take. Because I don't think we can just say, oh, well, look at this and apply what is appropriate for that type of COA.

Because this still is very much PRO-centric,

PRO measure centric. And so I, I think it really would be helpful. And I hear this from my colleagues within the Critical Path Institute who are attempting to move forward with performance outcome measures in terms of the qualification program. And they really don't have a good set of steps that they would actually follow to get to the end goal.

And so I think if, indeed, the time can be taken and you're willing to give up on a one-page document that it would really be helpful to do these other things. Thank you.

DR. CAMPBELL: Okay. You have followup Alicyn? Okay.

MS. ALICYN CAMPBELL: Yeah, just to echo what Stephen said, I know when discussing this internally we were really hoping for a similar level of detail as Stephen talked about for ClinROs and PerfOs. So in some section the agency has identified differences in the requirements for different types of COAs. For example, inter-rater reliability is required for ClinROs, but not PROs. But further guidance, particularly around differences in determining content

validity would be helpful.

For example, it might not be appropriate in some cases to ask patients and caregivers about the conceptual relevance of performance-based tests, particularly cognitive assessments. A clinician or other expert might be better placed to comment how well that PerfO captures the concept of interest. And so more detail around that, I think, would empower sponsors and other researchers to provide the level of evidence the agency is looking for.

DR. CAMPBELL: Phyllis, do you have anything to add?

MS. FOXWORTH: Sure. Thank you. I really like decision trees. They're very easy to follow, and they're very concise. I think this does a great job of describing the what. And I also, you know, I must say that I really respect the agency's commitment to bringing in the patient advocacy organizations as a major stakeholder and with some, with stakeholders that are relevant and have something meaningful to say.

So my comment is more focused on that. It's around the how. Because we don’t have the legacy as

patient advocacy organizations that sponsors and the agency has, we don’t necessarily have the information around the how. So how are -- how do we identify the COA and whether there's one that’s already of use.

How do we engage the patient input and make sure that they're polled through the entire process. And, again, that may be very obvious to many, to the majority of the people in the audience. But as the patient advocacy organizations who are newer stakeholders, it's not as obvious to us.

And then just, you know, echoing what has, I think, already been said with regards to the how is that once we've gone through this process, how do we as a patient advocacy organization collaborate with the other stakeholders to move the process along into implementation.

DR. CAMPBELL: Nancy, any additional thoughts?

DR. KLINE LEIDY: I support the replacement of this, the replacement of the wheel and spokes diagram. I often thought we were going in circles with that. There was no exit.

DR. CAMPBELL: Literally going in circles,

right?

DR. KLINE LEIDY: A couple of just brief comments. One is, many of these boxes are kind of loaded, and I wonder whether they deserve a definition or a description as a separate document. For example, is the existing COA being used for its original context of use. That is a loaded question in the sense that, what do you mean by being used.

You mean in drug development and/or academic settings, for example. And what do you mean by original use? Is it completely within the original COA, COU framework, or is it just slightly modified and what evidence does that provide you to support its continued use in that form. So it may be that you want to describe it as a separate -- each of these boxes in a separate annotation or document or appendix.

The other piece, the other component of that loaded is used. Does that mean that it's been validated and it's interpretable? Assuming that it's already been used in a label, and the answer should be theoretically yes.

The other piece here is -- which we all know,

I think, is that each of these yes's and no's are actually not dichotomous. It's kind of a continuum. And that gets at the, is this good enough for this purpose, which was brought up earlier.

So but I think for the purpose of a decision tree you kind of have to go with a yes or no and assume that the continuum is part of the consideration.

And then last, but not least, is where in this diagram can we actually put the FDA input? For example, if you go from yes, no it has not been used for its original context of use, can the existing COA be used for the new context of use. Is that where the FDA can actually provide input before you get too long in the process, or too far in the process.

So I really like this in terms of another component of that process of readying a measure for a use in a trial in that it should be generic enough to apply to all the types of outcomes, assessments we're talking about here. So that we need to get the PRO language out of there and make it much more generic.

DR. CAMPBELL: Okay. So are there any other thoughts -- I want to make sure we have plenty of time

for question and answer from our audience. But I wanted to highlight something that we're going to be seeing a lot. You've already heard it this morning, but the big picture of why are we here. So are we missing anything out of this document? And then how do we show flexibility while maintaining the regulatory standards in terms with the COAs?

A couple things I did hear already that maybe expansion is particularly in the modification area, and this we need to kind of maybe decentralize our PRO terminology to make it more COA-centric. If this is the goal of being a COA guidance. But is there any -- does anyone want to expand on some of those things? I know, Nancy, you brought up some of this modification and what does it mean.

And I think we are, I feel like we are seeing modification is okay. You can do it. We've been saying that for some time now. But you brought up some good concerns. And so I don't know if you want to expand on that right now on what they are and what we should be thinking about.

DR. KLINE LEIDY: Sure. I do think that we

could actually lay out a process for modification in the decision making around modification. To use an example, the EXACT is a nice 14-item daily diary that we've used originally for COPD and exacerbations, but over time we've been able to evaluate it for possible other uses. Why recreate the wheel?

And if, in fact, these items are suitable for a certain target population, could it be used or modified in a new context of use. So rather than going through and assuming we have to modify the instrument, we've actually gone back to the new target populations, IPF patients, for example, asthma patients, for example, and to see whether or not what patients are telling us, map and match to what the EXACT currently looks like in terms of content and structure. And then if it does, that's great, but will scoring need to be changed because the structure of the instrument is slightly different with this new population.

So we're not just going in and twisting and turning items based upon what we know about the new target population, but rather sort of going back, seeing what patients will tell us, and almost do a

mini, if you will, sequence of steps, as though we were developing a new instrument, but actually mapping it to an existing measures so we're not starting from scratch.

And theoretically we shouldn’t, theoretically we shouldn’t require huge sample sizes for either content validity or validation if, in fact, the measure seems to be working in one form or another in these new populations. So I actually think there are steps that we could follow and/or recommend to people so that it's an easy way of understanding what would constitute the reason for modification and then what would constitute a modification.

And get away from, you know, I really don’t like item four, so let's modify that because, you know, I personally don’t like item four. That, we don’t want to go there. I think that’s not a good use of our time or our efforts, so.

DR. CAMPBELL: Does anyone else have any thoughts on that?

DR. KLINE LEIDY: And one other comment related to that.

DR. CAMPBELL: Sure.

DR. KLINE LEIDY: Which is, the other thing we're being very careful about is because the EXACT is a standardized measure, and the evaluating respiratory symptoms instrument, which is a derivative of that, by the way we were able to use it for another purpose, we're actually developing a naming convention so that everybody knows the origin of the instrument, ERS is for COPD. But the ERS for IPF will be named that way so you can see the origin of the instrument.

So that's another reason why we really have to think about this modification business very carefully. And then last but not least, all of these items have been translated in a reliable way using the standardized process into, I don't know, 45 or 50 different languages now. We don't have to start from scratch there. We can actually use those languages and translations as a starting point for the new context of use. So I'm a proponent of modifying instruments in a very systematic evidence-based way, so.

DR. CAMPBELL: Thank you. Kevin, do you have anything to add, or does anyone else have any thoughts

about this idea of modification, adaption before I turn it over to audience question and answer? We're about to go there. So if you have questions, start thinking about them and heading to the microphones.

The word flexibility comes up a lot. We say we're flexible. But how should we really show what flexibility is when we still need to maintain our regulatory standards and our COA development aspects? So do you have any thoughts or things we should think about as we're going forward with this? And you may -- Kevin?

DR. WEINFURT: This is kind of -- addresses both three and four. I think the thing that is, that's missing right now and that is an opportunity to demonstrate what flexibility means is a focus on starting with what inference you want to make. What's the labeling claim? Starting with that and figuring out what kind of a story that you need to tell that will make sense.

What is the rationale for making the claim? What are all of the things that need to be true in order for that last step to be true? How do you tell a

persuasive story drawing on different supports for different pieces of that story. 'Cause right now, despite the state of commitments to flexibility and reasonableness and everything, absent examples of how you craft a story like that and what kinds of stories would be regarded as acceptable, you will get what Nicki Bush referred to earlier today as just a checklist mentality.

Absent some picture of what that looks like, people will just start checking off the stuff that's listed again. And so I would actually suggest that everything is here to make incredible progress, but if we don't supply some narrative examples of compelling arguments to justify the final inference, all of the good work that's been done will just result in the exact same type of behaviors again.

DR. CAMPBELL: Thank you, Kevin. So if our panelists have no other comments or thoughts, I'm going to turn it over to our audience to make sure we have, we'll have a good question and answer session. I do ask that you state your name and your affiliation. So I'm going to start in the front, and then I'll go to

the back next.

DR. AMTMANN: Dagmar Amtmann, University of Washington. Disclaimer, I haven't read Guidance 3, so I apologize if it's like flushed out in the document. Any chance you could go back to the framework, the box three, box two?

So I think that in 2A we need to strengthen that statement. We not only need to identify the concept, we have to define it in a way that allows us to check whether our measure actually measures that construct. And we need to run that definition by patients to make sure that we're not missing something. And that kind of ties into modifying measures. 'Cause I get really uneasy when we start cherry picking.

So I want to know when we drop items, I want to know that we're still measuring the domain that we set out to measure. And I want to know whether there are pieces that should have been added that are not there in this new context. And I don't see any evidence of that in, anywhere in these steps. And, again, you may flush it out a little later on, I don't know.

And can you show the other part, the steps of measure development? Yeah, perfect. So in box three we talk about assessment of score reliability and give the examples of test/retest or inter-rater reliability. And I worry that that is a very limited view of reliability. Reliability is amount of random error in the score. And where that random error comes from may be less relevant whether, you know, whether it's random error that we observe in test/retest.

I would really like to bring in a little more modern psychometrics here and maybe acknowledge that we have better ways of assessing score reliability within item-response theory framework. Where we can look at the information where we get reliability at every level of the trait that we're measuring.

But we're using language and concepts that are firmly rooted in classical test theory, which makes it suggest that IRT has no place here. And since we're doing this for future, I would really like that kind of pulled through the whole guidance.

DR. CAMPBELL: Thank you, Dagmar. Those are really great comments that we'll take back. Just for

my people who are lined up for question and answer, the person behind Steve will be our last one so we can stay on track. So I can make sure we end at the right time. So I'm going to go back to the person at the microphone in the back. You're next.

MS. LEITMAN: Thank you. My name is Amy Leitman. I'm the Director of Policy and Advocacy for NTM Info and Research. So we're a rare lung disease. And I wanted to just address something. And this is more a comment than a question. But with the issue of modifying COAs instead of, you know, creating new ones, I think everybody would prefer to modify a COA instead of reinventing the wheel, but I think especially in certain rare disease spaces that's not necessarily as feasible.

So my concern is that there's going to be an overemphasis on that. And particularly since these guidances are meant for all constituents, including the agency, I wouldn't want to see there be too much overemphasis. So for example, you know, if you don't have as much natural history on a patient population, or you don't have any drug development or you have very

little drug development.

So as you go into drug development, you're learning about these patient populations and subpopulations. Yeah, we've seen this happen in our patients. We've seen this happen with bronchiectasis patients. I've seen this happen with acromegaly. And it can stem from anything, including, for example, the physicians who treat them, making these assumptions about these patients, like, oh, well, when they are treated they feel better, and that's not necessarily the case.

So I would just say that in the guidance it needs to address the fact that there needs to be allowance made for different rare disease populations where you can't necessarily modify a COA or where you're going to try to do that, and all of a sudden you're going to find like this isn't really feasible, and it has to be a completely different kind of COA.

DR. CAMPBELL: Thank you. Those are some good comments that we'll take back. Sir?

MR. TEWELL: Matt Tewell [ph], University of Rochester. And this will be a comment and not a

question. I completely agree with that statement. Just looking at this flow diagram up here, can the existing COA be modified for the new COU? I think that really should be, should the existing be modified.

We can certainly modify any COA, but the question is, is that really the right thing to do? Whenever you modify an instrument, you're going to lose the relevance potentially, you're going to lose the responsiveness, the statistical qualifies that make it really a useful instrument for a clinical trial.

And I think we maybe shouldn’t be encouraging so much. I mean certainly it's convenient to do that, but it might not be the right thing to do, especially in rare diseases.

And so I think we have to acknowledge that and realize that it's not always going to be the right thing to do. It might be the easy thing to do. But in some instances it's better to go ahead, and it's probably not that much work, honestly, in some instances to develop something from scratch. And then you have a disease-specific very powerful instrument. You do it once, and you're done for that point on.

So I think, you know, this diagram is interesting, but I think we have to allow for sometimes it is the right thing to do to make something from scratch.

DR. CAMPBELL: Thank you for that comment. The person in the back? Hold on. Megan is going to look and see. I think she's bringing a different mic.

MS. MANSFIELD: My name is Carol Mansfield from RTI Health Solutions. And I heard this morning that patient preference methods are beyond the scope of this, but I guess when you have a lot of comments about what's most important to patients, how patients trade off the benefits and risks, what is a clinically meaningful difference to patients, how does that change with their circumstances.

All of those things are things that patient preference methods are one method you can use to address. And I feel like there should at least be some reference to their existence in the guidance document and their usefulness, even if you're planning on a second guidance document to address patient preference methods.

And the other thing I'll say is that we often try to design patient preference studies using a PRO instrument where the PRO change in score doesn’t actually mean anything to the patients. You know, your score went up by three. So I don't know how difficult -- designing PRO instruments where the change in score is something that you can translate into a benefit that patients can relate to. Then that will make it easier to use those instruments in preference studies or in evaluating whether the benefits are worth the risks to patients.

DR. CAMPBELL: Well, thank you, you're highlighting tomorrow's session on, within meaningful change. So that's critical. And that's some nice comments on patient preference we'll take back. Steve?

MR. BLUM: Hi, Steve Blum, Bristol-Myers Squibb. First, thanks for a great day. I mean a lot of really great insights and comments and really applaud the agency for going through a thoughtful approach for revising these documents.

I do want to challenge the notion of context of use. What concerns me is it doesn’t reflect the

fluidity of clinical trial design. I have studies that aspects of the design change on a daily basis. And I think we have to recognize the fact that, you know, there are certain aspects of this strategy that we can get right up front before we select the COAs, but there was a lot of aspects that are very fluid.

And I think we need to appreciate the fact that some of those maybe fall further down on the right-hand column. So when I think about context of use, what I think we really want to talk about is, is the concept of interest relevant to the population of interest. Within the therapeutic context, other aspects of the clinical trial design, that’s not so much the strategy, that’s the implementation.

And we need to tailor the use of the COA measure that we've selected to fit the clinical trial design. So I'd like to see us consider, and I'll make this in the comments to the docket.

DR. CAMPBELL: Thank you.

MR. BLUM: When we think about context of use, let's really think about identifying what's relevant to the population of interest. And acknowledge the fact

that there are implementation challenges that are at the study level that we need to think about later on down the road. Thank you.

DR. CAMPBELL: Thank you. And I will encourage all people who have made comments make sure you do add it to the docket. So I've got two left, and then we're going to, promise, get to Megan for closing statements. The person in the back? We're doing our best.

MS. BRAVERMAN: This is Julia Braverman from Celgene. So I would like to challenge a little bit of a dichotomy we have here, but when using the existing instrument and modifying instrument. That modification requires concept elicitation and, you know, somewhat. I think we do have a third option that I think in the guidance and in the discussion we didn't pay attention to this. And this is using individual models or individual subscales from the existing instrument.

For example, in fact, we all know, you know, FACT-G score or EOTC. In FACT-G we have physical wellbeing, emotional wellbeing. Is it possible, and what's the updated perspective from this of using an

individual subscale that has already been validated and has already been scored individual and even have calculated its own MID. So we have it for physical wellbeing on FACT-G, EOTC we have it. So how about this situation, and should we consider it separately in the guidance.

DR. CAMPBELL: Okay. Thank you. We'll take that back and think about how to approach that, about using existing instruments and potentially point out the main usage that's already existing. We'll focus on that. And to our last comment.

MS. GODWIN: Hi, Miriam Godwin, Roche Genentech. I've been sent up here by a colleague in South San Francisco to ask this question. So what she would like to know is --

DR. CAMPBELL: Was it Liz?

MS. GODWIN: It was.

DR. CAMPBELL: Liz should've come. Hi, Liz. On the webcast, right?

MS. GODWIN: Given the opportunity to use flexible item banks instead of static questionnaires, how does the agency and the panel recommend including

this in the selection diagram?

DR. CAMPBELL: That's a great question. So if you didn’t hear it -- Liz's question, really, from Genentech Roche was the idea of using the item banks and the flexibility of pooling there instead of using a static. For the essence of time, I will defer that. Perhaps we can get to that tomorrow in another session because I don’t want to keep us any later. But that is a really great question. And we'll take back that concept in general and see if we can address that as we continue writing this guidance.

I want to thank our panel and the people that asked our questions today. I think we had a really great discussion. It sounds like everyone likes this concept of the decision tree as a replacement for the wheel and spokes. But we do need to add onto it. And we also potentially need to add onto the roadmap.

I do ask of our panelists, we'll just sit there while Megan comes up to make her closing remarks so we can move this flow and get us, everyone out of here at 5:00. But I thank you, and I thank our panelists for this. And let's give them a round of

applause.

(Applause.)

MS. MONCUR: Okay. And I promise I will make this very quick. But most importantly, we really want to thank everybody that has come together here today, those listening on the webcast, those here in the room, and also to our exceptional panelists throughout the day. And you will hear more tomorrow.

You've really enabled us to come together and have a really wonderful fruitful discussion. So we thank you for that. So my job is to do a recap today of the high-level themes, get you set up for tomorrow, and cover some logistics.

In the interest of time, I have been reminded about what an excellent job all of our moderators have done throughout the day recapping. And we will also have a recap tomorrow morning. So I am going to skip right into the logistics.

So we will -- the meeting will go from 9:00 to 5:00 tomorrow, just like it did today. However, registration desk will be open at 8:00. We also wanted to mention that starting at 8:00 those who want to sign

up for our open public comments can start to do that tomorrow at 8:00. And that list will be there out at the registration desk.

We also, pop quiz, when does our docket close?

(Crowd responds, December 14.)

MS. MONCUR: Thank you. And we might -- I think we have a slide just to reinforce that. So, again, this is such an important resource for us. So topics you've heard today, terminology clarification, whatever it is that you want to communicate to us, and something else that we've also heard is we really -- we've heard from you that you want more examples, more case studies. So we would love to invite you to submit those to the docket.

And that might be -- you might want to create a whole case study for us, or you might just want to say, hey, could you target this with a case study. It could be as simple as that. But that would be extremely helpful to us. And I just -- turn to my left to get -- any, okay, any other parties -- with that we will adjourn. And we look forward to seeing you tomorrow. So thank you, very much.

(Applause.) (Meeting adjourned.)

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October 23, 2018

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