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US FOOD & DRUG ADMINISTRATION

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PATIENT-FOCUSED DRUG DEVELOPMENT

Incorporating Clinical Outcome Assessments into  
Endpoints for Regulatory Decision-Making

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DATE: Friday, December 6, 2019  
TIME: 9:00 a.m.  
LOCATION: Food and Drug Administration (FDA)  
White Oak Campus  
10903 New Hampshire Ave  
Bldg 31, the Great Room  
Silver Spring, MD 20993-0002  
REPORTED BY: Michael Farkas, Notary Public  
JOB No.: 3207312

## 1 P A R T I C I P A N T S

2

3 MEGHANA CHALASANI

4 THERESA MULLIN

5 SCOTT KOMO

6 MARTIN HO

7 KEVIN WEINFURT

8 GIANNA MCMILLEN

9 LINDA NELSEN

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12 LARISSA LAPTEVA

13 FRASER BOCELL

14 EBONY DASHIELL-AJE

15 BILL BYROM

16 MICHELLE CAMPBELL

17 ANDREA CORAVOS

18 MATTHEW DIAMOND

19 MARK FRASIER

20 ABIGAIL LUO

21 ANDREW POTTER

22 DIANE STEPHENSON

- 1     MARC BOUTIN
- 2     STEPHEN JOEL COONS
- 3     KATARINA HALLING
- 4     TELBA IRONY
- 5     LAURA LEE JOHNSON
- 6     PANDU KULKARNI
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## 1 P R O C E E D I N G S

2 MEGHANA CHALASANI: Okay, everyone. I  
3 think we're ready to get started. We have a full  
4 agenda today, so we do want to get started.

5 Good morning everyone joining us in  
6 person and on the webcast. Okay. This time for real  
7 we're getting started, everyone.

8 Good morning. My name is Meghana  
9 Chalasani from the Patient-Focused Drug Development  
10 Program staff in the Office of the Center Director in  
11 the Center for Drugs here at the FDA. I'd like to  
12 welcome everyone to our public workshop. This  
13 workshop is the fourth in a series we've been  
14 conducting as we work towards developing a  
15 methodological, patient-focused drug development  
16 guidance series.

17 Let me first start by saying, wow. We  
18 have a very full room here, and I know we still have  
19 folks trickling in. And we've expanded from our  
20 typical use of two sections of the great room to all  
21 three sections, and we still have a very full room  
22 here. And I'm happy to see so many patients and

1 patient advocates, academic researchers,  
2 practitioners, medical product developers, and other  
3 key stakeholders in the audience. And I understand  
4 that we have nearly 200 or maybe even more by this  
5 point in time joining us remotely from the web as  
6 well. And we have many more registered who I'm sure  
7 will be joining us, both from here in the U.S., but  
8 also internationally. Thank you all for being a part  
9 of this very important workshop.

10 The purpose of the methodological PFDD  
11 Guidance Series is to facilitate the advancement and  
12 use of systematic approaches to collect and use robust  
13 and meaningful patient and caregiver input that can  
14 better inform medical product development and  
15 regulatory decision-making.

16 We kicked off the public dialogue on  
17 this effort when we conducted the first Guidance 1  
18 workshop in December of 2017 and then continued the  
19 conversation last October during the PFDD Guidances 2  
20 and 3 workshop. And so now we are here today to  
21 discuss incorporating clinical outcomes assessment  
22 into endpoints for regulatory decision-making.

1                   Throughout the day, we want to hear  
2 from you on the approaches and considerations proposed  
3 in the discussion document for this workshop. If you  
4 haven't had a chance to read the document, that's  
5 okay. We will have a presentation to go over the key  
6 topics and set the context for us all.

7                   For today's agenda, we will have Dr.  
8 Theresa Mullin, the Associate Director for Strategic  
9 Initiatives here at FDA Center for Drugs, get us  
10 started in the morning with opening remarks. We will  
11 then have a presentation that provides an overview of  
12 the discussion document for this workshop from Dr.  
13 Scott Komo, followed by a series of panel discussions.

14                   We have five panel discussions today.  
15 The first one will be focusing on General  
16 Considerations for Developing an Endpoint From  
17 Clinical Outcome assessment data, followed by a second  
18 session on using the estimand framework to design,  
19 conduct, and analyze data from a trial with a COA-  
20 based endpoint.

21                   The third session today will focus on  
22 considerations when there is a heterogeneity in

1 disease symptoms and functional status between  
2 patients and within same patient over time.

3 The fourth session we'll really work on  
4 discussing a working example, putting all the pieces  
5 together. And then we'll end the day with a session  
6 highlighting the themes that emerge throughout the day  
7 as well as reflect on the entire PFDD Guidance Series.

8 During each panel session, the audience  
9 will have an opportunity to ask questions and provide  
10 their views. We have a full agenda today. And for us  
11 to keep the conversation flowing, I am going to ask  
12 all of you to please be succinct and cognizant of the  
13 time.

14 We also have a public docket that will  
15 be open until February 4th, 2020, to which the public  
16 may submit general or detailed comments or examples  
17 regarding specific aspects of the discussion documents  
18 or topics raised during the workshop.

19 In the interest of time, during the  
20 audience questions and answers, our moderators may  
21 need to jump in to provide additional comments or  
22 flesh out your comments further through the docket or

1 discuss with our colleagues during the breaks that  
2 we've provided.

3           With our large number of webcast  
4 attendees, we will not be able to take comments or  
5 questions from the webcast during the workshop live.  
6 However, we also encourage our web stakeholders  
7 joining us via webcast to submit comments through the  
8 public docket. And we will take back any of the  
9 comments that you're putting in through the webcast  
10 after the meeting to review as well.

11           Following the panel sessions today, we  
12 will provide time for open public comment. If you  
13 wish to sign up to speak during this period, please do  
14 so at the registration tables outside. We'll have the  
15 sign-up sheets available through lunch. Participation  
16 is on a first-come-first-serve basis.

17           And so with that, I would just like to  
18 close with a few brief housekeeping points. We have  
19 an hour-long lunchbreak at noon. We do recommend that  
20 you preorder lunch. If you have not had an  
21 opportunity to do so yet, we will make that service  
22 also available at the ten AM break that we have. And

1 then -- sorry, 10:30 AM I believe is our break. And  
2 then we have an afternoon break at two PM as well.  
3 The food and beverages are available, as I mentioned,  
4 at that kiosk. If you aren't able to preorder, you  
5 will have an opportunity to do so throughout the day  
6 as well during the breaks.

7           Bathrooms are down the hallway in the  
8 lobby and on the left. The Wi-Fi password is up here  
9 on the slide. If you have any issues connecting to  
10 the Wi-Fi, you can also reach out to our colleagues at  
11 the kiosk and the information desk out front, and  
12 they'll be able to help you.

13           And with that, I ask at this time that  
14 you please turn off or silence your cell phones. And  
15 I'd now like to invite Dr. Theresa Mullin to the  
16 podium to provide opening remarks. Thank you.

17           THERESA MULLIN: Good morning,  
18 everyone. To everyone in the room, thank you for  
19 joining us today, and also for those of you on the  
20 webcast. I'm going to keep it brief. I think Meghana  
21 mentioned managing your time at least three times. So  
22 I'm going to try to heed that and give you a very

1 quick intro and just a quick recap of the background  
2 for these guidance documents. And this is the fourth  
3 in a series of four. They all have rather long names,  
4 but this one is about incorporating the COAs into  
5 endpoints for regulatory decision-making and some  
6 other related things that need to be addressed to  
7 operationalize this.

8           And this is really based on five-plus  
9 years, just to remind us all of where we got to this  
10 series of guidelines, from listening to patients in  
11 patient-focused drug development meetings and other  
12 kinds of venues over the last several years,  
13 recognizing and doing this that patients are uniquely  
14 positioned to inform us about the clinical context of  
15 the treatments that they will be taking and the  
16 disease context. In those patient-focused meetings,  
17 we took a systematic approach to getting their  
18 patients' perspective on the burden of their disease,  
19 of available treatments, and what they would most  
20 value in new treatments. It was a very powerful, eye-  
21 opening experience for us. And at this point we've  
22 had 26 FDA-sponsored patient-focused drug development

1 meetings and externally-led meetings. We're now up to  
2 30 of those meetings. And that's quite remarkable  
3 when you consider that we just began having patients  
4 began running these meetings in 2016. So we've  
5 learned a lot.

6           And what we keep getting reinforcement  
7 of is this message from -- these takeaways about not  
8 only patients with chronic and serious conditions, but  
9 patients with acute conditions or maybe even less-  
10 serious conditions are really experts in what it's  
11 like to live with those conditions. And in talking to  
12 us about their experiences, we really have come to  
13 realize that often their chief complaints are not  
14 being factored into the drug development programs  
15 explicitly and as much as would be desirable, and  
16 including the measures of benefit and even better  
17 measures of what risks and what burdens patients are  
18 experiencing.

19           They've indicated they like to be as  
20 active as possible considering that they do have lives  
21 to live, families to raise, jobs to hold down, et  
22 cetera, but they want to help advance the development

1 of treatments for their disease. And these meetings -  
2 - and typically what we would hear after the first few  
3 meetings where there's always very powerful, a lot is  
4 shared. Patients would come up and ask us, okay,  
5 we've been telling you things that we haven't even  
6 told our doctor; what are you going to do with this  
7 information? So what's next, FDA?

8           And we really took this very much to  
9 heart. We thought these meetings are great and they  
10 are a very powerful source of information. But what  
11 else? What can we do next? And so this series of  
12 guidance that's being developed is really to help  
13 stakeholders get beyond and build on that initial and  
14 maybe qualitative narrative so they can collect  
15 information that could be used as endpoints in  
16 studies.

17           And in this picture we show it really  
18 informing the COAs, Clinical Outcome Assessments being  
19 used to inform benefit. But certainly they also can  
20 inform risk and safety and the burdens associated with  
21 the treatment. And so this is really where we're  
22 headed. We want to not only have the benefit of that

1 qualitative information that we would get in a  
2 patient-focused type meeting or a patient listening  
3 session, but really have it going to the next step and  
4 being data, become data that can be used for decision-  
5 making.

6           And so this is the series of guidance  
7 that we committed to do in a very similar kind of  
8 framing of this series of guidance is put in 21st  
9 Century Cures, Section 3002, the first one on  
10 collecting comprehensive patient input on the burden  
11 of disease. Moving on to the next -- and that  
12 guidance was published in draft in 2018 and we're  
13 working on looking at a final version of that now and  
14 publishing that in the next year we anticipate.

15           The next one, guidance two, developing  
16 a holistic set of impacts of burden of and disease and  
17 what matters most to patients. And that guidance is  
18 out in draft now.

19           And the third one will be on developing  
20 good measures of identified sets of impacts that can  
21 be used in studies. So developing or selecting  
22 clinical outcome assessment measures that would suit

1 and be appropriate for a particular concept.

2           And finally, this is where we're  
3 focusing today, on incorporating those COAs into  
4 endpoints that are considered sufficiently robust --  
5 not significantly -- sufficiently robust for  
6 regulatory decision-making. I hate to say it, but  
7 it's even correct in the commitment letter. It should  
8 have been sufficient, not significant.

9           And so with that, here's the PDUFA  
10 commitment that we're satisfying in working through in  
11 publishing this guidance. Rather lengthy words. I'm  
12 not going to repeat all the PDUFA commitment language,  
13 but essentially it's talking about really putting  
14 something out that -- this Guidance 3 and 4 together  
15 in this series we think could potentially replace our  
16 2009 guidance on PROs. And this covers a broader set,  
17 covers COAs more generally. And it would also address  
18 ways to incorporate those endpoints in decision-  
19 making.

20           The statute also asks that we put in  
21 information about standards and technologies to  
22 collect and analyze this information for decision-

1 making. So that's going to be covered in this  
2 guidance as well.

3 And so with that, I'd like to turn it  
4 over to Scott Komo so we can get into more of the  
5 substance of today's meeting. Thank you.

6 SCOTT KOMO: Good morning. My name is  
7 Scott Komo from the Office of Biostatistics at Center  
8 for Drugs. I want to thank you all for attending the  
9 workshop. Your input is crucial in developing this  
10 guidance on incorporating clinical outcome  
11 assessments, sometimes known as COAs, into endpoints  
12 for regulatory decision-making. I will now give an  
13 overview of the Agency's approach to this guidance.

14 This guidance will cover the  
15 methodologies, standards, and technologies to collect  
16 and analyze COAs for the purpose of regulatory  
17 decision-making. Guidance 4 builds on the work of  
18 Guidance 3, where Guidance 3 looks at the  
19 considerations when developing, modifying, or  
20 selecting a COA into a fit-for-purpose -- to be fit-  
21 for-purpose. Guidance 4 assumes you have a fit-for-  
22 purpose COA and discusses the considerations,

1 construct, and meaningful endpoint using the COA data.

2 As part of the discussion, it is  
3 important to note that the COA is not the same as the  
4 endpoint. We have heard this misperception, and I  
5 think it's important to clear up this confusion. As  
6 an example, let's assume you have a daily symptom  
7 score that measures the symptom severity over the past  
8 24 hours. This is not the endpoint in your study.  
9 Instead, an example of endpoint would be the average  
10 symptom severity score over the last week prior to the  
11 end of therapy.

12 The guidance is targeted at a broad  
13 audience that I will now discuss. This could include  
14 stakeholders involved in design, conduct, analysis,  
15 and review of clinical studies incorporating COAs. In  
16 order to be useful for the statistical data management  
17 and related audience, (indiscernible) has been  
18 included in the discussion document and anticipated to  
19 be included in the guidance.

20 The audience includes medical product  
21 sponsors, clinical research organizations,  
22 consultants, academic researchers, FDA reviewers, and

1 patient organizations. Other audience (indiscernible)  
2 guidance include organizations involved with the  
3 development of registries, natural history studies,  
4 and endpoint or COA development.

5 I will now provide a brief overview of  
6 the sections in the discussion document. The first  
7 section is the introduction. It includes the overview  
8 of the four guidances in the PFDD series. This  
9 information is similar to that just presented by Dr.  
10 Mullin. It also includes a summary of the document.  
11 The next section is a discussion of the estimand  
12 framework.

13 The aim of this framework is to better  
14 align the study design, endpoint, and analysis with  
15 the clinical study objectives to improve study  
16 planning and interpretation of analysis. I'll give a  
17 brief overview of this framework in a few minutes.

18 The next session includes a discussion  
19 of the methods to determine meaningful within-patient  
20 change (indiscernible) their termination of study  
21 results. And finally, the last section includes the  
22 discussion of additional considerations which includes

1 topics on other study design considerations tied to  
2 blinding and the use of non-randomized or non-  
3 concurrent controls using COA-based endpoints. Also  
4 the use of computerized adaptive testing in clinical  
5 trials, and finally, formatting and submission  
6 considerations.

7 The document also includes an appendix,  
8 which contains two examples. The first example is a  
9 case study of the estimand framework looking at a COA-  
10 based endpoint as part of a breast cancer clinical  
11 trial. This example will be presented in Session 2.  
12 The second example is a gene therapy treatment.

13 I will now give a brief explanation of  
14 how the discussion document is formatted. Because of  
15 the broad audience of this guidance, we have used the  
16 following format. For the sections just discussed in  
17 the previous slide, the document contains a section  
18 summary that is aimed at a broad audience, a technical  
19 summary that is aimed at a more technical audience,  
20 and the technical details following in the section.

21 These details are derived in part from  
22 the reviewer comments that have been sent to medical

1 product sponsors and patient organizations. Several  
2 questions related to the document will be presented in  
3 the next several slides. We encourage you to provide  
4 feedback to the docket.

5           The first question, do you find this  
6 formatting approach helpful in understanding the  
7 material? If yes, do you recommend the guidance use  
8 this formatting approach? If no, what other  
9 recommendations do you have?

10           I will now go through a brief  
11 introduction of each of today's topics. The focus of  
12 Session One are factors to consider when constructing  
13 a COA-based endpoint. Some important factors to  
14 consider are you need to ensure that each COA-based  
15 endpoint is stated as part of the specific clinical  
16 study objective. Want to ensure that the COAs are fit  
17 for purpose and sensitive to meaningful change, the  
18 disease subtypes, the disease type, the treatment  
19 objective. Is the clinical study duration adequate to  
20 support the COA research objectives and also whether  
21 the frequency and timing of the COA administration is  
22 appropriate given the patient population, clinical

1 study design and objectives, and the COA  
2 (indiscernible) properties.

3 Other factors to consider would be  
4 ensure that the plans for scoring are specified and  
5 consistent with those used during tool development,  
6 including the handling of missing data. Also ensure  
7 the plans for COA measurement after discontinuation  
8 from treatment are driven by the research questions.  
9 Also need to consider the effect of lack of blinding  
10 for COA-based endpoints in open label or single-blind  
11 trials. And for non-randomized or non-concurrent  
12 controls, considerations could include whether the  
13 versions of the COAs are consistent between the study  
14 test group and the external control and also whether  
15 the COA administration methods are consistent within  
16 the study test group and the external control.

17 Next question. What factors should be  
18 included? Do you have additional factors that should  
19 be included and why?

20 I would like to introduce the estimand  
21 framework that will be presented in greater detail in  
22 Session Two. The first thing to note is that estimand

1 is the quantity used to define the treatment effect in  
2 a clinical study. The framework aims to align the  
3 study design, endpoint, and analysis with the clinical  
4 study objective to improve study planning and  
5 interpretation of analyses.

6 Here is a listing of the framework  
7 attributes that we discuss today. Important questions  
8 to answer are who is a target population for the  
9 study, what is the endpoint, how will events  
10 precluding observation or affecting interpretation be  
11 accounted for in the analyses, and what is the  
12 population level summary?

13 The following important issues to note  
14 regarding these attributes just discussed. These  
15 attributes are present in every data analysis and the  
16 choices made strongly impact the interpretation of the  
17 analysis, power, and data collected.

18 The document also discusses  
19 considerations and endpoint construction when there is  
20 heterogeneity in symptoms and/or functional status.  
21 This topic will be discussed further during Session  
22 Three. The heterogeneity could occur between

1 patients. Examples are having various disease  
2 subtypes where patients have differing symptoms and/or  
3 functional status, having a wide range in the rates of  
4 disease progression, a wide range in the baseline  
5 disease symptom severity, or wide age range of  
6 patients, which is especially an issue in pediatric  
7 studies. Or heterogeneity could occur within the same  
8 patient or time. Examples of this type of  
9 heterogeneity could be a disease with a waxing and  
10 waning nature or you have changes in functional status  
11 as children age. For example, as children get older,  
12 their walking ability normally increases, and this  
13 impacts the interpretation of the treatment effect on  
14 input like a six-minute walk test.

15 The following topics were included in  
16 the discussion document but were not directly  
17 discussed today. This is meaningful within patient  
18 change. This topic was previously discussed at the  
19 October 2018 PFDD workshop, so will not be discussed  
20 today.

21 Also the use of computerized adaptive  
22 testing in clinical trials and formatting and

1 submission considerations. If you have comments on  
2 the discussion document related to these topics,  
3 please submit it to the docket.

4 Please submit your docket comments by  
5 11:59 February 4th of 2020. The topics could include  
6 but not limited to the content, the level of technical  
7 detail, formatting, examples for online materials,  
8 responses to the questions in the document. Also  
9 responses to the questions in this presentation. It  
10 is important to note that this is the last workshop in  
11 the PFDD series, so please include any additional  
12 comments for the guidance services. Note, if your  
13 comments are directed at a guidance other than  
14 Guidance 4, please clearly indicate which guidance  
15 your comments address. Please send in your comments.  
16 This slide provides the details and will be shown  
17 throughout the day during the breaks.

18 Thank you for your attention as well as  
19 your participation in this workshop.

20 MARTIN HO: Good morning, everyone. My  
21 name is Martin Ho. I am from the Office of  
22 Biostatistics and Epidemiology. Today we are going to

1 have several sessions. In the first session we will  
2 be covering high-level concepts. And in the  
3 subsequent sessions we will be having deep dive in the  
4 individual components of the discussion document.

5 So in the next sessions we are going to  
6 cover how to explore and discuss factors that need to  
7 be considered when developing a COA -- okay -- when  
8 developing a COA-based endpoint.

9 There are two points that I want to  
10 repeat, since we have to repeat the same point three  
11 times so that you can form memory (indiscernible).  
12 The first one is that endpoint is not the COA and vice  
13 versa. So I hope that over time you will recognize  
14 the importance of the distinction between the two.  
15 And the second point is that our discussion, we are  
16 focusing on the clinical trials or clinical studies  
17 that are being done, designed, and conducted for  
18 regulatory consideration. That is also a very  
19 important focus of the scope of the discussion.

20 So with no further ado, I would like to  
21 invite all of the panelists coming onto the -- taking  
22 a seat. And while they are taking their seats, I am

1 going to introduce them. Very happy to have a very  
2 good mix of expertise and perspectives. We have  
3 representatives from patient advocacy groups and also  
4 academics and sponsors as well as the FDA. And in  
5 terms of expertise, we have psychometrists, we have  
6 statistician, and we have clinicians.

7 Fraser Bocell is a psychometrician. He  
8 is coming from the Office of Strategic Partnership and  
9 Technology Innovation from Center for Devices.

10 Kendra Hileman, she is the Vice  
11 President, head of the Clinical Research and  
12 Development from Alcon.

13 Hylton Joffe, he is from the Office of  
14 New Drugs, CDER.

15 Larissa Lapteva, she is from the Office  
16 of Tissues and Advanced Therapies, Center for  
17 Biologics.

18 Gianna "Gigi" McMillen, she is a  
19 patient advocate and program administrator. She is  
20 from Bioethics Institute at Loyola Marymount  
21 University.

22 Linda Nelsen, she is a senior director

1 and head of Patient-Centered Outcomes at  
2 GlaxoSmithKline.

3 And last but not least, Kevin Weinfurt.  
4 He is Professor and Vice Chair for Research,  
5 Department of Population Health Science from Duke  
6 University School of Medicine.

7 Thank you for taking part in this  
8 panel.

9 So the first questions that I would  
10 like to ask of you is should the future guidance  
11 provide any additional details on the currently-  
12 proposed factors or considerations? First I would  
13 like to call on Kevin.

14 KEVIN WEINFURT: Hey. Good morning and  
15 thank you. And thanks very much for the opportunity  
16 to review this. And thanks to the FDA colleagues for  
17 all of your hard work. It was really a very  
18 comprehensive and helpful document I thought and will  
19 be of great use.

20 There were a couple of high-level  
21 issues that I noted where there might be opportunity  
22 for a little more detail or clarification. One was --

1 and I know we'll have a whole third panel on this.  
2 But the heterogeneous symptom and functioning  
3 presentation section was of course of most interest to  
4 me. And it was mostly things that will not work too  
5 well. And so I was excited to see more details about  
6 suggestions for things that might work well.

7           And the other, it was so helpful to  
8 have the first example, walking through the estimands  
9 and taking the time with a good example. And the  
10 second example was a very interesting example, and I  
11 wondered if we could get a little bit more structure  
12 about what aspects of the future guidance are being  
13 exemplified by different parts of that example. The  
14 first example was structured so beautifully and walked  
15 you through the estimand considerations. And so some  
16 similar structuring with the second one would be  
17 great.

18           But I thought that the considerations  
19 that were reviewed were relatively comprehensive and  
20 clear.

21           MARTIN HO: Thank you, Kevin. Next,  
22 Gigi, who represents the patient advocates.

1                   GIANNA MCMILLEN: Thank you for having  
2 me here today. I thought this document was a clear  
3 presentation of many layers of information and I  
4 appreciate the logical sequence of the sections and  
5 the definitions of the key terms. It's still a bit  
6 unwieldy, and I am considering that if this document  
7 will be put in the hands of a patient or an advocate.  
8 A welcome added detail to the formatting of the  
9 guidance would be to indicate where patient input has  
10 been taken into account at each step of the process.

11                   Now, I know there's a blanket statement  
12 at the beginning. But one idea would be to have a  
13 code or a symbol or a color cue that indicates the  
14 points in the described sequences when patient voice  
15 has already been incorporated into this plan and also  
16 where it will be needed in the future.

17                   Even if this document does not actually  
18 enjoy wide patient or advocate perusal, I think that  
19 such indications of where the patient voice has been  
20 incorporated would add meaning to the descriptions of  
21 these unfolding processes.

22                   MARTIN HO: Thank you, Gigi. Linda.

1                   LINDA NELSEN: Thank you. I echo the  
2 previous speakers in finding this a very valuable  
3 initial draft of the approach to thinking about  
4 endpoints for COAs. And I especially value the  
5 emphasis differentiating the COA measure from the COA  
6 endpoint. It's a box that I jump on multiple times a  
7 day in my daily work. And the value of going from the  
8 concept to the COA measure, which is the way you're  
9 collecting that information from the patients to  
10 deriving meaningful endpoints.

11                   And so I think one area that we can  
12 further clarify is really thinking through as part of  
13 the protocol design and development of endpoints is  
14 the nuances of the disease experience, the treatment  
15 benefit, and timing of the treatment benefit and that  
16 a single COA can create multiple, really valuable,  
17 insightful endpoints to help patients truly understand  
18 their treatment experience.

19                   Scott mentioned a symptom diary where  
20 you get a 24-hour recall of symptoms. Well, you can  
21 use that single COA measure to derive so many  
22 different endpoints depending on the treatment

1 population. A mild population, you might look at  
2 symptom-free days. A severe population, you might  
3 want to look at change in severity. If you have it  
4 over the length of the trial, you might want to look  
5 at time to onset or durability of treatment effect.  
6 And so I think additional examples and emphasis on how  
7 to think through endpoints across all of those factors  
8 would be valuable in here.

9 I think that's all I had to say for  
10 here.

11 MARTIN HO: Thank you. Kendra, please.

12 KENDRA HILEMAN: Thank you for this  
13 opportunity to review the document and provide  
14 comments.

15 Especially because I come from a  
16 medical device perspective, most of the document kind  
17 of refers to drug, although the footnote has device  
18 included within it. So just maybe a bit more emphasis  
19 or inclusion in device in component of it.

20 And in particular there is a reference  
21 to real world evidence in one of the sections on non-  
22 randomization. But I see us having a lot more trend

1 toward studies that use real world evidence and  
2 endpoints based on that real world evidence, and maybe  
3 a little bit more inclusion of that information into  
4 the document would be helpful.

5 MARTIN HO: Thank you very much. Next  
6 is going to be the three colleagues from the FDA.  
7 First, Hylton, please.

8 HYLTON JOFFE: Good morning, everybody.  
9 So I agree with much of what's been said already. I  
10 thought this was a very comprehensive document.  
11 Actually, many of the concepts in this discussion  
12 document actually apply to endpoints in general when  
13 we think about designing trials. And we want to make  
14 sure the line up with the objectives of the trial, we  
15 want to minimize bias to the greatest extent possible,  
16 we want to have a pre-specified plan for analyzing the  
17 endpoint, controlling type 1 error and having a plan  
18 for missing data. So those concepts come through  
19 here. And then of course there are things that are  
20 unique to COA that are in this discussion document as  
21 well.

22 And I think at FD we think through a

1 lot of these things one-on-one with sponsors, so I'm  
2 quite excited to have a document that nicely in one  
3 place articulates some of these things that we are  
4 having one-off discussions with. And furthermore,  
5 when the guidance is published.

6 I would say that many of the things  
7 that come to incorporating the COA as an endpoint are  
8 not super-challenging. Of course there are some  
9 challenging issues. Kevin brought up a very good one,  
10 which is on the top of my list as well, which is when  
11 you have a lot of heterogeneity, for example, in the  
12 patient population.

13 So, for example, for seven years I've  
14 been a director of the Division of Bone, Reproductive,  
15 and Neurologic products. And we just published a  
16 draft guidance on interstitial cystitis bladder pain  
17 syndrome. Their patients have, you know, bladder pain  
18 or discomfort, and then they also have usually a lower  
19 urinary tract symptom. More frequent urination,  
20 waking up at night to urinate, urgency. But not all  
21 patients have all symptoms. So how do you best assess  
22 whether your drug is having an effect with an

1 appropriate endpoint? Because if your COA endpoint is  
2 measuring something that a lot of patients aren't  
3 experiencing or aren't experiencing much, you're not  
4 going to see much of an impact.

5 So I think the biggest challenge we see  
6 -- and I'll just take a moment to say this, I'm almost  
7 done -- is getting to this point where you're ready to  
8 pull the COA instrument into an endpoint. You know,  
9 how do you develop the fit-for-purpose instrument? I  
10 think that's where we have a lot of challenges. And  
11 getting those instruments as early as possible into  
12 trial so you can learn about those instruments early  
13 than Phase 3.

14 So in terms of additional details, I  
15 think the heterogeneity is a big one. The other thing  
16 I thought was -- on open label trials. I know you  
17 touched it on the example and there's a paragraph on  
18 blinding. But one dilemma we often face is in an open  
19 label trial is there any way that you can use a COA  
20 instrument, particularly if you're asking a patient  
21 about his or her symptoms. If it's unblinded, what's  
22 the framework around thinking about how that could

1 generate useful data.

2           Also another point worth making is  
3 making sure patients at baseline have severe enough  
4 symptoms so that you could see a reduction in those  
5 symptoms if the drug or device works. Because if you  
6 start off with very low levels of symptoms, there's  
7 not much opportunity for showing improvement.

8           And then my second-to-last point is  
9 also there's a section here about analyzing data. And  
10 I know Bob Temple has been on this for a while. We  
11 look at central tendencies, but I think it's also  
12 important to think about what the distribution of the  
13 treatment effect shows.

14           So, for example, we approve a drug for  
15 nocturia, which is waking up at night to urinate. And  
16 the mean treatment effects were pretty small, but we  
17 had endpoints there that looked at the patients who  
18 had zero episodes of nocturia, and that provided some  
19 additional useful context for gauging whether the  
20 treatment effects are meaningful or not.

21           And then lastly, again, putting in a  
22 plug to try and get COAs as endpoints tested earlier

1 in development. Like in Phase 2 it can help you  
2 consider guidelines for what's meaningful change. You  
3 can kind of see how the endpoint -- you know, how it  
4 performs in early trials before you then go ahead in  
5 Phase 3. So I'll stop there.

6 MARTIN HO: Thank you. Next, Larissa,  
7 please.

8 LARISSA LAPTEVA: Thank you. So I've  
9 read this document. And what I'd like to do first is  
10 I would like to commend the authors of the document  
11 for putting together a number of relatively complex  
12 and highly technical topics and going through this I  
13 thought very challenging task of presenting it to the  
14 stakeholders who may or may not have exposure to  
15 clinical research on a daily basis like some of us  
16 here. So I thought they've done a really good job  
17 with that. I am sure they will receive a lot of both  
18 positive and demanding feedback today. But overall, I  
19 thought it was a pretty good document. I would like  
20 to make a few comments and save one for later.

21 And so my first comment is about other  
22 elements that you would have to take into

1 consideration when successfully transforming a  
2 clinical outcome measure into a study endpoint. You  
3 know, we're in the business of drug development. And  
4 in no way anybody who has ever designed a trial would  
5 take only disease manifestations and only the COA  
6 measure, only those elements as the basis for how to  
7 transform a clinical outcome assessment into an  
8 endpoint. You will absolutely always think about what  
9 is the product that you're investigating, what is the  
10 treatment, and what would be the effect of that  
11 treatment.

12           And so one of the contextual elements  
13 in here is the effects of the investigational product.  
14 And of course the document is made applicable to a  
15 variety of medical products -- biologics, drugs,  
16 devices perhaps -- into different therapeutic area.  
17 But in some of the places throughout the document, I  
18 thought it may be helpful to mention that effects of  
19 the product would need to be taken into consideration.

20           For example, in the timing for  
21 assessments and the clinical trial duration and COA-  
22 based endpoint, when we're talking about things like

1 recall period or anticipated rate of change in the  
2 underlying construct to be measured, it is I think  
3 appropriate to mention the effects of the product when  
4 the (indiscernible) occurs, when the peak is expected,  
5 when the effect may plateau, and how long it would  
6 last. Because all of these things would be taken into  
7 consideration for applying a clinical outcome  
8 assessment measure to an endpoint measurement.

9 Another potential place is when we're  
10 talking about the choice of a clinical outcome  
11 assessment. Multi-domain responder index can be  
12 applied and connected with products when certain  
13 effects would be anticipated. And by the time when  
14 the estimand framework is considered, this is  
15 typically later-phase studies. And with these later-  
16 phase studies, you already have some anticipation of  
17 how the treatment might work. So for something like a  
18 multi-domain responder index, you would probably want  
19 it to be used in assessment of effects of a product  
20 that may have multiple effects. When it may influence  
21 say a uniformed or a very central pathway, like  
22 inflammatory response pathway for example. Or if it

1 is a substitution of a protein that will eventually  
2 downstream have effects on multiple organ systems. So  
3 that's one comment that I would make, is to ensure  
4 that the effects of the product are not overlooked,  
5 because they are a very important contextual element.

6 The second comment that I wanted to  
7 make is an expansion of what Gigi said earlier. We do  
8 talk a lot about how we could engage patients, how we  
9 could bring them to the table, how they are equal  
10 partners in product development. But in doing so, I  
11 think we should really be able to make space for this  
12 participation. And by having these discussions and  
13 publishing guidances and engaging patients, we are  
14 making space. But also when it comes down to this  
15 pretty technical aspect of product development, it  
16 would be also important to bring patients perhaps even  
17 at the design stage when they could be members of  
18 research teams and help out with some of these  
19 aspects. Because their input could be really very,  
20 very valuable.

21 Again, for example, in section where we  
22 talk about intercurrent events. And here we have

1 practice events and participant burden. And in the  
2 example at the end of the document, there is this talk  
3 about gene therapy, multi-luminance mobility testing,  
4 MLMT, and how to avoid the practice and learning  
5 effects. We had 12 different investigators in the  
6 study had 12 different configurations of the obstacle  
7 course assigned randomly to patients. And that's how  
8 they tried to avoid the practice and learning effects.  
9 So this is something where patients could really bring  
10 a very important perspective at the time when this  
11 clinical outcome assessment is taken and applied as an  
12 endpoint.

13 I'll tell you just very briefly a story  
14 from my own life. I used to work as a clinical  
15 investigator some time ago before my job at FDA. And  
16 I was a lead investigator on a study that was  
17 evaluating cognitive functioning in patients with  
18 autoimmune disease. And when you evaluate cognitive  
19 functioning, the outcome measure there is a battery of  
20 testing, of tests that have to be performed within the  
21 period of one-and-a-half hour. And before I started  
22 the study, I actually asked one of our clinical

1 research test administrators to give the test to me  
2 because I wanted to know what people have to go  
3 through when they take these tests and what the  
4 experience. You have the test and you have the  
5 instructions and you have various advice that's been  
6 developed for how to interpret the test. But until  
7 you actually have somebody who has gone through this,  
8 you may not see some of the very important aspects  
9 that would be useful in the interpretation at the end.

10 So I did the battery of tests. And  
11 after taking the test, I knew exactly how you can  
12 compensate one function for another and where in the  
13 test you can trade speed for accuracy and where you  
14 get tired and all the different stumbling points. And  
15 it was very, very useful for me at the end knowing  
16 what people had to go through and knowing their  
17 performance scores.

18 So, again, bringing patients as team  
19 members at the time of design I think would be helpful  
20 and useful. And if we could -- even though this is a  
21 technical document, but I completely agree with Gigi.  
22 Even if we have -- you know, if we can identify a few

1 places where patients' input can be of importance, I  
2 think we should do it in the document.

3 MARTIN HO: Thank you, Larissa.

4 LARISSA LAPTEVA: Thank you.

5 MARTIN HO: Next, Fraser, please. He  
6 is a psychometrician.

7 FRASER BOCELL: Good morning and thank  
8 you. I think I would agree with my colleague, Hylton,  
9 that it's quite a comprehensive document and covers a  
10 good bit of material. But at the same time, it does  
11 need to be accessible. And the goal is to make it  
12 accessible not only to professionals who do this for a  
13 living, but for other medical professionals who might  
14 be involved in medical product development. And so I  
15 think that even though it's comprehensive, it also  
16 provides just a starting point, a starting point for  
17 discussions to be had. Because especially in device  
18 trials and in mini trials, there's many challenges  
19 involved in including clinical outcomes assessment.  
20 And one of the key parts of this is this provides a  
21 starting point to engage with the agency, to engage  
22 with the centers and begin those discussions and

1 provide clarity in those discussions. And so I really  
2 think that this provides an excellent place and  
3 excellent information for us to move forward with.  
4 Thank you.

5 MARTIN HO: Thank you, Fraser. So we  
6 hear some common themes across the panelists,  
7 including patient -- laying down perhaps  
8 participation, how patient can participate in the  
9 process is important. Also that we would like to have  
10 more understanding or perhaps discussion on  
11 heterogeneity.

12 Last but not least is about the early  
13 and often interaction with the FDA when they are  
14 developing these COAs and then use it for clinical  
15 studies. And of course this is also important for us  
16 to get to understand how these effects are impacting  
17 patients in various aspect.

18 So the next question is what additional  
19 factors should be included in the guidance. Gigi,  
20 please.

21 GIANNA MCMILLEN: So I think the FDA is  
22 doing a good job with their intentions of including

1 patient input about all these different processes in  
2 drug development.

3 In the end, if you have this what I  
4 consider to be a pretty good draft of guidance, if you  
5 just drop it at the feet of a patient or an advocate,  
6 it's not very accessible or absorbable. My background  
7 is as a high school teacher. And so I get a little  
8 bit excited when I look at something like this. I  
9 think there's good information, there's many layers,  
10 it's compelling, the topic's important to the  
11 audience. How can you turn this into a meaningful  
12 teaching tool?

13 So I say okay, maybe -- the executive  
14 summaries that are in the document are in gray boxes.  
15 Those are excellent. But how about let's put them all  
16 together into a coversheet so that at one glance a  
17 normal human patient can just look at them and see  
18 what the context of the document is.

19 Also, I think patients need to have a  
20 statement about why this document is important and  
21 some guidance about where are the key points that they  
22 need to pay particular attention.

1           I think we're moving, I hope, forward  
2 to a place where meaningful instruction is not just  
3 paper-based. But I think a multimodal way of  
4 providing this information. For example, an  
5 interactive web-based document where you could click  
6 on terms and get a little interactive sort of  
7 description or video or something that explains each  
8 of the very important parts that this document covers.  
9 That would go a great distance towards having a fully-  
10 informed patient who, with this knowledge and with  
11 this understanding and with an appreciation of the  
12 context of their participation, that informed patient  
13 can more meaningfully participate as you gather this  
14 data.

15           So to keep my comments directed  
16 specially to the guidance document, I think there is  
17 good content here and it has great potential for being  
18 an excellent teaching tool. And that attention to  
19 that end will enhance the ability of patients to  
20 meaningfully participate.

21           MARTIN HO: Thank you, Gigi. I just  
22 want to echo what you have just said. In fact, I

1 think it's an excellent idea to be extended to all  
2 four guidances within the sequence. And that  
3 basically remind me some of the patient journey  
4 picture that we had presented by Dr. Theresa Mullin  
5 earlier. And I think by having perhaps a toolkit to  
6 demonstrate or perhaps to suggest points where  
7 patients can play a part from beginning to finish in  
8 the development process, I think it would be  
9 excellent. But it's my personal opinion only. But  
10 thank you.

11 Next, Kendra, please.

12 KENDRA HILEMAN: Great. So I guess the  
13 additional factor I would include is when you go  
14 through the document, it talks about different ways  
15 that you can evaluate endpoints or design endpoints as  
16 more of a you can do this or that or that. But what  
17 we find lately is that our endpoints are sometimes  
18 multiple factors within an endpoint. For example, you  
19 can have a statistical significance using a continuous  
20 variable analysis of difference in means. But perhaps  
21 the clinical relevance component of that endpoint  
22 might be based on a responder-type analysis. So what

1 we're finding is that a lot of our more current  
2 protocols have multiple elements you need to meet  
3 within an endpoint. And that complexity I'm not  
4 really seeing in the document right now.

5 MARTIN HO: Thank you. Next, Linda,  
6 please.

7 LINDA NELSEN: Yeah. I think one  
8 element that's missing that perhaps could have a  
9 little bit of attention is thinking about out are the  
10 way you're deriving and presenting the endpoints going  
11 to be things that are meaningful and important to  
12 patients. We do a tremendous amount of work to make  
13 sure that the COA measure itself is measuring  
14 important concepts to patients, but we make it very  
15 difficult for patients and providers often to  
16 interpret what that really means. And we think of  
17 COAs as a way of bringing the patient's voice into the  
18 clinical trial to quantify the important aspects of  
19 treatment benefit. And if we don't think through are  
20 these endpoints going to be interpretable, are there  
21 ways to display them, are there ways to explain them  
22 to patients so they can truly understand that

1 treatment benefit and use it to make good treatment  
2 decisions is incredibly important. And so I think we  
3 need to have a little bit of balance in the  
4 statistical rigor and intensity. And also are these  
5 endpoints going to be approachable and interpretable  
6 by patients.

7 MARTIN HO: Thank you. Next, Kevin,  
8 please.

9 KEVIN WEINFURT: I'm not sure what  
10 factors might be missing here, but I'll just share an  
11 experience I had. I actually had it this morning at  
12 breakfast. I was thinking about sexual functioning,  
13 which for me is one of my main measurement areas, so  
14 it wasn't that I was just thinking about that at  
15 breakfast.

16 And I really did -- I enjoyed this  
17 document. It's so comprehensive. But I was thinking  
18 we've got this measurement issue in sexual function  
19 where it's difficult to measure the functioning of  
20 someone over the last X period of time if they've not  
21 engaged in any activity. And so you get this  
22 interesting dependency. And past approaches have

1     tried to address that by assigning a zero score for  
2     functioning if you didn't have sex, and that has a  
3     whole lot of problems with it. Our (indiscernible)  
4     instrument takes a different approach and keeps having  
5     the activity and the functioning conditional upon  
6     having activities separate things.

7                     And I thought, well, if I were to -- if  
8     this were the guidance in its current form and I were  
9     to go through and say how do I think the FDA would  
10    like me to think about taking the responses from our  
11    measure and creating an endpoint here from that. I  
12    wasn't sure that I could thread the needle all the way  
13    through there. I still have uncertainty about what  
14    would be an acceptable approach there.

15                    And so I just offer that as one case  
16    example where it might be interesting to think of  
17    those and some other ones and go through and see do I  
18    come out of that with a better sense or less  
19    uncertainty about what I ought to do than I did  
20    before. So I would just offer that.

21                    MARTIN HO: Yes. Kevin, I think it's a  
22    very good point. In the guidance documents we talk

1 about estimand. We talk about what estimand  
2 individual unit. But yes, it would be ideal to have  
3 perhaps a roadmap or a story-telling process or  
4 engagement process to think about these translation or  
5 development process.

6 Next, Larissa, please.

7 LARISSA LAPTEVA: Okay. So I would  
8 like to add and talk a little bit about the meaningful  
9 within-patient change. And I know that this is one of  
10 the topics that was listed as not supposed to be  
11 covered, but we were offered to provide comments about  
12 it.

13 MARTIN HO: Yes, yes.

14 LARISSA LAPTEVA: I thought this was a  
15 very important topic to bring up. And as I see in the  
16 documents, the section is written from the perspective  
17 of the mainstream clinical trialist who is doing  
18 comparative research and trying to assess within  
19 patient change and how it is related or not related or  
20 could be applicable to understanding and evaluating  
21 the differences between the treatment groups. And  
22 this is all great and in no way -- I want to make a

1 disclaimer. I am not a heretic; I am a scholar of the  
2 adequate and well-controlled and all the comparisons  
3 and the statistics that's behind it. But in certain  
4 situations you just can't have an appropriate or the  
5 best in the world comparison. And in those situations  
6 where you can't use a concurrent control or where --  
7 and this may be something looking forward to -- where  
8 you have an effect of the product that is so  
9 compelling where within patient change, the meaningful  
10 within-patient change can become a very important  
11 metric. And so I think the within-patient change with  
12 any outcome assessment measure should be a necessary  
13 attribute of that outcome assessment measure.

14 And I saw the discussion here in the  
15 description. And there is methodology that's offered  
16 to be used. Very useful. In fact, we've seen it in  
17 practice. But I also saw that there wasn't a  
18 discussion about the variability in the disease and  
19 the variability for individual patient performance.  
20 And these are very important factors that would need  
21 to be taken into consideration, because the  
22 variability of the disease -- and I'm not talking

1 about just relapsing-remitting type of diseases. Even  
2 chronic diseases that are considered to be progressive  
3 may have certain periods in them where the disease  
4 stabilizes or can improve even -- we call them  
5 honeymoon periods on its own. Another aspect is that  
6 each patient may have better days or worse days for  
7 various reasons. And so here is this within-patient  
8 performance on a COA, right, variability.

9           So these are two factors that would  
10 need to be absolutely included I think in the  
11 meaningful within-patient change evaluation. And  
12 again, many of you have probably heard about  
13 (indiscernible), maybe you have seen publications  
14 about it. Trying to consider how we could potentially  
15 develop individual therapies for patients. And if you  
16 have a product that's tailored to an individual  
17 patient, then you may not have the comparator arm.  
18 There may be no study. And so in that case, the  
19 meaningful within-patient change may become one of the  
20 metrics that are extremely useful in evaluating how  
21 the product works in that patient.

22           MARTIN HO: Thank you, Larissa. As you

1 can tell, people from CBER were very mindful about how  
2 to evaluate and understand innovative products, as we  
3 are encountering quite a bit.

4 Now last but not least, Fraser will  
5 have the honor of wrapping up the question one and  
6 question two. He is the last panelist to share his  
7 thoughts. Thank you.

8 FRASER BOCELL: Thank you, Martin. I  
9 would like to kind of echo what Linda said about the  
10 interpretability of this and that when you're going  
11 into this, not only should the COA be interpretable,  
12 but the analysis you do should present something that  
13 is then interpretable as well. So the endpoint needs  
14 to be interpretable when it goes into the labeling.

15 And then I also want to talk a little  
16 bit about some of the device-specific considerations  
17 that need to be made. Because this document is not  
18 the only consideration that should be made. There are  
19 device-specific guidances as well as device-specific  
20 standards that also touch on clinical outcome  
21 assessment as endpoints, the types of endpoints you  
22 need, and things that are necessary. And so it's

1 always important to look at this and use it as a guide  
2 in conjunction with other things that might be  
3 important within your product area, within your  
4 thoughts.

5 One example is interocular lenses that  
6 specify certain types of measures from patients that  
7 need to be done within their standards. And so these  
8 are things that you always have to keep in mind moving  
9 forward when developing your endpoints.

10 MARTIN HO: I apologize. In fact, I  
11 think Hylton will be the next person.

12 HYLTON JOFFE: I thought I was off the  
13 hook.

14 MARTIN HO: No, no, no. Not that  
15 easily.

16 HYLTON JOFFE: I've actually been  
17 wracking my brains trying to think what additional  
18 factors are missing. I interpret factors as the  
19 general categories that were laid out earlier. And I  
20 really couldn't think of any. I think there is  
21 further details that can be added into each of the  
22 factors that you have. I echo some of the other

1 comments about making sure the document is accessible  
2 to the primary audience. We had the slide of who the  
3 primary audience is for the documents. So just  
4 thinking through the perspective from each of those as  
5 to how to make the document most accessible.

6           And then the other is just adding in  
7 more details in some places. And this is a balance of  
8 how much details do we put in. But we talk about  
9 things like rescue therapies or intercurrent  
10 conditions effecting interpretation. But, you know,  
11 maybe adding color on how do you handle that exact --  
12 maybe giving some examples of how you would handle  
13 someone who needs a rescue mediation that's going to  
14 impact the COA. So I don't think those are different  
15 factors per se. I'm thinking of them more as filling  
16 in some of the spots here and there.

17           MARTIN HO: Thank you. I have a  
18 follow-up question to Hylton. You and Larissa and  
19 Fraser gave excellent feedback about from your  
20 perspective what you would propose to pay attention to  
21 from the therapy, beginning to the end. Do you think  
22 in this guidance there would be a useful -- perhaps

1 description or discussions about when it comes to  
2 developing these COAs and then translating them or  
3 developing endpoint based on those COAs, what would be  
4 perhaps a typical engagement process for sponsors and  
5 for others when they want to elicit inputs from the  
6 FDA?

7 HYLTON JOFFE: That's a good question.  
8 So within CDER -- and I'm sure there's analogous  
9 processes in the other centers. The review divisions  
10 work very closely with our COA colleagues and also  
11 biostatistics. It's really a joint effort to evaluate  
12 these things, because no one group has all the  
13 expertise you need when you're bringing this all  
14 together.

15 We sometimes have what we call Type C  
16 meetings, which are meetings where we just focus on  
17 discussing these instruments, because there's so much  
18 detail in there. So we encourage sponsors to request  
19 those types of meetings if they really want to have a  
20 dedicated focus on their instrument.

21 We're trying to get the work on the  
22 instruments to happen earlier in development, as I was

1 mentioning before, and really try to get folks getting  
2 some of these endpoints into their earlier trials.  
3 Because if you have a phase 2 trial that uses one  
4 endpoint, and then your phase 3 trial is going to use  
5 a different one, that introduces some risk. Maybe  
6 it's not going to translate to the new instrument in  
7 phase 3 and you end up with a failed phase 3 trial for  
8 example.

9           In the OND divisions, our regulatory  
10 project managers are our point of contact. We  
11 encourage folks to reach out, request meetings if they  
12 feel that would be helpful. I think a lot of the  
13 discussions with endpoints going into phase 3 trials  
14 happens at the end of phase 2 meetings. But again, we  
15 are hoping we have information before that can really  
16 help inform how we think about the phase 3 trial  
17 development.

18           MARTIN HO: Thank you. It's very  
19 useful feedback. Yes, Larissa.

20           LARISSA LAPTEVA: So I think this  
21 guidance on its own, the fourth guidance in the  
22 series, is an important tool to help development of a

1 COA, because it gives the ability to begin with the  
2 end in mind. When somebody is interviewing patients  
3 and trying to figure out what are the important  
4 domains for a disease and then develop a clinical  
5 outcome measure and then validate it, you would need  
6 to know how it will be applied. And so this is how it  
7 will be applied. So this guidance on its own is an  
8 important feedback. So that's one.

9           The other is that, as Hylton mentioned,  
10 we have a number of pathways or ways to interact with  
11 sponsors, with those who develop products. And Hylton  
12 talked about how we could speak with individual  
13 sponsors within their individual development programs.  
14 This could be done very early, at even pre-IND  
15 consultation meetings. In CBER we have a former pre-  
16 pre-IND program. It's called Interact. Even there  
17 certain aspects of clinical development can be  
18 discussed for an individual product within an  
19 individual product development program. And then  
20 later in phase 2 of course, and then in phase 3.

21           So the other way to get assistance in  
22 development of a COA is to work with the agency

1 through the Drug Development Tools Qualification  
2 Program. I think both CDER and CBER now participate  
3 in this program. This is a process where people could  
4 develop a measure in what we call a precompetitive  
5 space where consortia or multiple stakeholders could  
6 get together and develop a measure for a particular  
7 context of use that could be applicable to more than  
8 one disease or more than one product.

9           There are other pathways, including  
10 Critical Path Institute and (indiscernible) for the  
11 innovative technologies in CBER. There is information  
12 about these different ways to interact online. If you  
13 have any questions about them, I'll be happy to answer  
14 after.

15           MARTIN HO: Thank you, Larissa. I also  
16 believe that there is a parallel opportunity to engage  
17 colleagues at Center for Devices as well. Given the  
18 available time for Q&A for the audiences, perhaps if  
19 you have any questions, please approach Fraser and our  
20 colleagues to discuss these potential (indiscernible).

21           So let me start with this audience Q&A.  
22 Please approach to the microphones in the middle of

1 the aisles if you have any questions. Okay, great.

2 While we are waiting for someone to come up with some  
3 questions, I think one thing that really strikes me is  
4 that there are some discussions about people needs to  
5 flesh out a little bit about heterogeneity. And I  
6 want to see if Kevin can elaborate on his thoughts on  
7 this part.

8 KEVIN WEINFURT: Well, given we're just  
9 sort of commenting at a high level for that section --  
10 and hopefully our later discussion will illuminate  
11 more aspects of this. But I think the section does a  
12 great job of addressing the challenges in trying to  
13 represent and analyze situations where you have  
14 heterogeneity in symptoms or functioning within or  
15 across people. But as a user of the guide, as someone  
16 who is actually trying to do the work, I've left with  
17 some options feel like they're going to be  
18 unfavorable, but I'm still left trying to figure out  
19 what to do. And it's really challenging. And so I  
20 don't expect that there was a magic solution hidden in  
21 the back room that they forgot to put in. And it's  
22 hard work to do. But to just highlight that that is

1 an area -- it's an issue in the guidance because it's  
2 an issue in the field. And so -- yeah.

3 MARTIN HO: Thank you, Kevin. I think  
4 Kevin is at the front line of research on this topic.  
5 So if he is still trying to wrap his brains around,  
6 then that means that a good solution is yet to be  
7 found. So therefore, I think it would be good for us  
8 to, as Kevin said, to mention these may be challenging  
9 topics. And perhaps in case-by-case basis we can  
10 engage with individual sponsors to figure out some  
11 fit-for-purpose solution for that.

12 And I think right now is our -- okay.  
13 So yes, Hylton, please.

14 HYLTON JOFFE: I was just going to  
15 follow up on this. I was wondering, maybe Kevin, do  
16 you have thoughts on using things like most-bothersome  
17 symptom or things like that as a way of trying to get  
18 around the heterogeneity? The document talks about  
19 personalized endpoints, and I actually wasn't quite  
20 sure what that meant exactly. I think that's worth  
21 clarifying. I wasn't sure if that meant each patient  
22 has his or her most bothersome symptom and that's

1 where we have a problem. I wasn't quite sure on that.  
2 But I don't know if Kevin or anyone on the panel has  
3 thoughts on most-bothersome symptom approaches.

4 KENDRA HILEMAN: Yeah. I thought that  
5 was probably the most confusing section for me, the  
6 personalized endpoint.

7 But one of the other things I wanted to  
8 mention about the complications with the different  
9 endpoints is oftentimes in the medical device area, we  
10 have a surgery involved in the study design, and that  
11 introduces a lot of different effects into what's  
12 happening with the patients. It oftentimes means that  
13 the clinical outcome assessment that's done before the  
14 surgery really has very little relevance to change  
15 from baseline for the patient afterwards. So  
16 sometimes we just look only at the postoperative  
17 outcomes between two treatment groups. And sometimes  
18 we do. It's often when that's the case when it's a  
19 surgical intervention, that's a good example of a  
20 study design where a control really isn't available.  
21 You know, we don't do sham surgeries very much in  
22 clinical literature. So those are some of the

1 complications that come with -- and what I meant by  
2 adding some device considerations into the document is  
3 it introduces a little bit more of the intermittent  
4 events and the heterogeneity across the patient across  
5 the study becomes more of an issue in some of those  
6 trials.

7 MARTIN HO: Yes. Kevin. Kevin first  
8 and then Gigi.

9 KEVIN WEINFURT: Yeah. And I know our  
10 third panel is going to get more into the weeds on  
11 this heterogeneity issue. So I don't want to do that.  
12 But at the high level it does seem like as that  
13 section gets developed and takes shape, there might be  
14 some opportunity to look back into the guidance that  
15 precedes this one where people are trying to figure  
16 out how to put together a measure. And this is an  
17 interesting area where some people are going to try to  
18 solve the problem through a scoring solution of the  
19 measure and some people are going to try to solve it  
20 by defining an endpoint in a certain way. And in my  
21 experience sometimes measurement folks like me are not  
22 even aware of some of the different options where you

1 could handle the complexity on the endpoint definition  
2 side as opposed to trying to come up with a scoring  
3 solution for it.

4           So this might be a place to earmark an  
5 opportunity to make some connections between the two  
6 guidances. So as I'm going through Guidance 3, trying  
7 to figure out how to make a measurement situation like  
8 this, I'm not assuming that I need to solve this  
9 problem in the scoring. I'm aware that I should think  
10 ahead through the estimand framework and be aware of  
11 these other options.

12           MARTIN HO: Yes, Gigi.

13           GIANNA MCMILLEN: I just want to point  
14 out that there's two different kinds of patient input  
15 here. You've got the patient who is newly exposed to  
16 this medical emergency and treatment. And so their  
17 evaluation of what is important or serious or  
18 bothersome could be different than a patient who is  
19 more experienced or further down the line in the path  
20 of their disease and treatment. So the more  
21 experienced patient has context and may realize that  
22 over the period of time what seems very bothersome in

1 the beginning is actually in context not such a big  
2 deal after all. So you have two different patient  
3 populations who are giving their personal input. Both  
4 inputs are valuable and valid, but they are different.

5 MARTIN HO: Thank you. So I see that  
6 there potentially is an audience who want to ask a  
7 question. Go ahead.

8 RACHEL LAWRENCE: Thank you. I'm  
9 Rachel Lawrence. I'm a statistician for Adelphi  
10 Values. So from a sponsor perspective. But I just  
11 wanted to have a listen to what the panel said today,  
12 and particularly perhaps Gigi's comments on what's  
13 highlighting in the guidance where the patient input  
14 is. I wondered if you could consider sort of also  
15 reflecting what the regulatory decision-making points  
16 are. So what is it -- which aspects of the guidance  
17 is really key, what are you needing at the COA  
18 endpoints and how does that feed into the overall  
19 risk-benefit decision-making part. It may be a  
20 question for the panelists to comment on.

21 MARTIN HO: I just want to add that, as  
22 you may have known, our agency has been working hard

1 on the benefit-risk part. And hopefully you will hear  
2 some good news on that. And in terms of the benefit-  
3 risk guidances and agency's thought on that, I think I  
4 would like to see if my colleagues, Hylton, Larissa,  
5 and Fraser have anything to say.

6 HYLTON JOFFE: Well, internally we are  
7 thinking through and having a lot of discussions on  
8 the benefit-risk framework and how to think of that as  
9 the endpoint in your drug development with that as the  
10 goalpost, maximize your chances for showing a positive  
11 benefit-risk assessment at the end of the day. If  
12 your drug has a serious risk, it's even more critical  
13 to really try and find the endpoints that are really  
14 going to maximize the benefit you're showing so that  
15 we can hopefully end up with a favorable benefit-risk.  
16 So I think it's very important to think about benefit-  
17 risk as where we're going and take that into account  
18 when you're thinking about the endpoints, whether it's  
19 COA endpoints or non-COA endpoints that are going to  
20 add to the benefit side of the equation.

21 MARTIN HO: Thank you. Larissa first  
22 and then we can go Bennett.

1                   LARISSA LAPTEVA: Well, I only wanted  
2 to add that in response to the question of where in  
3 the guidance you could put some goalposts for  
4 potential patient input. I think most of the section  
5 in the intercurrent events can benefit from patient  
6 input. But patient input in drug development is much  
7 more complex and goes beyond this guidance. There are  
8 many other aspects where patients could be extremely  
9 important in giving their perspective of how to  
10 develop a particular product or how to design a  
11 particular study. So this is a much larger  
12 conversation I think.

13                   MARTIN HO: Thank you, Larissa.  
14 Fraser, do you have anything to add? No, okay.  
15 Bennett.

16                   BENNETT LEVITAN: Bennett Levitan from  
17 Janssen R&D. So I wanted to ask people for your  
18 thoughts on the comment that Kendra made earlier.  
19 Many times an endpoint is based on a continuous change  
20 in a COA measure. And that has a lot of fidelity, but  
21 it's also rather abstract. And often when we talk to  
22 physicians for getting to benefit-risk, they want to

1 see a measure of response, some threshold change. And  
2 that is often not measured with a statistical  
3 hypothesis test. And we're in an awkward position of  
4 doing benefit-risk with an endpoint that wasn't in the  
5 hypothesis chain.

6 So since you just brought up this  
7 benefit-risk point, the idea with the endpoint is not  
8 only to use it alone, but to use them collectively to  
9 render a benefit-risk decision. What are your thoughts  
10 about possibly suggesting moving towards the  
11 dichotomization of these endpoints so that they are  
12 more clinically meaningful for some of your physicians  
13 who are ultimately going to do a benefit-risk balance?

14 MARTIN HO: So before I ask for my  
15 panelists' comment on that, now I am wearing my  
16 statistician hat. And I have to say that in testing a  
17 hypothesis, continuous outcomes often are more  
18 powerful to detect the differences between groups than  
19 our responder analysis which are dichotomized. And in  
20 the process of dichotomization, we lost some  
21 information. So this is one part of -- one of the  
22 considerations of how to pick an endpoint. But with

1 that, I would like to see if my colleagues have  
2 additional comments.

3 LARISSA LAPTEVA: This is a question  
4 that comes up so frequently. It's almost like a  
5 chicken-and-egg argument sometimes with some  
6 endpoints. Continuous versus binary. And you've  
7 heard the perspective that Martin just shared, and  
8 that's one side of the argument. If you're using a  
9 continuous variable, you're absolutely going to lose  
10 on the accuracy of the comparison. If you're using a  
11 binary outcome, it may help a little bit  
12 mathematically and it may look like clinically it is  
13 pretty meaningful. But then how do you say separate  
14 somewhat responder from really high responder who has  
15 improved very significantly. So this is something  
16 that we encounter pretty frequently. And there is no  
17 universal answer to this question. We have used and  
18 advised in using and sponsors have used and drugs have  
19 been approved on both. It really depends on the  
20 disease. I know it's a disappointing answer, but it  
21 depends on the setting on the disease and how valid  
22 either continuous or binary variable would be in a

1 specific setting.

2 MARTIN HO: Thank you, Larissa.

3 Hylton, do you want to have anything to say?

4 HYLTON JOFFE: Yeah. I think the  
5 continuous interpretations can be quite challenging.  
6 Things like cumulative distribution curves and things  
7 like that are not very accessible. Even folks like us  
8 who see them quite a bit have to always wrap our brain  
9 around them. It would be nice and ideal if you could  
10 use information from both to help -- you know, going  
11 back to the nocturia example for example, bringing in  
12 -- so this is when you urinate at night. You know,  
13 having no episodes or having at most one. Most folks  
14 think that having up to one episode of nocturia, some  
15 folks think that that's actually completely normal.  
16 So grounding a responder analysis in something that  
17 makes clinical sense, and also pre-specifying all  
18 this. Because when you start cutting the data in  
19 different ways, you can get different answers. So I  
20 think it is a challenge. And in the ideal world it  
21 would be nice if we could get information from both.  
22 But I think Larissa makes a good point that the

1 specifics of the development program, the disease, and  
2 so on and so forth may move it towards one or the  
3 other.

4 MARTIN HO: Yeah, thank you.

5 LARISSA LAPTEVA: The key -- sorry.

6 MARTIN HO: Larissa --

7 LARISSA LAPTEVA: Just one sentence to  
8 add to this, that consistency is important, if the two  
9 are consistent in their performance, responder versus  
10 continuous, then this is something that provides  
11 reassurance there. You know, measuring the same  
12 thing.

13 MARTIN HO: Thank you.

14 FRASER BOCELL: And I was just going to  
15 say that we do look at the totality of evidence. And  
16 you're also thinking about not only what you're  
17 submitting to get approval, but then what's going to  
18 go into your summary of safety and effectiveness,  
19 what's going to go into your patient brochure, what's  
20 going to go into your physician documentation. And so  
21 it is something where you can focus on what's going to  
22 be your primary endpoint, but then specify secondary

1 endpoints or other things that they're going to use  
2 for that further documentation. So it's really  
3 talking to us and seeing about how you want to  
4 approach that and what your goals are and what we can  
5 look at and do.

6 MARTIN HO: Thank you, Fraser. So we  
7 are just three minutes past. And last thing, our  
8 outstanding panelists. Okay, I didn't know that.  
9 Please.

10 CARRIE BARNHART: Hello, my name is  
11 Carrie Barnhart. I am a patient advocate. I used to  
12 be a teacher and I used to work in pharma. I used to  
13 be somebody, and now I'm just here on behalf of all  
14 rare disease patients.

15 And going off of what Ms. Larissa was  
16 saying about every patient is different, we have good  
17 days and bad days, with rare disease, often we are  
18 misdiagnosed, we have comorbidities, we have many,  
19 many, many diseases, especially with autoimmune  
20 disease. So oftentimes there is nobody driving that  
21 ship. So how are you -- I don't see in the document  
22 how patients like myself and other patients with rare

1 disease are going to be contacted if there's no  
2 specialist for that disease. There's not -- it  
3 doesn't fall under rheumatology, it doesn't fall under  
4 genetics. So I'm just wondering how to include  
5 patients that fit outside of the box.

6 MARTIN HO: Any comments from our  
7 panelists?

8 LINDA NELSEN: When we're doing  
9 certainly COA development, we are beginning to look at  
10 more innovative ways than recruiting through  
11 individual patients to bring patient voices in. We  
12 are looking at social media to have online  
13 discussions, we're looking at communicating with  
14 patients through sort of advertisements perhaps on  
15 Facebook and other ways where there might be online  
16 communities that we can tap into. And I think it's a  
17 really important way to make sure we have a much more  
18 diverse population when we discuss, make it easier for  
19 patients with limited mobility or limited stamina to  
20 participate in these discussions. And so I think  
21 formalizing and finding acceptable ways to use those  
22 in regulatory product support is important.

1           One of the biggest areas that we fall  
2 into when we do this online research is the FDA  
3 obviously want us to have confirmation that a patient  
4 has a certain diagnosis. And if we're interacting  
5 with someone only through an online interface, it's  
6 very complicated and it takes many steps to get that  
7 confirmation. And so that's a challenge for us. But  
8 we like these ways of interacting with patients  
9 outside of standard clinical trial or clinical sites.  
10 You may be more comfortable discussing your issue with  
11 us when you're in the comfort of your home. You may  
12 have more time to think about it. You may have more  
13 time to look around and realize a lot of concepts that  
14 when you're in a face-to-face interview won't  
15 necessarily come through. So I think those are ways  
16 to reach out to patient groups. The online  
17 communities, and patient advocacy groups are one way  
18 we can do it.

19           MARTIN HO: Thank you. Fraser first  
20 and then Larissa.

21           FRASER BOCELL: So at the Center for  
22 Devices, I am part of the Patient Science and

1 Engagement Team. And while I am more of the patient  
2 science side, we do have a group on our team that  
3 deals specifically with patient engagement and  
4 including the patient voice. And so that's something  
5 that -- that's an avenue, and we have several  
6 different avenues throughout that that provide the  
7 opportunity for patients to become involved and to  
8 include their voice in different aspects.

9 MARTIN HO: Larissa?

10 LARISSA LAPTEVA: So we collaborate  
11 with a number of patient advocacy organizations. And  
12 you may know that there is a National Organization for  
13 Rare Disorders, NORD. And NORD has a patient registry  
14 where patients themselves -- this is not about data  
15 entry done by physicians or investigators, where  
16 patients could put in their data. And there is a  
17 large network of connections with natural history  
18 registries, with those who may be looking in an  
19 investigational way or collecting data about very rare  
20 disorders. So that is I think a good network and a  
21 good avenue to tap into for something like an outside-  
22 the-box type of condition.

1                   MARTIN HO: Thank you. So in the  
2 interest of time, I think let's wrap this up. And the  
3 gentleman over there, please feel free to contact our  
4 panelists during the break time.

5                   So the next session will start at  
6 10:45. Please come back. Thank you.

7                   (Break)

8                   MALLORIE FIERO: All right. So in the  
9 interest of time, because we're running a little bit  
10 late and I want to make sure that you all can get to  
11 lunch on time, because I also want to get to lunch on  
12 time.

13                   So good morning, everyone. My name is  
14 Mallorie Fiero and I am in the Office of Biostatistics  
15 in the Center for Drug Evaluation and Research. And  
16 before I begin, I wanted to acknowledge that we  
17 originally had Allison Campbell as part of our panel  
18 today, but unfortunately she could not make it. So we  
19 have Kevin Weinfurt, who was just in Session 1, that  
20 stepped up for us today. So we appreciate him and his  
21 feedback.

22                   So for Session 2 -- or I'll step back a

1 little bit. In Session 1, we kind of talked about  
2 broad considerations of this discussion document of  
3 the COA-based endpoint. I heard a lot of really good  
4 discussion there, so I hope that we can continue on  
5 with our discussion in this session.

6 So in Session 2, we begin with a  
7 fundamental issue that must be addressed for COAs,  
8 which is to ask ourselves, what is the question that  
9 the clinical study is designed to answer. If we are  
10 not in alignment on the right question, interpretation  
11 of COA results will be difficult. The estimand  
12 framework is based on the ICH E9(R1) addendum and aims  
13 to improve alignment of the research objective with  
14 the endpoint analysis. And this will help us to  
15 improve interpretation of results. Okay?

16 So now, I know a lot of you who are  
17 non-statisticians are thinking like, oh, she's talking  
18 about the estimand framework, this does not apply to  
19 me. But this is false. This applies to all  
20 statisticians and non-statisticians because this  
21 framework aims to improve dialogue between all  
22 disciplines who are involved in the objectives,

1 design, conduct, analysis, and interpretation. So  
2 this is also important for you, too.

3 So in this session, we will re-  
4 introduce the estimand framework and then we will  
5 apply it to a case study using physical function as an  
6 example in an advanced breast cancer trial setting.  
7 And in this case we aren't detailing any specific  
8 estimand that you should pick, but rather we're  
9 talking about the conversation that should take place,  
10 this multidisciplinary conversation that should take  
11 place early on.

12 So we have a great set of panelists for  
13 Session 2 today. I'm going to ask each of the  
14 panelists to please introduce yourselves by telling us  
15 who you are and where you're from. And I will start  
16 with Jessica Lee.

17 JESSICA LEE: Good morning. My name is  
18 Jessica Lee. I am in the Division of Gastroenterology  
19 and Inborn Errors Products in OND.

20 GREGORY LEVIN: My name is Greg Levin.  
21 I am in the Office of Biostatistics, Center for Drug  
22 Evaluation and Research, FDA.

1                   JOHN SCOTT: My name is John Scott.  
2 I'm in the Division of Biostatistics in the Office of  
3 Biostatistics and Epidemiology at the Center for  
4 Biologics, FDA.

5                   DANIEL SERRANO: Daniel Serrano. I'm  
6 the Director of Psychometrics at Pharmerit  
7 International.

8                   KEVIN WEINFURT: Kevin Weinfurt. I'm  
9 with the Center for Health Measurement at Duke  
10 University.

11                   LISA WEISSFELD: Lisa Weissfeld. I'm a  
12 Senior Investigator at Statics Collaborative.

13                   MALLORIE FIERO: Great. Thank you very  
14 much. I look forward to our panel discussion later on  
15 today. And just as a reminder, this example will be  
16 an oncology example. However, we want to think about  
17 how the estimand framework can apply to any COA  
18 objective. So this is why our entire set of panelists  
19 here does not -- is not necessarily in oncology ranges  
20 across the therapeutic areas.

21                   Okay. So what is an estimand? So the  
22 goal of the estimand framework is to provide

1 transparency in what is being estimated. Okay? So  
2 the definition of an estimand is the target of  
3 estimation based on your question of interest. Okay?  
4 So basically what am I trying to estimate and  
5 explicitly define what you are estimating based on  
6 this question.

7           The draft addendum identifies four  
8 attributes that make up the estimand. Okay? So the  
9 first one is the population. So the population are  
10 the patients that are targeted based on your  
11 scientific question. This could be something like  
12 maybe you are interested in efficacy population or  
13 perhaps I have more of a safety objective. In that  
14 case, maybe I'm more interested in a safety type of  
15 population.

16           Next we have our variable or endpoint  
17 of interest. And this is the measure that is required  
18 to address this scientific question of interest. For  
19 a COA objective, this would involve defining the tool,  
20 the score, perhaps the type of endpoint if we're  
21 interested in being changed from baseline if we're  
22 interested in proportion of patients that deteriorated

1 in say pain, or maybe we're interested in a timed  
2 event outcome.

3 In addition to that, thresholds and  
4 estimates that are important in interpreting clinical  
5 relevance are also important to specify up front.

6 Next we have intercurrent events. And  
7 this is a relatively new term that was introduced in  
8 the estimand framework. And an intercurrent event is  
9 an event that can occur after randomization that can  
10 impact interpretation of your results. Okay? So an  
11 example of an intercurrent event is say if a patient  
12 is on a trial and then they discontinue treatment.  
13 How does that impact the rest of their COA  
14 measurements say for pain? Or perhaps a patient moves  
15 on to initiate subsequent therapy. How does that  
16 impact how they will score their COA? And so anything  
17 after these intercurrent events, it can impact the  
18 interpretation.

19 So it's important to up front in your  
20 multidisciplinary discussions list intercurrent events  
21 that might be important in your trial and then list  
22 how you would want to address them in your analysis.

1 And that would be in alignment with your question of  
2 interest.

3 So lastly, we have our population-level  
4 summary. And this is the basis for comparison. So  
5 perhaps we have a randomized trial, we have two  
6 treatment arms, and we want to compare the two  
7 treatment arms. Well, what summary measure are we  
8 using to compare these two treatment arms? This could  
9 be something like a difference in mean change from  
10 baseline or say a difference in proportion of patients  
11 who deteriorated in physical function. And so it's  
12 important to also explicitly state what the summary  
13 measure is.

14 So you can see that by specifying all  
15 four of these attributes, then it provides  
16 transparency to within the multidisciplinary team of  
17 what's being estimated. Because these are not new  
18 terms. Or they're not new ideas I should say. Right?  
19 Statisticians are already making a decision on what  
20 analysis population to use. We're already making  
21 decisions on how to deal with intercurrent events.  
22 It's just that we need to specify them up front and we

1 want to think about them together as a team more and  
2 think about the assumptions that are being made when  
3 we have questions.

4           And one last thing I would like to  
5 mention is that there's one final attribute, which is  
6 treatment, that was just specified in the final  
7 addendum of ICH E9(R1). And this just went live on  
8 Wednesday. But for the purposes of today's  
9 discussion, we will just go over these four  
10 attributes. Okay.

11           So this figure basically shows how the  
12 estimand attributes are placed in context of the  
13 research objectives, the analysis, and communication  
14 of results. So what I will do is I will go over a  
15 case study and then we'll go over each of the estimand  
16 attributes, and then we'll stop there. Okay.

17           So just as a disclaimer, we are not  
18 endorsing any particular design, endpoint analysis,  
19 but rather we are emphasizing how to think through  
20 your research questions. Okay.

21           So now we go into our clinical case  
22 study scenario. So in our scenario, we have a

1 metastatic or advanced breast cancer trial. And these  
2 patients have already progressed out of first-line  
3 therapy. So this is a second-line setting. So for  
4 patients with breast cancer, they have heterogeneous  
5 disease symptoms. And many of them are asymptomatic  
6 at baseline, or they don't have symptoms.

7           So second-line prior studies have shown  
8 that -- it says median overall survival of two to two-  
9 and-a-half years. So this means that they have a  
10 fairly long survival of two to two-and-a-half years  
11 median with second-line therapy alone. And that  
12 median progression-free survival is 10 to 12 months.  
13 Progression-free survival is the time from  
14 randomization to either date of death or disease  
15 progression. And so OS and PFS are common efficacy  
16 endpoints that you would see in oncology trials. So  
17 the treatment goal here is that the addition of our  
18 targeted therapy will improve PFS by six to eight  
19 months.

20           So we have a randomized control trial.  
21 In the treatment arm we have standard of care plus an  
22 oral targeted investigational agent. And in our

1 control arm we have standard of care plus placebo. So  
2 for our efficacy endpoint, our primary efficacy  
3 endpoint here is progression-free survival. And we  
4 expect there to be an improvement of six to eight  
5 months in the treatment arm compared to the control  
6 arm.

7 Secondary endpoints will include  
8 overall survival. So how long will the patient  
9 survive from randomization? However, this can be  
10 impacted because patients might initiate subsequent  
11 therapy as these patients tend to live fairly long.

12 So the COA measure that we are looking  
13 at here is a physical function score using -- and  
14 we're already assuming that we have a well-defined  
15 measurement tool, and we're saying that we're going to  
16 collect them at every treatment cycle. So perhaps  
17 this is every 28 days.

18 So one thing to note is that in our  
19 multidisciplinary discussions, we noted that physical  
20 function was an important concept for patients. And  
21 that is the reason why we decided to include this in  
22 our hypothetical trial. And another thing to note is

1 that since patients are expected to live fairly long,  
2 we expect most of our patients to be on trial at the  
3 time of our analysis, which you'll see in a bit.

4 Okay, so lastly, we have expected  
5 safety, symptomatic toxicities. We'll include  
6 diarrhea, fatigue, and rash on the investigational  
7 arm.

8 Okay, so now that we have gone over our  
9 scenario, the first thing we're going to do is define  
10 a research objective. You can see that the rest of  
11 the panels here are gray. And we're going to go  
12 through each of the estimand attributes and then we'll  
13 stop there for the purposes of this presentation.

14 Okay, so we have defined our broad COA  
15 research objective, which is to evaluate efficacy  
16 related to physical function. So perhaps we are  
17 interested in seeking a labeling claim using physical  
18 function. And in this case, we would want to compare  
19 treatment arms. For efficacy we want to show that  
20 perhaps the invitational arm is superior to the  
21 control arm. And in this case we would have to pre-  
22 specify a hypothesis and make sure to include them in

1 our statistical analysis to adjust for multiplicity  
2 and testing for multiple endpoints.

3 So we had many discussions on different  
4 types of research questions for this example. And we  
5 came up with this one for now, which is, is the  
6 average change in physical function from baseline to  
7 week 28 better or superior in the investigational arm  
8 compared to the control arm?

9 So as I mentioned, since we're looking  
10 at efficacy, we're specifically stating that we expect  
11 or we want to see if the investigational arm is  
12 superior compared to the control arm. So we're  
13 comparing the two treatment arms. We are stating that  
14 we're looking at physical function. Because, again,  
15 based on patient input, they told us physical function  
16 is important to them.

17 Next, we were thinking about the time  
18 of analysis. So if you have a specific timepoint of  
19 your analysis, it's important to say justify your  
20 reasoning for this timepoint.

21 So in this case, we chose week 28,  
22 which is about six months. And in our discussions,

1 the clinician told us that week 28 is about the time  
2 where the effects of the drug in terms of efficacy and  
3 toxicity will have equilibrated at this time. So that  
4 is why we chose week 28.

5 So now that we've defined our research  
6 objective, we're going to define our target study  
7 population. So based on our research question, we  
8 defined our target study population to be defined  
9 through inclusion and exclusion criteria to reflect  
10 the targeted patient population for medical product  
11 approval.

12 So these are the same patients  
13 basically that we're using when we want to show that  
14 we want to approve for this medical product. So an  
15 example is say we want to include all of our patients  
16 who are randomized, right? Since we want to compare  
17 treatment arms, we want to include all randomized  
18 patients regardless of adherence. So here we're  
19 defining our target study population based on our  
20 research question.

21 Next we have our endpoint of interest.  
22 So based on our research question, we defined our

1 endpoint of interest. This is going to be a change  
2 from baseline in physical function score. We are,  
3 again, assuming already that we have a well-defined  
4 measurement tool and that we will use measurements at  
5 baseline and week 28.

6           So now we get into intercurrent events.  
7 And again, an intercurrent event is an event that can  
8 occur after randomization that can impact  
9 interpretation of your results. So based on our  
10 research question, you can see on the left-hand side  
11 we listed several intercurrent events. So we had a  
12 few discussions, multidisciplinary discussions talking  
13 about what are intercurrent events that might be  
14 important in this particular trial. And so from what  
15 I heard in the first session, this is a place where  
16 you can include patient input in terms of what might  
17 intercurrent events are important and maybe how this  
18 could impact their interpretation of the endpoint.

19           So we listed the intercurrent events.  
20 And then on the right side we listed how they will be  
21 addressed in our analysis. And they need to be  
22 addressed in alignment with your research question.

1           So first we listed patients who  
2       discontinue treatment, disease progression. If a  
3       patient goes on to take say physical therapy, after a  
4       patient takes physical therapy, how does this impact  
5       their physical function score, right? And then we  
6       have subsequent therapy. So how do these events  
7       impact how a patient might interpret their physically  
8       function score. And it might be positively or  
9       negatively impacting the score. But it's important to  
10      have these discussions early on.

11           And so what we state here is that we  
12      will continue to collect and include the observations  
13      in the analysis regardless of whether these  
14      intercurrent events occur.

15           For example, if a patient say moves on  
16      to have physical therapy or disease progression, we  
17      will still continue to collect them. And that's  
18      because we want to make sure we have the least amount  
19      of missing data. And eventually we would want to  
20      compare the two treatment arms to avoid bias in the  
21      case of any missing data.

22           So next we had the intercurrent event

1 of death. In the unfortunate case that a patient  
2 dies, we cannot collect their physical function after  
3 that intercurrent event occurs. Right? So how is  
4 that dealt with in our analysis? And oftentimes I  
5 don't necessarily see how this is dealt with in the  
6 analysis in a statistical analysis plan for COAs,  
7 which can be surprising. But we had many, many  
8 discussions on different ways to address death as an  
9 intercurrent event in our analysis. And so what I  
10 will say here is that it needs to be addressed in your  
11 analysis plan, and it may be included as part of an  
12 endpoint. This is one option to address death as an  
13 intercurrent event.

14 But as I mentioned, our clinicians  
15 stated that we don't expect a high proportion of  
16 patients to die at the week 28 timepoint because they  
17 are -- the patients are expected to live fairly long.  
18 So we don't expect many patients to die in this case.

19 Okay, so lastly, we have our  
20 population-level summary. So based on our research  
21 question, we have our population-level summary. And  
22 if you remember, our endpoint was mean change from

1 baseline in physical function score. So our  
2 population-level summary is the difference between  
3 treatment arms in mean change from baseline in  
4 physical function score using baseline and week 28  
5 measurements.

6           Okay, so this is our summary slide of  
7 say all of the decisions that we made for this  
8 particular COA objective. Okay? So we are explicitly  
9 defining the target population, the endpoint of  
10 interest. We thought about intercurrent events as a  
11 team. We thought about how to address them. And I  
12 also wanted to note that you don't have to address all  
13 of your intercurrent events in the same way. In this  
14 case, you can have say two different ways that you're  
15 addressing your intercurrent events, but that should  
16 be pre-specified up front. And then we have our  
17 population-level summary.

18           And so again by doing this, we are  
19 providing transparency between our multidisciplinary  
20 teams as well as the regulators and industry in terms  
21 of what exactly is being estimated. And this will  
22 help us to improve our interpretation of COA results.

1                   And so this is a final slide just  
2 showing you, again, the figure of how the estimand  
3 attributes are placed in the context of the research  
4 objective, statistical analysis plan, and  
5 communication of results. Excellent.

6                   So now we will move on to our panel  
7 discussion. So I will have two panel discussion  
8 questions. And we will make time for audience Q&A.  
9 So start thinking about any questions that you might  
10 have. Since lunch starts at 12:00, we'll have  
11 audience Q&A at about 11:50. Okay?

12                   So the first question that we would  
13 love to hear from our panelists is what do you foresee  
14 as real-life challenges when using the estimand  
15 framework for a COA research objective. And in  
16 addition if you could please discuss any  
17 considerations in addressing intercurrent events. And  
18 I'd like to remind our panelists that this question  
19 isn't specifically for the case study that we just  
20 talked about, but rather it's for any COA objective.  
21 And if you could limit your speaking time from one to  
22 two minutes, that would be fantastic. And we will

1 start off with Lisa and then we will move down the  
2 line.

3 LISA WEISSFELD: First of all, I'd like  
4 to point out what I think the advantage of this  
5 approach is. And that is that it provides a framework  
6 to have a discussion around the study design and it  
7 sets up essentially a common terminology for the  
8 group, the team to discuss the issues. And so there  
9 are real advantages to having a framework. There also  
10 can be disadvantages in that they can be -- you can  
11 treat them in a very prescriptive manner and limit  
12 your options. But the real advantage is that it's a  
13 framework. And that framework invites people to the  
14 table to have a discussion using common language. And  
15 I think that that's the single most important  
16 contribution of this framework. And also, to make it  
17 a little simpler, it's like who are we studying and  
18 what are we interested in. When we give patients a  
19 treatment, what is the real effect? What's the effect  
20 that we are going to measure? And then how as  
21 statisticians, since I'm a statistician, my focus is  
22 on summarizing the information. And so how at the end

1 of the study will we summarize that information and  
2 how will we do that in a manner that fits on a label  
3 nicely, but also has meaning to both the clinicians  
4 and the patients.

5 With respect to intercurrent events, I  
6 think that that is a really difficult problem. And  
7 it's something that we all are faced with when  
8 designing study. And in the particular example there  
9 that was presented, the intercurrent events were all  
10 grouped together. And one of the challenges I think  
11 going forward is that those vents are not equivalent.  
12 And so when we have events like disease progression  
13 versus some of the other events that were on that  
14 slide, is there a way to treat those differently  
15 within the framework? How do we go about doing that?

16 MALLORIE FIERO: Thank you. Kevin?

17 KEVIN WEINFURT: I agree with Lisa too  
18 that the framework is so helpful. And as someone who  
19 is at the table lots of times with clinicians,  
20 biostatisticians and others, and patients who are  
21 giving their perspectives, it's a really nice way of  
22 organizing those discussions.

1           I had two specific areas where it  
2           seemed like there might be some opportunity for  
3           clarification though. And they both touch on  
4           intercurrent events in a way, and they both deal with  
5           multi-component endpoints.

6           So one of the great things about  
7           considering that class of intercurrent events that are  
8           things people do to try to make themselves feel  
9           better, like taking some extra drugs or use some  
10          assistive device. When that's happening and I want to  
11          be measuring degree of symptoms of functioning, I've  
12          got this interesting situation. And the guidance  
13          rightfully points out, well, one thing you could do is  
14          to decide to bring those intercurrent events into the  
15          endpoint as part of the endpoint definition. And  
16          that's terrific.

17          As the discussion document stands right  
18          now, there is a little bit of a tension created.  
19          Because if I've got some continuous or ordinal symptom  
20          or functioning scores and I've got some type of  
21          indicator of that thing the person did to make  
22          themselves feel better, I want to bring them together

1 to define a multicomponent endpoint. One thing I  
2 might come away from the discussion document with is  
3 FDA doesn't like responder criteria using thresholds  
4 in the definition that will be used for the hypothesis  
5 testing. And so then I'm trying to figure out how  
6 would I put that multicomponent endpoint together if I  
7 can't do that? What are some of my options? So  
8 that's one thing about the multicomponent endpoints.

9           And the other thing the document  
10 rightfully points out too that one of the  
11 considerations for multicomponent endpoints is the  
12 weighting of the individual components. And it uses  
13 the term reasonably similar clinical importance at one  
14 point as one of the statements. And as we look across  
15 guidances, look at the draft guidance for multiple  
16 endpoints, there there's reference made to the  
17 weighting, but there the language is clinical  
18 importance (indiscernible) is substantially different.

19           And so I, as a researcher and a user of  
20 these, might be wondering, well, what would reasonable  
21 approaches be for arguing for a particular weighting  
22 scheme? I know that it's a consideration, but what

1 type of things would I bring to bear to make an  
2 argument for one or another weighting scheme. But  
3 other than that, I thought it was extremely helpful.

4 MALLORIE FIERO: Thank you.

5 DANIEL SERRANO: I'd like to agree with  
6 everybody else and also echo back to Fraser's point in  
7 the first panel about these being very useful points  
8 to begin conversations with.

9 I guess when I think about some of the  
10 potential challenges to implementing this, especially  
11 thinking about intercurrent events and a related  
12 concept. I think one of the things that's kind of  
13 implicit and in some cases kind of very explicit in  
14 this document is the idea that post-randomization --  
15 right? Randomization does a very good job of kind of  
16 wiping out other-worldly effects. And any of the  
17 things that we need to consider are the intercurrent  
18 or intervening effects that would occur post-  
19 randomization.

20 But I think even the practice effect  
21 example kind of speaks to the fact that things that  
22 can occur say in a run-in period prior to

1 randomization can propagate into and influence the  
2 post-randomization phase.

3           So while I think it's very important to  
4 think about all the intercurrent events or  
5 intercurrent effects that could crop up and how to  
6 deal with them, I think there are also potentially in  
7 some cases very important and meaningful intercurrent  
8 effects, right? We saw this in several trials we were  
9 working on last year.

10           One of the ones that I think  
11 crystalizes the most was a really interesting migraine  
12 trial. And there were two double-blind periods. And  
13 subjects who were randomized in the DB1 were then re-  
14 randomized in the DB2. What we found in doing some  
15 sensitivity analyses was that the single best  
16 predictor of response in DB1 was the subjects' report  
17 of their typical response to their typical migraine  
18 treatment outside of the trial, whether you're in  
19 placebo or treatment. When we went into DB2, the  
20 single best predictor of response in DB2 was response  
21 in DB1.

22           So I think the intercurrent effects

1 framework is very useful for thinking about potential  
2 problems and how to kind of address those that could  
3 disrupt our ability to (indiscernible) the effective  
4 interest.

5 But I think to implement this  
6 effectively, I think probably viewing this as a kind  
7 of starting point for discussion, perhaps we can also  
8 use that framework to then step back out and say,  
9 well, are there other individual variables that could  
10 come into the trial and are not really mitigated  
11 effectively by randomization.

12 JOHN SCOTT: I think those were all  
13 good and useful points. Also I'm obligated to say  
14 that Lisa's points are good and useful, because she  
15 was my professor. So I'm sure there's some way she  
16 can go back in time and fail me for inference.

17 I think the main challenge for  
18 implementing the estimand framework is really the same  
19 for COA and for hard endpoints or non-COA endpoints.  
20 And it's two things. One is that there's a lot of  
21 careful thought that's required for going through each  
22 of those four or five things. People are kind of used

1 to sort of default analysis sets, giving a little bit  
2 of thought to a missing data technique and then you're  
3 done. In the estimand framework, you're really called  
4 upon to think very hard about things. And that is a  
5 challenge.

6 The other challenge is very real-world,  
7 which is the change management to get people to feel  
8 like they need to do something new, they need to use  
9 the estimand framework. So those are the main  
10 challenges.

11 There is one area where I think COAs  
12 present a greater than average challenge, which is  
13 specifically the population-level summary element of  
14 the estimand definition. So if you're working with  
15 something like mortality, it's quite clear that you  
16 can use a difference in proportion of surviving  
17 patients as an endpoint or as a population-level  
18 summary. It's unambiguous what that means.

19 If you're using a symptom score and you  
20 want to use for example difference in mean symptom  
21 score between groups or difference in mean change in  
22 symptom score between groups, then you're asking

1 questions like what does a mean difference of 1.7  
2 mean. Excuse me for repeating mean.

3           And so that can be a very difficult  
4 question to address. And for many COAs, 1.7 doesn't  
5 necessarily mean the same thing at every point in the  
6 scale. So that's worth considering. Also, people are  
7 sometimes tempted to create binary endpoints out of  
8 underlying continuous COAs. I think that tends to  
9 make the interpretation even worse, even harder. And  
10 it definitely makes the statistical power worse. So  
11 it requires a lot of extra thought for these  
12 endpoints.

13           GREGORY LEVIN: So I have two comments,  
14 and I think that they are for kind of any objective  
15 and not just the COA research objective, but I'll try  
16 to give some examples to illustrate them using COAs.

17           The first one is that I think to do  
18 this well, the interdisciplinary conversations, the  
19 relevant input, including from patients, needs to  
20 happen early and often. And the first reason is the  
21 reason that John said, which is that this is hard.  
22 And the second reason is that -- I like this question

1 because it says a COA research objective, it doesn't  
2 say the COA analysis or the COA endpoint. This is  
3 about the objective which needs to be determined  
4 before you come up with a design.

5           So I think one of the things that we've  
6 seen a lot is that the protocol is already  
7 established, design is already established. Maybe  
8 even the sponsor is at the stage of submitting a  
9 statistical analysis plan, and that's the first time  
10 that the estimand framework is being discussed and  
11 brought to us. And that's too late.

12           I think the ultimate goal of this is to  
13 think about things like the control arm, like how  
14 background standard of care and ancillary medication  
15 is handled in the trial, whether patients are followed  
16 or how they are followed after certain intercurrent  
17 events. Those things need to be determined early.

18           So just to give an example with an  
19 intercurrent event, if there's a thought to be an  
20 interest in a treatment policy strategy that there is  
21 some interest in knowing, say, a patient's function  
22 even after they discontinue treatment, the design

1 needs to incorporate strategies to follow patients and  
2 assess their physical function even after they  
3 discontinue treatment. That's something that needs to  
4 be built into the design and the protocol.

5           The second I guess challenge is I think  
6 trying to answer too many questions at once, trying to  
7 think that we have to answer every single question and  
8 address every single objective in a single analysis --  
9 I mean, I'm a statistician; I think the primary  
10 analysis is important. But I think the addendum talks  
11 about something called supplemental analyses or  
12 supplemental estimands. And I think that's something  
13 that we should pay a little bit more attention to.

14           An example of that is the one that John  
15 just mentioned, which is you could have a primary  
16 analysis that looks at effect on a mean, but there  
17 could be important supplemental estimands or  
18 supplemental analyses that address other summary  
19 measures of the distribution such as looking at the  
20 cumulative distribution function or looking at the  
21 proportions of patients that meet certain thresholds.  
22 Those are answering slightly different questions, but

1 they can be important to understanding the benefits  
2 and doing a benefit-risk assessment.

3           So those are -- I guess one other  
4 comment on that is that -- another example of that is  
5 when you have a composite strategy where you  
6 potentially consider a patient who discontinues  
7 treatment or uses a rescue medication as say having a  
8 poor response. You know, that kind of an analysis, as  
9 with any composite strategy, you can have a drug  
10 effect driven by an effect on adherence alone.

11           And so something like a supplemental  
12 estimand where you look at functional improvements  
13 regardless of whether patients discontinue treatment  
14 can be important.

15           So I think the challenge is paying a  
16 little bit more attention to the importance of  
17 supplemental estimands and supplemental analyses to  
18 better understand benefits.

19           JESSICA LEE: I guess I'm the only  
20 clinician on this table. So I agree with everyone,  
21 what has been said so far. I guess from a clinical  
22 standpoint, one of the major challenges that we face

1 is that we don't always have the best understanding of  
2 the natural history of the disease for many diseases,  
3 even the diseases that we think we know. When we  
4 speak with patients, we realize that we may not be  
5 targeting the symptoms that really matter to these  
6 patients. And this is particularly challenging in  
7 rarer diseases where natural history is not very well  
8 known. But even for common diseases that our division  
9 encounters -- and I predominantly oversee GI  
10 applications -- we are struggling with trying to  
11 figure out an endpoint that's going to be assessed in  
12 a heterogenous population with various different  
13 symptoms and a disease course that's not always  
14 predictable.

15           And so we're always faced with what are  
16 the COAs that need to be collected to help inform that  
17 endpoint so that the data will be as generalizable as  
18 possible to the intended patient population and how  
19 frequently and how long these assessments need to be  
20 made so that we can get meaningful and interpretable  
21 data at the end of the day. And we also have to be  
22 mindful of the patient burden of taking these daily

1 diaries.

2 In our division, we actually frequently  
3 have patient listening sessions to try to understand  
4 what is the patient burden and what are the signs and  
5 symptoms that are most important to them and what  
6 would they consider to be a meaningful outcome.

7 And, you know, I've taken care of  
8 patients, but it's not always the same what the  
9 physicians think are important versus what the  
10 patients feel is important. And I'm not saying one is  
11 -- you know, both of those are important. But really  
12 until you have that dialogue, it's really hard to know  
13 for sure.

14 And I'll just give a quick example  
15 about the intercurrent events. In GI because we're  
16 often faced with these chronic diseases with  
17 relapsing-remitting type of nature and with  
18 heterogenous presentations, that we usually request  
19 long-term clinical data to help characterize the  
20 efficacy as well as safety to inform chronic  
21 administration.

22 But the requirement to collect daily

1 data from patients for a large proportion of the trial  
2 duration can be very burdensome for these patients and  
3 can result in a lot of missing data. And there's  
4 definitely a high likelihood of having intercurrent  
5 events such as rescue medication use that needs to be  
6 taken into consideration when we're thinking about the  
7 estimand framework.

8           So I am very fortunate that we have  
9 great statisticians and COA staff that we work with.  
10 And I have to say in our GI diseases, they're in  
11 almost all of our meetings and we have these very  
12 frequently. So I'm actually very excited to see this  
13 document where we're trying to explain all of the  
14 things that are very -- that we struggle with on a  
15 day-to-day basis.

16           MALLORIE FIERO: Thank you very much.  
17 There were a lot of good points that were brought up  
18 by the panelists. And a few of the things that I  
19 heard was that the framework provides a common  
20 terminology and that there's a lot of thought that is  
21 required for us, and the estimand framework helps us  
22 to do that more so. And one of the things that you

1 mentioned, Jessica, was that you have frequent  
2 discussion about it. And I do think that's very  
3 important, to have frequent discussions and early  
4 discussions about the research objective, the design,  
5 analysis, and interpretation. So in the interest of  
6 time, we will move on to our next question.

7           So for question two, how does a  
8 treatment's mechanism of action, disease's natural  
9 history, et cetera, impact steady duration and timing  
10 and frequency of assessments for COA endpoints. And I  
11 know that Jessica kind of touched base a little bit on  
12 that. And since she is our resident clinician, I would  
13 like to start with her first, and then we will move  
14 down the line. Jessica?

15           JESSICA LEE: Okay. So I actually  
16 think that those are probably two of the most  
17 important factors that go into help determining the  
18 study duration and timing and frequency of assessments  
19 for COA endpoints. So it's critical to understand the  
20 natural history, to identify the patient population  
21 that's most likely to benefit from a given treatment,  
22 especially based on its mechanism of action and

1 endpoints that would be most meaningful for these  
2 patients. And how frequently and how long COA  
3 assessment should be made could be informed by natural  
4 history as well. And this is largely informed by an  
5 understanding of the disease course, whether it's  
6 acute versus chronic, is it slowly progressive or a  
7 rapidly-progressing disease, is it a relapsing-  
8 remitting disease, is it episodic, or is it mostly  
9 stable? All of these things are important to  
10 understand for us to figure out how long should this  
11 study be and how frequently do we need to assess these  
12 COA endpoints.

13 And the drug's mechanism of action is  
14 especially important because that's going to help  
15 determine what is the aspect of the disease or key  
16 signs and symptoms is the drug able to target. And  
17 this is particularly important for disease that  
18 present with heterogenous presentations where you may  
19 not be able to target all of those signs an symptoms  
20 with one drug. And time of efficacy assessment and  
21 trial duration is also affected by the type of drug  
22 that you have, because they all have different

1 expected onset of action. And when the drug is likely  
2 to take effect on the effective outcome of the  
3 interest could differ depending on the mechanism of  
4 action of the drug.

5 MALLORIE FIERO: Thank you. Greg?

6 GREGORY LEVIN: Yes. I guess the quick  
7 answer is that it impacts it a lot. And to illustrate  
8 that, I guess I can just talk through a specific  
9 example. And so that would be the difference between  
10 say an acute pain setting and a chronic pain setting.  
11 So suppose we have a COA that is a patient-reported  
12 outcome assessment of a patient's pain perhaps with a  
13 numeric rating scale, either asking for a patient's  
14 average or worse pain in the last 24 hours or maybe  
15 asking about a patient's pain now.

16 We take that COA or some variation of  
17 that COA and we put it into a chronic pain setting.  
18 Maybe a drug intended to treat patients with say knee  
19 osteoarthritis or chronic lower back pain. And the  
20 goal there would be to have a treatment that has  
21 chronic benefit on a patient's pain. So long term,  
22 durable improvement in their pain over time.

1                   And so to evaluate that research  
2 question, you would often want some duration of a  
3 trial to have a reasonable kind of surrogate for  
4 longer-term benefit. I think the approach is often to  
5 use something like three months. And the endpoint  
6 would often be an assessment at the end of the  
7 treatment period. Maybe an average over a week, with  
8 the idea that -- for example, if you have a patient  
9 who has a very short-term benefit in their pain but  
10 then can't tolerate or adhere to the drug or the  
11 effect of the drug goes away, that wouldn't be a very  
12 good outcome for their chronic indication. So that's  
13 the goal of perhaps using something at the end of the  
14 treatment period as an endpoint.

15                   On the flip side, if you had an acute  
16 pain treatment maybe post-surgery, surgery for  
17 bunionectomy or hernia or something like that, the  
18 goal is short-term improvement in the patient's post-  
19 surgical pain, you might only need a trial of a week  
20 or certainly an endpoint that captures a patient's  
21 pain over a few days, which is really the intention of  
22 the treatment and the goal of the treatment. And that

1 might be something like an area under the curve. They  
2 often use something called SPID, which is essentially  
3 the area under the pain curve over a few days. So  
4 that's just an example of how both the nature of the  
5 expected effect of the drug and the disease's natural  
6 history can greatly impact things like the duration  
7 and the timing and the choice of the endpoint even  
8 with a similar underlying instrument.

9           JOHN SCOTT: My answer is very similar  
10 to Greg's, so I'll keep it brief. I agree that these  
11 considerations are extremely important for trial  
12 design considerations, including duration and timing  
13 of assessments. I have a similar acute example. I  
14 think mine is even shorter-term.

15           At CBER, we have approved multiple C2  
16 esterase inhibitor products for acute attacks of  
17 hereditary angioedema. And the way these studies work  
18 is that patients come into the clinic or to the  
19 hospital in significant distress. They are given  
20 treatment. And then maybe every 15 minutes or every  
21 half hour they are asked to self-assess how they're  
22 feeling. And the endpoint is how quickly they get

1 relief from those attack symptoms.

2           So the whole trial for one patient  
3 lasts about 24 hours. So what that's based on is  
4 understanding that the mechanism of action of the  
5 product, it's a therapy that should have a very quick  
6 effect. And the natural history is that these attacks  
7 are somewhat self-limiting anyway. So if you haven't  
8 responded in 24 hours, you're sort of out of the  
9 window for an effect.

10           On the other end of the spectrum with a  
11 lot of our gene therapy products, you're looking at a  
12 situation where it may take a long time for a new  
13 protein to be produced and then for that to have a  
14 downstream clinical effect.

15           For the gene therapy that was approved  
16 last year for a rare form of childhood blindness,  
17 really the only endpoint assessment, the primary  
18 endpoint assessment was one year after treatment  
19 because it was understood that it would take a while  
20 first of all for the treatment to have an effect. And  
21 second, you wanted to make sure that it had some kind  
22 of lasting effect.

1 DANIEL SERRANO: So I think the  
2 panelists have to my mind, at least for my  
3 considerations, addressed the general question here.

4 I guess I would take this then and I  
5 would extend it just one step to the estimand. I  
6 think there are definitely implications here for these  
7 sorts of things and the nature of the estimand that is  
8 selected for a given efficacy assessment.

9 A brief example. You know, what's  
10 something we see in the context of say prophylaxis  
11 trials for chronic diseases with episodic attacks or  
12 relapsing-remitting is you can have inclusion-  
13 exclusion criteria where you do a run-in to kind of  
14 make determinations of the subject. It's like  
15 sufficiently symptomatic at baseline prior to  
16 randomization. And in a lot of these diseases like  
17 that where you kind of have these kind of cyclical  
18 episodes, you kind of effectively roll them at zenith.  
19 And then what comes next, even in the comparator or  
20 placebo arm, is nadir. And so when you think about  
21 deployment of a change from baseline estimand in that  
22 context, you know, you can very easily run into

1 trouble. And so thinking about the natural history of  
2 the disease and then how we're going to kind of  
3 quantify the benefit of effect in that context, you  
4 can think of alternatives in this kind of estimand  
5 framework. For example, you know, minimizing  
6 volatility. Right? Making someone's day-to-day life  
7 more predictable and that sort of stuff. Right? And  
8 that kind of may be a greater or more sensitive  
9 framework than say the change from baseline.

10 So I guess all I'm saying is that I  
11 think natural history and the nature of how this  
12 disease is going to function just independent of  
13 intervention is probably likely going to affect things  
14 beyond simply the administration of the schedule of  
15 assessments, but what endpoint or what estimand you're  
16 going to end up using or will be most effective for  
17 you.

18 KEVIN WEINFURT: I don't have anything  
19 to add to my colleagues' comments.

20 LISA WEISSFELD: Yeah. I think people  
21 did a great job, actually, going through the  
22 possibilities. The only thing that I would add or

1 reiterate is knowing the natural history is really  
2 important. And particularly when it's a slowly-  
3 progressing disease. And in the rare disease space  
4 when you have a slowly-progressing disease and you're  
5 trying to design a study, that is incredibly  
6 challenging to say the least. And also the acute  
7 versus chronic is also another -- these are nice  
8 categories. Statisticians like to categorize things.  
9 So these are also two fairly distinct categories of  
10 problems with the acute oftentimes being easier  
11 because you have the subject captive during that acute  
12 phase and you have less missing data to deal with than  
13 you do when it's chronic. But anyways, so that's it.

14 MALLORIE FIERO: Thank you. So just as  
15 a follow-up question -- and I will ask my FDA  
16 statistical colleagues first -- if we moved back to  
17 the example that we have. And we had our target  
18 population as defined here based on  
19 inclusion/exclusion criteria to reflect the targeted  
20 patient population for approval. So my question for  
21 you is is this -- will this always be our target  
22 population? What are some considerations in thinking

1 about your target study population?

2                   JOHN SCOTT: Thanks, Mallorie. So I  
3 think this came up in our discussions earlier, and  
4 it's an important question. There's sort of different  
5 levels of target population as you sort of expand  
6 through the drug development timeline. When you're  
7 talking about a phase 3 clinical trial, there's  
8 typically a very large number of inclusion and  
9 exclusion criteria which are there for several  
10 reasons. They're there to protect study subjects,  
11 they're there to enrich the population, to get  
12 patients who are more likely to respond to the  
13 treatment. And they may be there for logistical  
14 reasons as well.

15                   And so assuming a trial is successful,  
16 some subset of those inclusion/exclusion criteria then  
17 typically go on to define the population. So the  
18 indicated population is not exactly the  
19 inclusion/exclusion criteria. That's always much more  
20 specific.

21                   And then the question is once it's  
22 approved, how is it going to be used in the real

1 world? How is it going to be used maybe a little  
2 broader than the indication but still more or less as  
3 intended. And then further to that, how is it going  
4 to be used off-label? So it's complicated questions.  
5 When we're talking about trial design, we are  
6 typically targeting what the indication and the  
7 product labeling will look like. But all of these  
8 things come into play.

9 MALLORIE FIERO: Thank you. Greg?

10 GREGORY LEVIN: I agree with all that.

11 And I'll just add that I think in some cases you may  
12 have a primary estimand that's looking at the  
13 indicated population or something more closely  
14 reflected to what's in the inclusion/exclusion  
15 criteria. But you may, for example, in some benefit-  
16 risk assessment discussions also consider the expected  
17 use of the product in the real world which may go  
18 beyond, as John mentioned, what's the indicated use.

19 MALLORIE FIERO: Great. Thank you very  
20 much.

21 Okay, great. So this concludes our  
22 pre-set discussion questions. I will now open it up

1 to the floor for audience Q&A. Please direct  
2 yourselves to the mics in the middle of the aisle.  
3 And we ask that you please be specific with your  
4 question and limit your speaking time to 60 seconds.  
5 Okay, great. Thank you. Yes.

6 LISA KAMMERMAN: Hello, this is Lisa  
7 Kammerman. I just want to comment that this framework  
8 is very helpful. Having been a reviewer at FDA and  
9 having worked in industry, I think we can make this  
10 framework a little bit more specific. And to build  
11 off of some of Greg's comments, the scientific  
12 question needs to be drilled down even more.

13 So, for example, among patients who are  
14 still on study drug at week 28, or is it all patients  
15 at week 28 regardless of what happened during the  
16 study? So that's an important distinction to be made.

17 And I have difficulty with the word  
18 handling. And it comes down to a distinction between  
19 the protocol and the statistical analysis plan. I  
20 think a better word when we're talking about a  
21 protocol design is actually collect. So what to  
22 collect really depends on the research question. So

1 if we're interested in the treatment policy, then  
2 obviously we have to collect all the COAs up to week  
3 28. But if we're only interested among those who  
4 stayed on treatment, then we don't need to collect  
5 events afterwards.

6 But when we get to the analysis plan,  
7 the word handle really goes into the analysis. How  
8 are we going to handle or treat these events in the  
9 analyses. And there is a common kneejerk reaction I  
10 think, well, let's just MMRM the data. But really it  
11 should be the other way around. Are we going to  
12 assume that deaths are missing at random or are they  
13 going to assume a value of zero, for example, or  
14 something else? And then you use that to define your  
15 analysis rather than saying let's MMRM the analysis.

16 MALLORIE FIERO: Thank you. Yes, John,  
17 please.

18 JOHN SCOTT: Lisa, those were great  
19 comments. I wanted to sort of second the idea that  
20 talking about handling intercurrent events is not  
21 necessarily the right psychic frame of mind to be in.  
22 I think the real question is how do the intercurrent

1 events, how are they reflected in your scientific  
2 question. Right? The intercurrent events change what  
3 question you're trying to answer. And so they're not  
4 a nuisance; they are core to what you're trying to do.

5 MALLORIE FIERO: Great, thank you. I  
6 think in the back, the very back. Yes.

7 GRACE WHITING: Thank you. I'm going  
8 to start my timer so that I don't talk over.

9 MALLORIE FIERO: Thank you very much.

10 GRACE WHITING: So I am Grace Whiting.

11 I am the president and CEO of the National Alliance  
12 for Caregiving. And I thank you for hosting this  
13 meeting. Thank you, FDA, for what we observe to be an  
14 increasing awareness of the role of the unpaid family  
15 caregiver.

16 I just want to raise the issue though  
17 that when we talk about clinical outcome assessments,  
18 it's not very well-defined when a caregiver may step  
19 in and provide information either as a proxy for  
20 someone with cognitive impairment or in the pediatric  
21 population. And in other cases where the caregiver  
22 may by default be providing information. You see this

1 in clinical settings all the time. For example, a  
2 family member may be the one that actually logs on to  
3 an EHR and puts in information or collects information  
4 or coordinates care.

5 So I don't know what the question  
6 should be, but I'm just raising the issue that there  
7 are unpaid caregivers across the lifespan that are a  
8 part of this process and that the relationship they  
9 have with the person receiving care can sometimes  
10 impact the way they report data out.

11 MALLORIE FIERO: That's an interesting  
12 point. Do any of the panelists have any comment on  
13 that? Thank you very much.

14 Okay, so moving on to the person in the  
15 middle. Thank you.

16 ANDREW TRIGG: Thanks. So I'm Andrew  
17 Trigg. I'm a statistician at Adelphi Values, a  
18 consultancy. And so one of the points was around kind  
19 of considerations into current events. And I think  
20 for me one of the big things is whether the occurrence  
21 of that intercurrent event has a kind of causal link  
22 with treatment.

1                   For example, we talk about kind of  
2 rescue medication and kind of -- so, for example, for  
3 pain. If you're on a poor treatment or control, then  
4 your pain may be getting worse. So your use of rescue  
5 medication could increase. Whereas I know in the  
6 discussion document we have something around -- I  
7 think it's like if a patient broke their leg and their  
8 physical functioning scores would be worse. Which,  
9 you know, that kind of wouldn't be related to the  
10 treatment causally.

11                   And so I guess kind of a thing to think  
12 about is if the intercurrent event is not causally  
13 related to the treatment, do we need to think hard  
14 about controlling for it, or do we just consider it as  
15 kind of part of the random error inherent in our  
16 measurement?

17                   MALLORIE FIERO: Okay. So what I heard  
18 is if you have an intercurrent event that's not  
19 directly perhaps related to the treatment, what are  
20 things to think about when thinking about how this  
21 event can impact your interpretation, how can you deal  
22 with this. Any thoughts from the panelists? It's a

1 touch question.

2 LISA WEISSFELD: We had something  
3 recently in a study where it was a physical function  
4 that was being measured. And there was one subject  
5 who broke their ankle. I mean, the same example. And  
6 I think what we ended up doing was until the ankle  
7 healed, we did not include those values because they  
8 were missing data. But then when we were doing the  
9 sensitivity analyses, we did impute those values.

10 MALLORIE FIERO: Greg?

11 GREGORY LEVIN: I think that's a really  
12 good question. I think the only thing I would say is  
13 that I would agree that the conversation is much more  
14 difficult about what you are trying to estimate and  
15 what the question is when you're talking about an  
16 intercurrent event that is plausibly related to the  
17 treatment assignment.

18 MALLORIE FIERO: Great. Thank you very  
19 much. In the front, please.

20 ROSS WEAVER: Thank you. Ross Weaver  
21 with Clinical SCORE. I have a simple question. When  
22 using the estimand framework, is there a role for

1 listening to the patient voices beyond just  
2 understanding the natural history of the disease, and  
3 if so, when during the process and where? Phase 2,  
4 phase 3? I'm just trying to understand where it would  
5 fit in.

6 MALLORIE FIERO: Yeah, that's a really  
7 great question. So how does patient voice fit into  
8 the estimand framework? Thoughts from the panelists?  
9 Jessica?

10 JESSICA LEE: I guess I can start. As  
11 soon as we start even getting applications, we  
12 actually start getting -- if we don't have enough  
13 information internally and we would reach out to  
14 patients to get their input. So I don't think it's a  
15 specific timeline, but I think as soon as possible as  
16 we start planning for it. Because I think we've heard  
17 from everyone that it's a lot of work and we need a  
18 multidisciplinary team And it's important to get  
19 patient input as early as possible and as frequently  
20 as possible.

21 JOHN SCOTT: Yeah, it is a very good  
22 question. I think patient input can help in every

1 stage of defining the estimand. The two stages that I  
2 think are particularly critical are defining the  
3 endpoint of interest; what is important to the  
4 patients. And also again back to what I was saying  
5 earlier about the population-level summary, what  
6 information can the trial provide that will be  
7 meaningful and will help people make medical  
8 decisions for themselves and their loved ones.

9 MALLORIE FIERO: Great, thank you. A  
10 question in the back?

11 CINDY GIRMAN: Yes. Cindy Girman,  
12 CERobs Consulting. Thank you for this session. I  
13 really enjoyed it. First, I was glad to hear that it  
14 was the effect on the intercurrent events on the  
15 analysis and interpretation. And that speaks to  
16 sensitivity analysis, and I think it's really  
17 important to emphasize that you should also be  
18 prespecifying the sensitivity analyses. Otherwise,  
19 there's just a lot of analyses that are done.

20 And second, I think you still have to  
21 prespecify a main analysis. And I wonder if it would  
22 be helpful to give some examples where you may have

1 non-trivial proportions of patients dropping out for  
2 AEs or for ineffective therapy. In other words, not  
3 missing at random, whether you should do a rank  
4 analysis where you're considering those to be the  
5 worst values, or if there are other approaches that  
6 would be suggested.

7 MALLORIE FIERO: That is a very tough  
8 question. And I know that at least for the  
9 statisticians at FDA, we think about these issues all  
10 the time. I don't have a specific answer for you,  
11 unfortunately, but just that it's important to think -  
12 - I think this is a real problem. Particularly for  
13 me, since I work in oncology, a lot of times there's  
14 issues with patients who, say overall survival, if  
15 patients die, it differs by the treatment arms, and  
16 how do you deal with this in our analysis? And this  
17 is not something that I know the answer to, but that  
18 is definitely something that we need to think about.  
19 And sensitivity analyses are definitely important.

20 Were there any other further comments  
21 on that? Okay, great.

22 I will take one last comment. In the

1 front.

2 ALYCIA SHILTON-LLOYD: Hi. I am Alycia  
3 Shilton-Lloyd from Gilead Sciences. My question is  
4 really around -- there was some discussion in the  
5 guidance about the different modes that you use to  
6 collect the information on the tool. And I think I'm  
7 a little bit confused by the discussion then on making  
8 sure that the flexibility exists around intercurrent  
9 events to capture them as needed when the modes  
10 themselves, there are very limited times that you can  
11 think about using multimodes. So it might be helpful  
12 to have some examples of what that means to the  
13 guidance. What are some of the examples of when you  
14 can shift modes, both from two perspectives. The  
15 first is if you have sort of a decline in function of  
16 in patient activity that limits their ability to --  
17 you know, more than just the broken ankle. But if you  
18 are taking input in vocal assay. So verbal assay  
19 using natural language processing or something similar  
20 and there is an unexpected decline in a significant  
21 number of your population in breathing ability. So  
22 that they purposefully choose shorter words in giving

1 their input. How would you adjust modes if it's  
2 unplanned for? You might not have seen it in a  
3 smaller population. And then second, because we're  
4 insisting on a specific mode, are we limiting in some  
5 ways who can participate in the trial if they  
6 communicate in a different preferential mode? So  
7 having some examples around what it might look like to  
8 have multi-modes would be helpful.

9 MALLORIE FIERO: Thank you very much.  
10 You raised a very important point, and I think  
11 definitely please submit that comment into our public  
12 docket so that we can address this comment.

13 Do I have any further thoughts from the  
14 panelists before I close this out? Okay, great. So I  
15 wanted to thank our panelists and our audience  
16 participants.

17 Just as a recap, I have a bajillion  
18 notes that I wrote here. So a few of the things that  
19 I heard is that the estimand framework is important  
20 because it provides common terminology for our  
21 multidisciplinary teams to talk about issues. We need  
22 to think about intercurrent events and

1 multicomponents, that there are also events and other  
2 variables that can happen not necessarily after  
3 randomization that may impact interpretation. A lot  
4 of thought is required for us in terms of thinking  
5 about the COA objective, and we need to make sure we  
6 stand up to this challenge. And there are challenges  
7 in a COA score that we can't just say make it a binary  
8 endpoint. It will be difficult to interpret. So we  
9 need to think about interpretation of our COA  
10 endpoint. That input of patients needs to happen  
11 early and I think at every stage of our study.  
12 Supplemental and sensitivity analyses are very  
13 important, and it's a challenge to understand your  
14 natural history, so it's important to discuss that  
15 with your multidisciplinary team.

16 I also heard that the two most  
17 important factors are treatment's mechanism of action  
18 and disease's natural history in determining your  
19 trial curation and timing and frequency of a COA  
20 endpoint assessment. And we heard a lot of really  
21 great examples of how these can impact trial duration  
22 and timing of assessments.

1           And so I'd like to thank our panelists  
2 for their thoughtful comments. Just as a reminder,  
3 I'd like to encourage everyone to comment on the  
4 discussion document. And the public docket will close  
5 on February 4th.

6           I would also like to thank Madeline Pe  
7 from EORTC in (indiscernible) and Chana Weinstock, who  
8 is our oncologist at FDA, and many others who were  
9 involved in developing the example that you just saw  
10 today, which is in Appendix 1 of the discussion  
11 document.

12           We are now going to enter into our  
13 lunch break, yay. Session 3 will begin at 1 PM. If  
14 you could please give a round of applause to our  
15 panelists in this session. Thank you.

16           (Break)

17           LILI GARRARD: So welcome back. I hope  
18 everyone enjoyed lunch and also has had a chance to  
19 catch up with friends and colleagues.

20           So my name is Lili Garrard. I am in  
21 the Office of Biostatistics, Office of Translational  
22 Sciences, in the Center for Drug Evaluation and

1 Research here at FDA. And I will serve as your  
2 moderator for Panel Session III: Considerations When  
3 There Is Heterogeneity in Disease Symptoms and  
4 Functional Status Between Patients and Within the Same  
5 Patient Over Time. And we have a great panel ahead of  
6 us today, and I really look forward to the exciting  
7 discussions that we will have.

8 As we have heard from earlier  
9 discussions, this is really a challenging area for a  
10 lot of us. And we all have a lot of thoughts and  
11 questions, but we don't have optimal solutions. But  
12 this is why we're here today, gathered around to talk  
13 about the consideration and the challenges.

14 So before we start with the panel  
15 discussion, I would like to first have my panelists  
16 just introduce themselves. So, Lisa?

17 LISA KAMMERMAN: Hi. I'm Lisa  
18 Kammerman. And this is the first time in my life that  
19 I've been at the top of the alphabetical list.

20 [LAUGHTER]

21 Oh, I'm sorry. I'm a biostatistician.  
22 I was a reviewer at FDA for 24 years, and have worked

1 in the industry, and now I'm an independent  
2 consultant.

3 ELEKTRA PAPADOPOULOS: Hi. I'm Elektra  
4 Papadopoulos, and I lead the Clinical Outcome  
5 Assessment Division and the Office of New Drugs here  
6 in CBER.

7 TEJASHRI PUROHIT-SHETH: Good  
8 afternoon. My name is Tejashri Purhohit-Sheth, and  
9 I'm in the Office of Tissues and Advanced Therapies in  
10 in CBER, where I'm the Director of the Division of  
11 Clinical Evaluation and Pharmacology Toxicology.

12 DAVID REASNER: Hello. I'm David  
13 Reasner. I work at Imbria Pharma. And I'm a  
14 psychologist by training, but have spent several  
15 decades developing medical products, working primarily  
16 in biostatistics and COA development.

17 STEVE ROBERDS: Good afternoon. I'm  
18 Steve Roberds. I'm the Chief Scientific Officer at  
19 the Tuberous Sclerosis Alliance, which is a non-profit  
20 advocacy organization based in downtown Silver Spring,  
21 not too far from here.

22 PATROULA SMPOKOU: Good afternoon. My

1 name is Patroula Smpokou. I'm in the Division of  
2 Gastroenterology and Inborn Errors Products. And I'm  
3 in the team that regulates products for inborn errors  
4 of metabolism. And that's in CDER at FDA.

5 R.J. WIRTH: Hello. I am R.J. Wirth.  
6 I am Managing Partner for Vector Psychometric Group.  
7 I'm a quantitative methodologist and psychometrician  
8 by training, and I oversee the day-to-day operations  
9 as well at VPG.

10 LILI GARRARD: Thank you all for being  
11 with us today. I think we can all agree that having a  
12 well-planned COA strategy is critical to support the  
13 selection and interpretation of COA-based endpoints in  
14 medical product development programs.

15 However, one of the major challenges to  
16 COA measurement and endpoint construction in clinical  
17 trials is the heterogeneity in diseases that all  
18 stakeholders often have to deal with.

19 So do help us kick off the discussion  
20 today, I've listed some example heterogeneity in  
21 diseases on the slide. And we all know this is a  
22 short list and these examples are not mutually

1 exclusive.

2           So there are genotypic and phenotypic  
3 heterogeneity in many diseases. For phenotypic,  
4 reliability may range from monosymptomatic to  
5 multisystemic diseases. Reliability can be seen in  
6 terms of disease manifestations, the rate of disease  
7 progression over time, and baseline severity of  
8 symptoms and functional status. Some diseases may  
9 also have a waxing and waning nature and may affect a  
10 wide age range.

11           So in a nutshell, we often deal with  
12 heterogeneity in diseases between patients and within  
13 the same patient over time. Therefore, it can be a  
14 real challenge to assess a single concept of interest  
15 across all patients.

16           So, with that said, I have a couple of  
17 questions for our discussion panelists today, and  
18 we'll start with the first one. What factors should  
19 be considered when developing a COA-based endpoint for  
20 diseases with heterogeneous patient populations and  
21 variable manifestations? And when you address this  
22 question, please also include any potential analysis

1 and interpretation issues that you would like to  
2 discuss.

3 So, to begin the discussion, I would  
4 like to first pose the question to Steve, coming from  
5 the patient perspective. Steve?

6 STEVE ROBERDS: Thanks. I thought I  
7 would take just half a minute or so to describe  
8 tuberous sclerosis complex, because that's the lens  
9 through which I guess I'm going to describe  
10 perspectives on heterogeneity. But there's a lot of  
11 heterogeneity among lots of different diseases. So  
12 that's why I wanted to describe this so it kind of  
13 puts it in perspective.

14 So tuberous sclerosis complex is a rare  
15 genetic disorder. People with TSC develop epilepsy,  
16 autism, tumors in various organs throughout their body  
17 at different times during their life. The cause is  
18 mutations in the TSC1 or the TSC2 gene, and the gene  
19 products form a complex that regulate the activity of  
20 mTOR. So much, so good, it sounds fairly  
21 straightforward.

22 But it turns out it's an autosomal

1 dominant disorder. So that means people who are born  
2 with TSC generally have one bad copy of either TSC1 or  
3 2 gene. But at different times during their life,  
4 they develop second hits, or loss of heterozygosity in  
5 some cells in their body, so determine the occurrence  
6 of when and where in the body and during their  
7 lifespan these second hits occur. Has a major impact  
8 on the phenotype because it's really those cells that  
9 lose completely the TSC1 or the TSC2 function that  
10 causes the problems for the disease.

11 So I wanted to kind of -- I think to  
12 address your question, an important factor to consider  
13 -- and I'll probably leave others to discuss the  
14 potential issues -- but is that with all of these  
15 different phenotypes in the disease that are caused by  
16 a consistent metabolic pathway, genetic cause and  
17 metabolic pathway, there's an opportunity to measure  
18 different endpoints in different people, but to  
19 actually expect a given drug to work on all of them.

20 So, as I mentioned, TSC1 and 2 regulate  
21 the activity of mTORs. So mTor inhibitors are  
22 approved by the FDA for the treatment of epilepsy,

1 treatment of a certain type of brain tumor which is  
2 independent of the epilepsy, and treatments of a  
3 certain type of kidney tumor in TSC.

4           These were all done in independent  
5 studies, but theoretically, they could be done in one  
6 study. It's just that not all of the people with TSC  
7 will have epilepsy, not all of them will have the  
8 kidney issues, and not all will have the brain tumor.  
9 Some will have two of those things and some will have  
10 three of those things.

11           So that's, I guess, a fairly simplistic  
12 examples, I think, with regard to TSC that needs to be  
13 taken into consideration when bringing forth a  
14 treatment. If the mechanism of the treatment is likely  
15 to affect the main disease process, there are lots of  
16 things that it potentially could affect in those  
17 people, but it'll be different from person to person.

18           I know you've got a second question, so  
19 I'm going to save a little bit more the discussion for  
20 that part too.

21           LILI GARRARD: Thank you. Elektra?

22           ELEKTRA PAPADOPOULOS: And thank you

1 very much. That was a really good introduction and  
2 important patient perspective.

3           You know, in terms of this topic of  
4 heterogeneity, it is very broad and the topic itself  
5 is heterogeneous. But you know, I think all of this  
6 also goes back to the patient. And as a common thread  
7 throughout all of the guidance series that we have,  
8 from the very first guidance in the series, which was  
9 focused on obtaining representative patient input,  
10 heterogeneity comes up very heavily in that guidance.  
11 And so it is a key starting point, understanding that  
12 heterogeneity and getting input from diverse patient  
13 populations.

14           And here at FDA, we have various  
15 mechanisms of doing that, from large public meetings  
16 to smaller patient listening sessions, even within  
17 drug development programs, sometimes sponsors will  
18 bring patient advocates to industry meetings. And so  
19 there are different ways of getting that critical  
20 patient input.

21           But for today, I think it's a very good  
22 idea to drill down in this broad topic two different

1 types of heterogeneity. And so we heard there is this  
2 phenotypic heterogeneity. Even when there's a common  
3 biologic source of a disease, manifestations can be  
4 very different. So different patients have different  
5 symptoms.

6 Take, for example, migraine, where  
7 migraine headache, all the patients by definition have  
8 pain, have headache. But then patients can vary in  
9 other symptoms, such as sensitivity to noise or light,  
10 or nausea, for example.

11 And so this is an example of the  
12 phenotypic heterogeneity in a disease. And there is  
13 FDA guidance on this as well of how to approach this  
14 challenge. Now, of course, migraine is a common  
15 disease, but we also have challenges in a lot of rare  
16 diseases as well, which we'll get into in this  
17 session.

18 And then in addition to that, there are  
19 numerous other intrinsic patient factors, such as the  
20 age of the patient, other demographic factors,  
21 comorbid conditions. And all of these things can pose  
22 measurement challenges.

1           And so it can be very difficult, for  
2           example, in pediatrics and in rare diseases which  
3           affect a lot of children and patients across their  
4           lifespans to identify a common measure that can't be  
5           used across the age groups.

6           And yet another type of heterogeneity  
7           is environmental. So patients live in different  
8           environments, they live in different culture groups,  
9           they may do different activities. And so how their  
10          disease impacts them is really -- could be different,  
11          just as a factor of their environments.

12          And so all of these types need to be  
13          carefully considered when we're constructing both our  
14          clinical assessment measures, as well as endpoints,  
15          and providing context for interpreting those  
16          endpoints. And so, you know, how do we then approach  
17          this in a systematic way?

18          And so, I will again refer back to  
19          earlier guidance in this series. The very, very  
20          useful tool that we turn to time and again is our  
21          roadmap to patient-focused medical product  
22          development. And this was described in the third

1 guidance in the series on selecting or developing COA  
2 measures.

3           And it really starts -- I mean, the  
4 fundamental basis is starting with understanding the  
5 disease or condition. And so, this includes  
6 heterogeneity, it includes natural history, and the  
7 environment in which patients live, as well as -- very  
8 important -- the patient perspective. And so you will  
9 find that explicitly named in the roadmap.

10           And then from there, we also need to  
11 understand the medical product and what it does and  
12 how it's expected to impact the patient, and the  
13 specific patient population and subgroup that we're  
14 going to be targeting with this medical product. And  
15 this helps us then do what we call conceptualizing  
16 treatment benefit. And it really then drives the rest  
17 of the endpoint measure selection down the line.

18           So these are some of the fundamentals,  
19 and they really do apply throughout the guidance  
20 series. None of these guidances is really -- can be  
21 taken in isolation. And so I think that's a really  
22 important point.

1           And this final guidance on developing  
2 the endpoint, I really view as sort of keeping the end  
3 in mind. And I think that was mentioned earlier  
4 today. But it's so important to always think about  
5 the endpoint all throughout the development of a  
6 clinical outcome assessment.

7           And patient input is really critical.  
8 I mean, we've spoken with patients, for example, with  
9 rare, very pruritic diseases, and have asked them,  
10 what's the most important thing to you? Is it the  
11 severity of your itching? Is it the frequency? Is it  
12 episodic or chronic or continuous? And what time of  
13 day is most impacted with the itching. Is it during  
14 the night or during the day? And so all of these  
15 factors are where patients can play a key role and  
16 influence how we define the endpoint.

17           And so, I'll just stop there.

18           LILI GARRARD: Thank you Elektra, for  
19 bringing that perspective through the other guidance.  
20 So we'll go with Lisa.

21           LISA KAMMERMAN: What I want to talk  
22 about is the rate of progression in different

1 conditions and how that affects the definition of a  
2 COA-endpoint. I'm also going to put it into the  
3 framework of the potential analysis and interpretation  
4 issues.

5 As you can imagine, I could talk a  
6 really long time on this topic. So I've distilled my  
7 short comments into a few brief topics and highlights.

8 The endpoint, in my opinion, the most  
9 important issues is the rate of decline. You can have  
10 a disease that declines slowly over time, has a  
11 moderate decline, or a really fast decline. And this  
12 has to be tied into the research questions question  
13 from earlier today that we discussed, and the  
14 scientific question more specifically.

15 So is the research or scientific  
16 question to show that your treatment in comparison to  
17 control is going to slow the decline, or prevent the  
18 declines, or improve the decline? And all those  
19 issues have an important consequence for defining the  
20 endpoint.

21 And finally, especially in rare  
22 diseases, there's always the concern of having a

1 mixture of patient population and different disease  
2 manifestations of the same condition.

3           This all translates into the length of  
4 the study and how long you have to conduct the study  
5 to show a treatment difference and durability. So a  
6 common type of analysis might be slopes. Is the rate  
7 of decline different? Is the change from baseline  
8 different, which would be a different analysis? And  
9 this circles back into the selection of the instrument  
10 you're going to use in the first place.

11           So you can imagine in a slowly  
12 progressing condition maybe very, very mild  
13 Alzheimer's, where you're using an endpoint --  
14 (indiscernible) boxes -- I know that's in the news  
15 right now -- that declines perhaps slowly over time in  
16 a very, very mild population, where you're going to  
17 need a really long study to perhaps just show a small  
18 difference.

19           So in that case, even though you're  
20 probably interested in slope, it's critical to be able  
21 to select a tool that is going to have little noise,  
22 and to be able to detect a change over time. Because

1 at the end of the day, if there's no difference -- and  
2 this goes to the interpretation question -- is there's  
3 no difference because the instrument you chose was too  
4 coarse? Or was there really no difference? So all of  
5 these points really interact with each other.

6 The other possibility is change in  
7 functional status, and there are different types of  
8 functional status outcomes that can be defined. And  
9 how do you measure that? Especially then when you  
10 have a difference of functional status, for example,  
11 that baseline, is it an improvement to a particular  
12 category, or is it alleviation of all symptoms? But  
13 that's another possibility for analysis.

14 For longer studies, there's also the  
15 concern of missing data. So if you have -- and also,  
16 if the study -- if the disease is progressing slowly,  
17 maybe you can alleviate that by having fewer  
18 observations over time, as opposed to a shorter study.  
19 Maybe FEV1, which is performance based, obviously, and  
20 the six-minute walk test. So there you'd have a  
21 shorter study, but your missing data may not be as  
22 much as a problem.

1                   Regard to mixture of functions at  
2 baseline, one way around that is to stratify your  
3 randomization. So if you stratify with high function  
4 versus lower function, the assumption is that the  
5 difference in treatments over time will be the same.  
6 So at the end, you can do a stratified analysis, which  
7 in effect averages over the strata. That might be one  
8 possibility in designing and analyzing such studies.

9                   In the next question that we're going  
10 to address, I'll come back and talk a little bit more  
11 about rare diseases. I think they need more  
12 discussion. Thanks.

13                   LILI GARRARD: Thank you, Lisa. And  
14 David?

15                   DAVID REASNER: Yes, thank you. I'm  
16 going to make a few comments about baseline disease  
17 severity. And while Imbria Pharma does have a rare  
18 program, I'm going to focus on larger patient  
19 populations, because there are significant sources of  
20 heterogeneity, even in these more common indications.  
21 And if you think about diseases like seasonal allergic  
22 rhinitis, where time of year has an influence in terms

1 of the severity of symptoms, and weather impacts the  
2 severity of symptoms, so you have regional effects.  
3 You can get quite a lot of baseline heterogeneity. Or  
4 diseases like bipolar disorder, where it matters  
5 exactly what the presentation is at the time of  
6 initiation of therapy.

7           So in terms of baseline severity -- and  
8 some of these points may have been touched on at one  
9 level or the other in the other panels -- certain  
10 concepts may be endorsed at a particular level of  
11 severity. So that creates heterogeneity because you  
12 have certain sort of dead items, depending on the  
13 severity of the disease in a particular patient.  
14 They're not adding any information.

15           One thing to think about is how to  
16 summarize -- how to create the endpoint -- so that's  
17 an algorithm, a calculation -- and how to summarize  
18 the endpoint. Oftentimes we see percent change from  
19 baseline, which is an attempt to normalize the data.  
20 And it's an imperfect attempt, so the statistician on  
21 your project will use baseline as a covariant to take  
22 care of the remainder of the normalization.

1           But you might want to actually consider  
2     studying your endpoint on what I call the native  
3     scale, which is more intuitive, and you can label the  
4     axis according to how the COA was actually developed.  
5     Again, your statistician will take care of baseline by  
6     doing something like an ANCOVA model, treating  
7     baseline as a covariant, along with maybe other  
8     covariants that will remove baseline heterogeneity.  
9     But if you leave it on the native scale, it's much  
10    more intuitive.

11           The other thing I wanted to mention in  
12    passing at least is that you can't hear baseline  
13    heterogeneity by using extreme qualification criteria.  
14    It's often suggested, but in my experience what you're  
15    doing is driving a really high proportion of false  
16    positives in your selected subsample.

17           And in addition, you'll drive  
18    regression to the mean, which in and of itself is not  
19    an issue, until it begins to interact with something  
20    like a floor or a ceiling effect. 03:01:12 And now  
21    you've sort of run out of room to operate and it will  
22    create problems for you. So the solution is not

1 necessarily saying, you know, you have to have a 9 on  
2 a 10 point scale. Just FYI.

3 In terms of analysis and  
4 interpretation, at the group level you might want to  
5 consider the fact that there could be an interaction  
6 between baseline severity and your treatment effect.  
7 And that's part of what Lisa was talking about when  
8 she asked to consider stratification.

9 So you'll look to see whether those two  
10 strata can be combined, pooled or not. And if there  
11 are only quantitative differences, maybe a modest  
12 effect in one stratum and a strong effect in the  
13 other, you can pool those, because the inference is at  
14 a higher level. It's about all the patients in your  
15 trial. But if there's an interaction, then it's more  
16 complicated, and we look at things like heterogeneity  
17 of the slopes in the ANCOVA model, and you might need  
18 to summarize your data by looking at key percentiles,  
19 like the median. So those are things, again, the  
20 statisticians on your team should be looking at,  
21 whether it's part of your primary analysis or  
22 something that's in an appendix.

1                   And in terms of analysis and  
2                   interpretation at the subject level, I think John  
3                   Scott mentioned this earlier. The differences that  
4                   are meaningful and the differences you observe may  
5                   depend on where the patient starts at baseline. So  
6                   that's an interaction. And that is hard to  
7                   investigate in the short time that you have a  
8                   development program moving forward. Because what  
9                   happens in terms of (indiscernible) development,  
10                  you're likely using your Phase 2 data to bootstrap  
11                  into your pivotal program.

12                  If you start looking at the subsamples,  
13                  you're working with smaller and smaller groups of  
14                  patients. And you might have a group of patients at a  
15                  particular level of baseline severity that are really  
16                  just outliers. And if you give them equal weight in  
17                  making decisions about what a clinically meaningful  
18                  improvement is, you'll probably not make a good  
19                  decision. So again, the goal is often to have a  
20                  single criterion, which may or may not be possible,  
21                  but looking at splitting your samples into smaller and  
22                  smaller groups of baseline patients and expecting to

1 have reliable judgment from what is always a modest  
2 dataset, I think is probably not realistic.

3 And then lastly, I just wanted to  
4 mention that it's important to make sure your COA is  
5 sensitive to remission and symptom-free days. And I  
6 think that was mentioned in the first panel as well.  
7 There might be patients for which it's appropriate  
8 that you improve their disease to the point where they  
9 wouldn't actually have symptoms, or they might  
10 actually remit. You'll have spontaneous remitters,  
11 but you may have remission due to treatment.

12 And sometimes I think we focus on the  
13 more severe patients. And ultimately, we would like  
14 to cure diseases, so please develop a COA that's  
15 sensitive so that if you should cure a disease, you  
16 will recognize it. And then ultimately, that level of  
17 change and whether it's important or not, you know,  
18 could be the difference between a particular impact, a  
19 proximal or distal impact, an activity that's a small  
20 change numerically, but to the patient, it could be an  
21 incredibly important change.

22 So, you know, this is patient-focused

1 drug development, so that's a question that you can  
2 put to patients. Thank you very much.

3 LILI GARRARD: Thank you very much,  
4 David. And Patroula?

5 PATROULA SMPOKOU: Thanks, Lily. So  
6 we've heard a lot about kind of general concepts of  
7 heterogeneity. So I'll give you just a few points  
8 from a perspective of rare genetic diseases, which is  
9 what we handle in our division.

10 So, you know, we talk about  
11 heterogeneity a lot, and of course, as we previously  
12 thought and discussed, it could be any type of  
13 heterogeneity. I think what we're talking about today  
14 is mostly for a typical heterogeneity in terms of  
15 symptoms at baseline, or over the duration of a trial.

16 When thinking about heterogeneity in  
17 rare genetic diseases, I think it's important to think  
18 about why we have heterogeneity. And of course,  
19 there's hypotheses and assumptions and some scientific  
20 (indiscernible) rationales, one being that genetic  
21 diseases affect individuals differently. There are  
22 many reasons for that. One simple reason may be

1 when you have a single enzyme defect, for example,  
2 phenylketonuria or some of the other endpoint errors,  
3 depending on what level of residual activity you might  
4 have, an individual may actually manifest different  
5 manifestations at different ages and also severity.  
6 So that sort of contributes to heterogeneity. The  
7 actual genotype contributes to heterogeneity,  
8 depending on how the actual genetic change affects the  
9 protein that's being made.

10           So those are some of the known factors.  
11 But there's many more that are unknown in terms of  
12 what causes this variability. And then on top of  
13 that, you deal with small patient populations, by  
14 definition, in rare diseases. So there's very limited  
15 opportunities to conduct really robust studies of  
16 untreated disease to really try to get a handle of why  
17 people behave differently or have different  
18 manifestations, and why that is.

19           So that brings me to the point of what  
20 we talked -- we always talk about natural history, so  
21 what this means, simply put, is what happens to a  
22 patient's disease when they are untreated.

1                   And so, in rare diseases I think we  
2 rarely, if ever, have the luxury of actually knowing  
3 what the untreated disease looks like in patients.  
4 And of course, that's because we have a small  
5 population, studies are not doable, feasible, many  
6 times. There are small patient numbers, and on top of  
7 that, there's many patients who go undiagnosed for a  
8 long period of time, because those are rare diseases.  
9 And so you have even less opportunity to study this if  
10 the patient is actually not diagnosed.

11                   The point to make that's very critical  
12 for the course of untreated disease is it gives you  
13 very critical information in terms of, of course, what  
14 endpoints to use, what instruments to use to assess  
15 those endpoints, but also what population would be  
16 appropriate for a given endpoint or clinical outcome  
17 assessment.

18                   And the reason for that is because  
19 there is this heterogeneity, for instance, that I  
20 described, we see that, for example, children with a  
21 genetic disease have completely different symptoms  
22 than the adults with the disease, and they may have

1 completely different severities, and also disease  
2 trajectory.

3 And so if that's not known ahead of  
4 time, then it becomes extremely difficult to actually  
5 choose an endpoint that would be meaningful to the  
6 patient and actually specific to the disease.

7 The second point is we discuss a lot  
8 about patient input. And I think that's very much  
9 more important in the rare diseases, because we just  
10 don't have a lot of the knowledge of untreated  
11 disease. A lot of times, we don't really know what  
12 matters to patients because it's not documented  
13 anywhere. So, you know, how can you know what bothers  
14 them the most, what's most meaningful for them to  
15 impact with a potential medical product or treatment.

16 And I think Jessica Lee earlier  
17 mentioned that in our division we have kind of a  
18 history of engaging in listening sessions. So that's  
19 patient listening sessions. We have found that really  
20 useful, really important. Some of those that we've  
21 recently had was with patient groups with  
22 (indiscernible) disease. We saw a three percent

1 (indiscernible) adrenoleukodystrophy, phenylketonuria,  
2 and some others.

3 And so these are sessions where we  
4 listen. We pose questions. We listen to patients  
5 with, you know -- and we're talking basic questions.  
6 What's important to you, what's the most bothersome  
7 symptom, what would be really meaningful for you to  
8 see a change in? We get very different answers,  
9 depending on the ages of the patient. Of course, if  
10 you have a child is affected, you would ask their  
11 caregiver or parent, especially when you have a very  
12 serious or neurodegenerative disease such as  
13 (indiscernible) syndrome.

14 If you have adults, for example, with  
15 Fabry disease, the adult would very much be able to  
16 tell you what's most bothersome to them, and that  
17 could be their neuropathic pain or it could be their  
18 cardiac disease and exercise intolerance, just as a  
19 few examples.

20 Other points to talk about would be  
21 what factors really may determine what clinical  
22 outcome assessments or endpoints to select on a trial.

1 I think one major factor, when it comes to rare  
2 diseases, is the actual trial design. So if it is  
3 feasible, and many times it is, to do controlled  
4 trials, randomized controlled trials, then you have  
5 some of the freedom of actually doing work ahead of  
6 time and this is a hard to hook it scientists that are  
7 doing clinical disease trials interesting especially  
8 when there from India selecting disease-specific fit  
9 for purpose critical outcome assessments.

10 In certain diseases, though, where it  
11 may not be feasible or ethical, or other consideration  
12 of actually doing a placebo-controlled trial, you may  
13 be quite limited. So examples of that would be a  
14 single (indiscernible) trial where there is a  
15 historical non-current control group. So there,  
16 you're very limited to the selection of endpoints  
17 because many times you have to base that on what was  
18 actually done in the studies that you are planning to  
19 use. And that becomes really challenging. You have  
20 to really operationalize that, and we certainly have a  
21 few examples of that that was very, very challenging  
22 applications and were used to conduct.

1           In terms of other factors to consider,  
2           of course the baseline level of functioning, the  
3           baseline to the severity, and also the age of the  
4           patient become really important. And so it could be  
5           that within the same trial you have both pediatric and  
6           adult patients.

7           And then you may have -- you know, the  
8           pediatric patients have very different symptoms than  
9           the adults. An example of that is in Fabry disease,  
10          the adults have sometimes cardiomyopathy, they have  
11          renal failure. You don't see those in the kids. You  
12          really never do. The kids tend to have more  
13          gastrointestinal symptoms, or they have this heat  
14          intolerance.

15          So very different endpoint, but unless  
16          you have a handle on a natural history in relation to  
17          the patients, you wouldn't necessarily know. So how  
18          do you approach that?

19          I guess different approaches that we  
20          consider from the genetic standpoint or rare disease  
21          standpoint -- and of course, we discuss with sponsors  
22          and academic physicians -- are using potentially

1 multiple different endpoint, and not a single  
2 endpoint. I would say it's extremely rare that a  
3 single or primary endpoint would be able to really  
4 give you a good picture of what's happening with a  
5 patient with multisystemic disease. And on top of  
6 that, you don't have a good handle of the natural  
7 history, so how do you truly know if that one endpoint  
8 is truly representative, or even if you're going to  
9 see observable changes within a trial.

10 So I think the traditional paradigm of  
11 primary, secondary exploratory kind of really a lot of  
12 times doesn't truly apply to some of those rare  
13 diseases with multiple symptoms.

14 And of course, at the end of the day,  
15 from a regulatory perspective, we're looking for  
16 multiple lines of evidence in terms of evidence of  
17 effectiveness. And so having multiple different  
18 clinical outcome assessments, assessing disease-  
19 specific symptoms and being fit for purpose becomes  
20 really critical.

21 I guess another approach may be to have  
22 very liberal inclusion criteria in trials because you

1 have a very small population. And so restricting your  
2 population a lot of times doesn't make sense in a rare  
3 disease. But then it becomes very hard to assess for  
4 efficacy if you have this heterogeneity in the  
5 population. And that's where you try to become  
6 somewhat creative, like we always try to, and maybe  
7 select one of the -- one of those subpopulations are  
8 being your true primary efficacy population, and that  
9 could be the population which has the highest disease  
10 severity, for example, or a particular symptom. And  
11 I'm sure there's other methods that could be creative  
12 and novel in that aspect.

13 And then the final point would be this  
14 individualized endpoints and personalized endpoints.  
15 So, you know, we hear that a lot. We heard about  
16 responder indexes and such. I think from a  
17 perspective of the rare diseases I would deal with  
18 becomes even more challenging. So identifying --

19 LILI GARRARD: So, if I -- you know, we  
20 could table that for the next question?

21 PATROULA SMPOKOU: Yeah.

22 LILI GARRARD: Because we are going to

1 get into the individualized --

2 PATROULA SMPOKOU: Okay. So I'll save  
3 that for later, then.

4 LILI GARRARD: Yeah. Thank you,  
5 Patroula.

6 PATROULA SMPOKOU: (indiscernible)

7 LILI GARRARD: Those are great points.  
8 So, Tejashiri?

9 TEJASHRI PUROHIT-SHETH: Yes. So, good  
10 afternoon, everyone. I echo everything that has been  
11 set throughout the day, and I think Patroula covered a  
12 lot of the comments that I was intending to make as  
13 well.

14 And I think when you're thinking about  
15 designing a clinical outcome assessment for  
16 heterogeneous diseases, natural history is the key, if  
17 it is available. Certainly, it will help define, you  
18 heard, that it will help clarify what the disease  
19 manifestations are, what subgroups, whether they're  
20 children, adolescents, adults, you know, how these  
21 disorders manifest within these different age groups.  
22 You think about from the baseline disease severity a

1 clinical outcome assessment may be distinct for a  
2 pediatric population versus an adult population.

3           And the other thing I'd like to discuss  
4 a little bit is heterogeneity also presents in how the  
5 disease manifests from the waxing and waning  
6 perspective. So if you have disorders that wax and  
7 wane, such as multiple sclerosis or disorders that,  
8 you know -- David mentioned allergic rhinitis,  
9 seasonal preponderance of the symptoms, or  
10 environmental issues that raise the symptoms. And  
11 even in asthma, you can see that. You know, how do  
12 you design a clinical outcome assessment for a  
13 disorder that waxes and wanes?

14           So understanding the pattern of the  
15 disorder is very important. What causes it to wax and  
16 wane? Are there exacerbating factors that lead to  
17 this? Could these exacerbating factors  
18 (indiscernible) the concept of our (indiscernible)  
19 framework be considered in our current events?

20           But when you're looking at this, you  
21 also want to consider from a clinical outcome  
22 assessment, is the timing and the frequency of the

1 administration of the COA. If the pattern is they get  
2 symptoms, they may be free of symptoms for five, six  
3 months, and then maybe six months later, you know,  
4 that also impacts how long your study will be designed  
5 for as well.

6 So taking into a lot of these factors  
7 that you've already heard discussed are very  
8 important, and particularly important when you have a  
9 disease that has waxing and waning manifestations.  
10 And from a study design perspective, it is, especially  
11 in this context, very important to have some sort of  
12 concurrent control. It may be very challenging to  
13 utilize external or historical controls in this  
14 context.

15 LILI GARRARD: Thank you, Tejashri.  
16 And R.J., if you could help us wrap up this question,  
17 so we can move on to the individualized endpoints.

18 R.J. WIRTH: Yeah, it's hard, but --  
19 [LAUGHTER]

20 All right. No more.

21 LILI GARRARD: (indiscernible)

22 R.J. WIRTH: No, I mean, there's a lot

1 of great discussion, and I think listening to all of  
2 it, it's obviously very hard. And it's a very  
3 complicated topic, and it's an issue that we all face,  
4 and what -- you know, Donna and me, when we were sort  
5 of prepping for this meeting, was that we never  
6 experience a single one of these. We usually end up  
7 experiencing a whole series of them at once.

8           And then you end up adding that  
9 complexity with missing data and restricted inclusion  
10 criteria. And before you know it, there's really just  
11 -- you know, you take something that's very hard and  
12 we make it harder.

13           And you know, unfortunately, I don't  
14 think there's a sort of -- even for any single one of  
15 these issues, there's no really straightforward single  
16 answer, because there's so many other sort of --  
17 there's so much other variability outside of this. I  
18 mean, just the different types of diseases we study  
19 and the different types of endpoints that we have, the  
20 different types of COAs, the different types of  
21 analyses we can use.

22           So I think that what we can hope for --

1 I mean, I don't even think there's a complicated  
2 answer to this, you know. What I think we can hope  
3 for is for each case here -- to sort of reiterate what  
4 a lot of the people up here have said, you know, I  
5 think you need to really understand what the disease  
6 is. How does it manifest itself? How can it manifest  
7 itself in different ways? You know, what are the  
8 other external sort of threats to our studies, you  
9 know, missing data. Is it something that's seasonal?  
10 And can we come up with something that's our best shot  
11 for where we're at right now, right? I don't think  
12 there's sort of a silver bullet. I was talking to  
13 Scott earlier, that I don't think there is a silver  
14 bullet that's going to solve all of these problems.

15 So we need to sort of figure out in  
16 every given situation what are the biggest threats,  
17 what can we do, hopefully, a decent job controlling,  
18 and we just really think we need to understand what  
19 we're not getting right. You know, it's not going to  
20 be perfect. So can we figure out what we're missing  
21 so we can at least think about how that's going to  
22 impact how we interpret our results?

1                   And that way, I mean, once we're  
2 upfront about it, then I think we can all live with  
3 that, right? Everybody say, I can't fix this, but I  
4 think this is how it would impact it. At least then  
5 we're being very transparent about it and we can take  
6 that into consideration when making decisions.

7                   I won't go into a whole lot of detail  
8 on analyses, I think. You know, a lot of people  
9 mention them, and David and Lisa went into a bit more  
10 detail on specific analyses. But I do think we need  
11 to be open to look at new methodology, or at least new  
12 approaches. That's not really new, right?

13                   But you know, if it's something that's  
14 cyclical and goes with the season, well maybe we  
15 should start thinking about using more nonlinear  
16 models, and we can model things using sine wave  
17 functions, we can take that into account. We can look  
18 at time variants and code variants of pollen levels,  
19 you know, from particular cities. AQ11 that stuff is  
20 sort of publicly available data that you could bring  
21 in as code variants to help control for some of that  
22 individual variability that -- from these external

1 threats.

2           So I think we just need to be creative,  
3 especially when we're dealing with these issues. And  
4 it gets even, I think, more complicated when we move  
5 to rare disease. I mean, when I think about trying to  
6 figure out how to control for these things, if we have  
7 enough data, we're not going to do a great job, but  
8 there's a lot of sort of tools at our disposal.

9           You start stripping away how much data  
10 we get, you know, now we have six people, and there's  
11 just not -- what we have at our disposal is just so  
12 much more limited that I think it just ratchets up the  
13 complexity that much more.

14           I love the idea about including more  
15 people and being more open, and then maybe having, you  
16 know, sort of a prespecified subset of the more  
17 patients that are more in line with what we typically  
18 do so we can see how that impacts the results. But  
19 any way that we can get more patients into the trials  
20 and get more data to bear on these questions, I think  
21 the better off everyone will be.

22           So my takeaway point is that it's hard.

1 And I think it's going to remain hard, and we just  
2 have to be really diligent and thoughtful, and if  
3 nothing more, really, really creative.

4 LILI GARRARD: All right. Thank you so  
5 much. Those are great discussion points. And you  
6 know, in the interest of time, I really want to hear  
7 your perspectives on the next question. And we don't  
8 have a lot of time left, so if you could all give me a  
9 quick comment on what factors should be considered  
10 when constructing personalized or individualized  
11 endpoint for use in studies.

12 And I'm interested to hear from your  
13 perspective what the concept of personalized or  
14 individualized endpoints mean to you, and if you have  
15 any potential analysis or interpretation issues. But  
16 I think the main point here is trying to understand  
17 what we actually mean by personalized or  
18 individualized endpoints.

19 So I think the first sub-bullet point  
20 is something to focus on. So we'll start from Steve,  
21 our patient perspective.

22 STEVE ROBERDS: Thanks. I think this

1 might be oversimplifying, but I'd break it down into  
2 two things. One is what is the most bothersome, for  
3 lack of a better word, or most impactful symptom or  
4 symptoms to the patient who's participating, to the  
5 individual patients. And we realize that's why we're  
6 here. It may differ from patient to patient. And  
7 then the second is, what defines a meaningful  
8 improvement to that patient in that most bothersome  
9 symptom.

10           So a couple of examples, Elektra  
11 mentioned the migraine guidance. It was actually Dr.  
12 Billy Dunn who brought that to my attention a couple  
13 of years ago. And it's a simplistic way that I think  
14 about complex diseases like TSC. For migraine, it's  
15 pain, photophobia, (indiscernible) phobia and nausea.  
16 And so pain becomes the coprimary endpoint, and then  
17 each participant in the study picks which of the other  
18 three is their most bothersome. And so then you  
19 always have these two endpoints. It's just that the  
20 second one is different from person to person.

21           So again, it's a fairly simplistic  
22 approach, but I think it illustrates the potential

1 that we have to think about how to implement these  
2 personalized approaches.

3 But the next one is then what's most --  
4 what's a measurement of improvement, what's the  
5 magnitude of meaningful improvement in those scores.  
6 And there was an example in the discussion document of  
7 the genetic eye disease and navigating -- you know,  
8 whether or not they could navigate this path under  
9 different lighting conditions. Really nice story.  
10 Really well-designed.

11 I was reading through this and then I  
12 got to the point where the meaningful improvement was  
13 two. What did I miss? What did I miss? Why is it  
14 two? So I don't understand why, and that might be  
15 something to add to the document, because maybe  
16 there's a story there. But why was it a score of two  
17 that was this improvement? Did patients say that's  
18 what was important and that the test is -- the study  
19 was with patients who --some have relatively mild --  
20 it's all relative -- relatively mild impairment in the  
21 levels of light in which they can see, and others are  
22 very severely affected. Is it meaningful to improve

1 two steps for everybody, wherever they are on that  
2 scale? Or does it depend on where they start, you  
3 know, to the baseline points.

4 So I distill it down to those two  
5 things. So I think I'll wrap up my comments on this  
6 with maybe a pat on the back to Panel 1 this morning.  
7 One of the comments that I heard from a couple of  
8 people is having that patient as a partner in the  
9 design steps.

10 And I think one of the things that I've  
11 seen, being patient advocacy for the past eight years,  
12 is we talk very openly and clearly with FDA about  
13 what's important. And the FDA listens. You know,  
14 we've had a patient-focused drug development meeting,  
15 et cetera.

16 We talk with lots of companies. We  
17 have CDAs that -- can't tell you how many CDAs, not  
18 because it's confidential but because I don't remember  
19 how many. But we've got CDAs with lots of companies  
20 and we talk to them about what's important. But then  
21 the FDA and the companies go behind closed doors and  
22 decide what they can measure that's most important to

1 their patients, and then come out and tell us what the  
2 study endpoints will be.

3 So my point would be, how can we get  
4 the patients behind those doors? Can we bring them  
5 back, the patient-to-patient advocates, to be there at  
6 the table when the discussions are happening? And I  
7 think that could inform things like how do you decide  
8 what are the most bothersome symptoms, and how do you  
9 decide what magnitude of change is enough?

10 Thanks.

11 LILI GARRARD: Thank you so much,  
12 Steve. And you know, in the interest of time, and  
13 this is a topic that everyone has a lot to contribute,  
14 and we certainly do not run out of topics to talk  
15 about, right? But I do want to save some time for our  
16 audience Q and A, and then perhaps, you know, our  
17 panelists can interact with the audience and dive more  
18 into this particular topic.

19 So with that said, let's open up for  
20 question -- audience Q and A. And please directly  
21 yourself to the mics in the center of the aisle so we  
22 can have further discussions.

1 Do we have no questions?

2 R.J. WIRTH: Maybe it's not hard.

3 LILI GARRARD: Thank you. Go ahead.

4 MICHELLE WHITE: Do I have to turn this  
5 on, or is it...? Okay. Michelle White, Optum. I  
6 have a question with the most bothersome symptom.  
7 What happens when someone's most bothersome symptom  
8 changes throughout the duration of a three-year trial,  
9 perhaps as a result of the treatment they're  
10 receiving, some symptom gets worse? How does that  
11 affect your endpoint model?

12 LILI GARRARD: Elektra?

13 ELEKTRA PAPADOPOULOS: So, I'll take a  
14 stab at that and then, you know, others chime in,  
15 please. But you know, one of the things that we --  
16 you know, we had a Duke Margolis meeting on this, a  
17 workshop, a few years ago on individualized endpoint.  
18 And one of the questions is, you know, do we frame  
19 this as most bothersome symptom? Because as you say,  
20 that can vary over time.

21 And so in cases where there's  
22 heterogeneity and symptoms among patients, our sort of

1 common advice that we commonly give in different  
2 situations may be to assess all of the symptoms at  
3 baseline and throughout the duration. Because as you  
4 noted, symptoms can change within a patient over time.  
5 And it's a particular problem in trials a very long  
6 duration and depending on the natural history.

7 And we also want to make sure that  
8 while some symptoms are improving, others are  
9 deteriorating at the same time. And so we really need  
10 to understand what is that clinically meaningful not  
11 only improvement, but also deterioration.

12 So those are just some ways. But  
13 clearly, I agree, with R.J. that it is hard.

14 R.J. WIRTH: That's why I'm here. Now,  
15 can I follow up on that, though? The most bothersome  
16 symptom -- I love the spirit of the idea, right? It's  
17 sort of when we're talking about patient-centered and  
18 sort of patient-focused, you really can't get much  
19 more than, just sort of what is it that bothers you,  
20 and let's measure that.

21 But from a measurement perspective,  
22 it's absolutely horrible. Because for one, we're

1 usually on a single item, which are horribly  
2 unreliable. And then two, what's most important can  
3 change over time. And then depending on how drugs or  
4 the treatment may impact different symptoms, you have  
5 people on different scales at potentially different  
6 severities, and where movement on the particular  
7 endpoint could mean different things over the  
8 different symptoms.

9           And it's -- I guess from a sort of  
10 psychometric standpoint, there's so many questions and  
11 potentials for error and messiness, that I think we're  
12 going to end up finding it harder to find treatments.  
13 And like I said, I love the spirit of it, but from a  
14 sort of statistical measurement perspective, I don't  
15 like it. So I like -- to sort of what Elektra said,  
16 recording all for them and tracking all of them. And  
17 if we can, think about a maybe more rigorous way to  
18 combine them in a meaningful way.

19           And if we are interested in the most  
20 bothersome symptom, at least have the other data there  
21 to fall back on if we are starting -- you know, if  
22 things do look a little messier than we were

1 expecting, making sure that we have that other data  
2 there to look at, and not just go, oh, wow, we really  
3 should have collected more. So I recommend the same  
4 thing. At least collect all of them.

5 LILI GARRARD: Lisa?

6 LISA KAMMERMAN: I think one thing we  
7 haven't discussed is the mechanism of action. So if  
8 we assume the mechanism of action of the product is  
9 the same for everyone and is of -- tempting to target  
10 the underlying problem, then having the most  
11 bothersome symptom, I think, is okay.

12 I think where you run into problems is  
13 where the mechanism of action may only be targeting a  
14 few of the symptoms. So in (indiscernible), there's  
15 a guidance on evaluating vasomotor systems associated  
16 with vulvar and agile atrophy. And in that particular  
17 condition, there are three coprimary endpoints, one of  
18 which is the most bothersome symptom. So women are  
19 receiving estrogen.

20 So in there, it's assumed that the  
21 estrogen has the same mechanism of action, and it's  
22 expressed -- the condition is expressed differently

1 with regards to symptoms. And that's a short-term  
2 study. I think it just gets more difficult when you  
3 have multifaceted symptoms in studies that run on for  
4 a long time. You don't really know what the treatment  
5 is doing.

6 LILI GARRARD: Thank you, Lisa. And  
7 then, Jean, you get our last comment for the session.

8 JEAN PATY: Hi. Jean Paty, with IQVIA.  
9 And for those of you that know me in the audience, I  
10 am going to make a comment and end with a question and  
11 do it in 60 seconds. And I challenge some of my  
12 colleagues to time me.

13 So a general comment, it's hard, but  
14 can we make it easier insofar as the whole idea of  
15 heterogeneity, personalized endpoints, to me, is  
16 coming up because in many situations, we are looking  
17 at rare diseases, fewer patients. And so this is the  
18 non-statistician approaching the technical panel.

19 At the end of the day, are we trying to  
20 understand is this patient better? Have we done  
21 something for them? So, to some degree, whether we  
22 need to go down the personalized endpoint route,

1 whether we need to think about most important symptom,  
2 et cetera, it seems to me that previous qualitative  
3 and quantitative data can be brought to bear for us to  
4 be able to come up with some metric that helps us  
5 understand, did we do something for this patient.

6 And that, to me, is our challenge. Our  
7 challenge to take this complexity and simplify it down  
8 so that we can just say, yeah, they got better, or  
9 they didn't.

10 So, R.J., in 30 seconds, give me the  
11 technical answer to that.

12 R.J. WIRTH: Was there a question in  
13 there? I didn't -- so --

14 [LAUGHTER]

15 JEAN PATY: It was directed to you.

16 R.J. WIRTH: Yeah, I know. I sorry, I  
17 would have listened.

18 [LAUGHTER]

19 R.J. WIRTH: No, well, I think -- you  
20 made me think of a lot of things. I mean, one of the  
21 -- obviously, one of the easiest places -- easiest  
22 places to sort of think about personalized endpoints,

1 and that is in rare disease, because it's a little  
2 more manageable when you have a very small set of  
3 people you're staring at.

4 But I also think the idea of  
5 heterogeneity is harder for me to conceptualize within  
6 rare disease because you have to have variability to  
7 have sort of heterogeneity. And when you only have a  
8 very small number of people, you don't really know,  
9 because you don't really have enough variability to  
10 know whether or not there's differences there. It's  
11 just you have like five random draws a huge  
12 population, they're not going to look the same. But  
13 is that indicative of the entire population?

14 So, I know. It's hard.

15 LILI GARRARD: Well, I suggest that you  
16 to get together during our breaktime and continue this  
17 discussion. You can have more than 30 seconds.

18 [LAUGHTER]

19 (Break)

20 EBONY DASHIELLE-AJE: Hello, everybody.  
21 It's now 2:15, so we're going to get started with  
22 Session No. IV. If you can make your way back to your

1 seats, that would be appreciated. Good afternoon,  
2 everyone. Thanks for coming back after break in a  
3 timely manner. I know we're toward the end of the  
4 day, so I also thank you for staying for our wonderful  
5 panel discussion.

6 Right now, we're going to begin Session  
7 IV, entitled, "Pulling it all Together -- An Example  
8 Across Guidances." Before we get started, I would  
9 like to ask my esteemed panelists to introduce  
10 themselves with your name and affiliation.

11 BILL BYROM: Perfect timing. Bill  
12 Byrom, I'm at Signant Health. We're an ePRO and eCOA  
13 provider.

14 MICHELLE CAMPBELL: Michelle Campbell  
15 from the Office of Neuroscience out of the Office of  
16 New Drug, CDER.

17 ANDREA CORAVOS: Andie Coravos. I'm  
18 the co-founder and CEO of Elektra Labs, which works  
19 and helps collect digital endpoints in clinical  
20 trials.

21 MATTHEW DIAMOND: I'm Matthew Diamond.  
22 I'm a physical medicine and rehabilitation physician,

1 and I'm the Medical Officer in the Division of Digital  
2 Health at the Center for Devices and Radiologic Health  
3 here at FDA.

4 MARK FRASIER: Good afternoon, I'm Mark  
5 Frasier. I lead the research team at the Michael J.  
6 Fox Foundation. We're focused on a cure and new  
7 treatments for Parkinson's disease.

8 ABIGAIL LUO: I'm Abigail Luo. I'm  
9 from the Office of Biostatistics and Epidemiology from  
10 the Center of Biologics.

11 ANDREW POTTER: Andrew Potter, Office  
12 of Biostatistics in CDER.

13 DIANE STEPHENSON: Hello, I'm Diane  
14 Stephenson. I'm the Executive Director of the  
15 Critical Path for Parkinson's Consortium, one of 15  
16 consortia of Critical Path Institute.

17 EBONY DASHIELLE-AJE: Thank you all so  
18 much. So today's Session IV is a little bit different  
19 from the previous sessions because we're going to be  
20 discussing a working example. Based on earlier public  
21 discussions for this guidance series, we both heard  
22 from you and we've listened to you. We understand the

1 tremendous value for providing stakeholders with  
2 pragmatic illustrations that encourage deep thought  
3 about how concepts in each of the Guidances can be  
4 effectively understood and applies in practice.

5 And as a result of what we've heard  
6 from the public, we've decided to develop a working  
7 example that can be used to demonstrate the guiding  
8 principles of COA and COA endpoint development.

9 And our primary goal today is to begin  
10 exploring how to frame an example like the one that  
11 we're going to talk about in a little bit regarding  
12 DHTs to help stakeholders understand how to get from  
13 measurement concept to an endpoint. And DHTs provide  
14 an appropriate backdrop for this exercise because  
15 considerations for DHT implementation in clinical  
16 trials are relatively the same as the considerations  
17 for any COA. DHTs also offer an opportunity to  
18 consider the current topic of incorporating and  
19 implementing technology in clinical trials, and also  
20 what to do when you're exploring how to capture  
21 patient experience data, for instance, outside of  
22 clinic in a patient's daily life.

1           So during today's session, I'll first  
2 outline the brief guiding principles that I just  
3 mentioned that are applicable for COA development and  
4 implemental in general, and outline specific  
5 considerations within the proposed example of DHTs.  
6 Then I'll engage my esteemed panelists in a rich  
7 discussion as they reflect on the guiding principles  
8 and provide recommendations on what practical  
9 information we should include in a working example  
10 using DHTs as the backdrop. They will also discuss  
11 how these principles can be fleshed out so they can be  
12 broadly applicable to COAs in general.

13           And then lastly, but not least, we'll  
14 open up discussion to the audience for you all to  
15 provide input on the discussion topics. And I'd like  
16 to note, though, that while we're specifically  
17 discussing a DHT example, we want to limit discussion  
18 to the generation of COA data in development of COA  
19 endpoints using a DHT. Discussion surrounding details  
20 about DHT regulation and technical validations of DHTs  
21 will be out of scope for this discussion.

22           So first, I'd like to level set a

1 little bit and talk about why DHTs are appropriate.  
2 First, I'd like to make sure we're on the same page  
3 regarding some terminology. Digital health  
4 technologies are technologies that use computing  
5 platforms, connectivity, software and/or sensors for  
6 healthcare and related uses. DHTs span a wide range  
7 of uses, from applications in general wellness to  
8 applications as a medical device.

9 DHTs are also used as companion  
10 diagnostics, companion therapeutics or adjuncts to  
11 other medical products, devices, drugs and biologics,  
12 and they may also be used to develop or study medical  
13 products.

14 And when evaluating the utility of  
15 technology-derived study endpoints in clinical trials,  
16 there are a number of factors that we consider.  
17 However, at the center of it all, as we see with all  
18 COAs, we're most concerned with how to translate the  
19 data generated through DHTs into things that are  
20 meaningful and how to determine what would be the most  
21 appropriate technology-derived endpoints for a  
22 clinical trial.

1 DHTs include, but are not limited to,  
2 wearable, implantable or ingestible sensors,  
3 environment sensors placed in a subject's home,  
4 software applications, other general purposes hardware  
5 and specialized hardware.

6 DHTs can be used to assess existing  
7 endpoints or novel endpoints, and they may be used to  
8 collect data remotely. An advantage of DHTs is that  
9 they can capture data both actively and passively.  
10 Passive data capture could include those generated  
11 through accelerometers, cardiac rhythm measurement  
12 throughout the day, or actively through measurement  
13 during task performance or through patient responses  
14 as captured from a PRO.

15 Now, as you know, when we talk about  
16 COAs broadly, we often talk about the evidentiary  
17 considerations, and study endpoints used to support  
18 regulatory decision making and labeling claims must be  
19 based on well-defined and reliable assessments. And  
20 like other types of COA data when used in this  
21 context, data generated through DHTs need to be well-  
22 defined and reliable and should not be potentially

1 false or misleading when described in labeling.

2           Additionally, as with other technology-  
3 derived measurement tools, data and the subsequent  
4 records generated by DHTs need to be in compliance  
5 with FDA regulatory requirements for recordkeeping,  
6 maintenance and access.

7           So now I'm going to go into the guiding  
8 principles that we would like to reflect in a working  
9 example for this guidance series. First is the idea  
10 of concept measurement. We've covered this concept  
11 across Guidances 1 through 3. And within the context  
12 of DHTs, you know, we want to determine what are the  
13 most important concepts to measure by talking to  
14 patients and discussing these concepts with FDA review  
15 staff. This is the same as all other COAs.

16           But with DHTs, we also want to know for  
17 the concept or symptom identified, is the DHT an  
18 appropriate measurement approach to use to capture  
19 that data and measure that concept. If you've  
20 determined that a DHT is an appropriate measurement  
21 approach, then you have to assess if the DHT that you  
22 would like to use meets performance specifications, so

1 including accuracy, reliability and validity for the  
2 proposed intended use.

3 Then we also want to introduce a  
4 concept of usability testing. You all have heard this  
5 before; it's been covered in Guidances 1 and 3. You  
6 need to also with DHTs plan to conduct usability  
7 studies to ensure that the DHT is usable by patients  
8 in the proposed context of use without serious errors  
9 or problems.

10 Next, we have endpoint measurement, a  
11 concept that is being covered extensively in Guidance  
12 4. So if you propose an endpoint using the DHT  
13 measurements, you need to capture the important  
14 concept that's been previously identified, and you  
15 also need to consider the statistical and measurement  
16 properties of this endpoint.

17 Lastly, after you have gone from  
18 concept to endpoint, you need to understand how are  
19 you going to deploy the DHT in a clinical trial;  
20 consider how to deploy and use the DHT in the study,  
21 including how patients will receive the DHT, how data  
22 will be collected from the DHT, and how clinical

1 operations will be adapted to incorporate into a  
2 trial.

3 So these are all common guiding  
4 principles that we have discussed throughout the  
5 Guidance series, from Guidance 1 through Guidance 4.  
6 And we have come up with a scenario within the context  
7 of Parkinson's disease that we think will be a good  
8 way to illustrate all of these guiding principles and  
9 then also bring it more specifically into the context  
10 of DHTs.

11 So the scenario that we're proposing is  
12 assessing gait in Parkinson's disease. So imagine --  
13 ready? Put your imagination hat on. Based on a  
14 literature review, a sponsor asserts that gait, for  
15 instance, ability to walk distances, gait speed is  
16 important to assess in patients with Parkinson's  
17 disease. They're interested in exploring the use of a  
18 general-purpose consumer accelerometer to measure gait  
19 variability to support medical product development.  
20 They actually hope that the data can be used to  
21 demonstrate difference in gait variability between  
22 treatment arms in their clinical trial.

1 Existing methods to assess gait  
2 variability in clinical investigations are based on  
3 in-clinical performance outcome assessments. So the  
4 sponsor is wondering can a DHT capture data reflecting  
5 how patients function in their daily lives, should  
6 they be using this in their proposed trial. Everybody  
7 get that, processed it?

8 So now I'm going to engage our  
9 panelists We're going to talk through all of the  
10 different overarching guiding principles that I  
11 discussed in the slides, and then we're going to talk  
12 about things that would be useful to include in  
13 example with this particular scenario, highlighting  
14 DHTs as the backdrop.

15 So I'm going to have two questions for  
16 our panelists. The first one is: what additional  
17 details would be helpful to clearly illustrate the  
18 guiding principles as applied specifically to DHTs  
19 when the data is intended for use as an endpoint in  
20 clinical trials? The second question we'll talk about  
21 is: how well do the guiding principles illustrate  
22 considerations for any type of COA implementation in

1 trials, especially the importance of considering  
2 patient input and knowledge of the natural history of  
3 the disease when deciding on a target concept; for  
4 instance, gait variability.

5 So going to our first question. As I  
6 mentioned in the presentation, we have five guiding  
7 principles: first, concept measurement; second, tool  
8 selection; third, usability testing; fourth, endpoint  
9 measurement; and fifth, clinical study deployment.

10 So I first want to focus on the concept  
11 or the guiding principles of concept measurement. And  
12 as we know, you know, there are multiple best  
13 practices for ensuring that you're measuring the  
14 concepts that are clinically meaningful to patients in  
15 a trial. And we need to determine what are the most  
16 important concepts for patients by talking to patients  
17 and discussing these concepts with a review division  
18 as you're developing your endpoint strategy.

19 So first, I'd like to punt to my  
20 panelist, Diane Stephenson, to just talk about broadly  
21 the different types of considerations that we should  
22 highlight in an example related to Parkinson's disease

1 with regard to establishing one of the most important  
2 concepts to measure in patients.

3 DIANE STEPHENSON: Thank you, Ebony.  
4 So this theoretical example is not that theoretical  
5 for what we're doing in the Critical Path for  
6 Parkinson's Consortium. We've convened seven  
7 different companies with the Michael J. Fox Foundation  
8 and Parkinson's UK to engage early with the FDA. We  
9 had a critical path innovation meeting in May to  
10 really talk through these issues that are being raised  
11 today.

12 One key issue that we addressed upfront  
13 is the idea of target population. This was very well  
14 outlined with using Parkinson's as a case example in  
15 Guidance 1. And in the project we're leading, you  
16 know, really fascinating for me to listen through this  
17 last session on heterogeneity, Parkinson's disease is  
18 the fastest-growing neurologic disease, incredibly  
19 heterogeneous, both within and between patients, and  
20 different stages of the disease have different  
21 manifestations. The historical concept that  
22 Parkinson's was only affecting motor function is

1 completely changed now with the recognition that non-  
2 motor symptoms can be even more burdensome to  
3 patients.

4 So we pay close attention in our  
5 project to the targeted stages of the disease. We're  
6 collaborating to go to the agency early to seek  
7 feedback on a case pilot study called Watch PD that  
8 includes collection of data on a mobile app, as well  
9 as a watch, to look at features such as gait.

10 In this example, we aligned to only  
11 choose patients that were within two years of  
12 diagnosis of Parkinson's disease. This is a very  
13 important concept aligned with the stages of the  
14 disease that companies were planning their trials on.  
15 But if we had chose at different stages of the  
16 disease, it may have been a different concept.

17 So I think this topic we've heard over  
18 and over today about the target population is really  
19 key and that will really have a key aspect of  
20 importance as you start refining your analysis plan  
21 looking at something like gait.

22 EBONY DASHIELLE-AJE: Michelle, I'd

1 like to call on you to expand on the target population  
2 concept.

3 MICHELLE CAMPBELL: Well, thank you  
4 Ebony, and thank you Diane for that, and I am familiar  
5 with the work that Diane's consortium is working on.  
6 I think the message that I've been hearing recurrently  
7 today from the other panelists is really making sure  
8 we understand, when we are selecting a target  
9 population is, what is the natural history of the  
10 disease course, what is going on -- and that really  
11 helps us figure out what is that target population  
12 going for when we have to consider a drugs mechanism  
13 of action. So we want to make sure we're going to be  
14 applying that correct target population when we're  
15 studying that.

16 And I think the careful consideration  
17 in the example that Diane's highlighted is examining  
18 where do I think I can target the population right now  
19 in a disease with a heterogeneity. Often, people will  
20 just want to, when we're looking at considerations for  
21 clinical outcome assessments when we have a wide range  
22 of symptoms or a wide breadth of age span or disease

1 course, it can be a daunting task to figure out where  
2 to start. And so, really understanding where that  
3 disease course is and that natural history is a  
4 fundamental piece that really is important a piece  
5 when we talk about developing any type of clinical  
6 outcome assessments. And it all starts also back with  
7 making sure that we talk with our patients as well.

8           And so, in order for us to be able to  
9 understand that natural history, it absolutely starts  
10 with our patients because they are our experts in  
11 their disease. So I think that's why the population,  
12 target population, is really an underpinning backbone  
13 of when we're really thinking about how we're going to  
14 develop a COA, how can we translate this to an  
15 endpoint.

16           EBONY DASHIELLE-AJE: It's great that  
17 you guys are bringing up target population, and the  
18 key to making sure that you are including the right  
19 population, but also understanding the population  
20 before determining what concepts are most important to  
21 measure. We get a question from multiple stakeholders  
22 about, well, do we need to generate new data, or how

1 can we leverage existing data that's been generated  
2 regarding, you know, patient input in the area of what  
3 concepts are most important to measure.

4 So, Bill, I'd like you to speak about  
5 the importance of leveraging existing data and how  
6 things can be done to properly identify the most  
7 important concepts.

8 BILL BYROM: Yeah. Thanks, Ebony and  
9 hello everybody. Just building on what Michelle and  
10 Diane said about the importance of the patient and  
11 their voice in this process.

12 As I looked at the case example, it  
13 wasn't very clear really from the description of the  
14 literature review whether that literature was  
15 referring to perhaps clinician opinions or other  
16 sources of ideas, or whether actually that research  
17 was done with patients to really find out what was  
18 important to them.

19 And, you know, it's interesting because  
20 when I look at the activity monitoring literature --  
21 and this is an example where we're considering using  
22 an accelerometer -- there aren't any examples that I

1 found in published studies where the endpoint that is  
2 being reported, or the set of endpoints that are being  
3 reported are defended in any way through initial  
4 evaluation with patients. Usually, it's a researcher  
5 judgment -- you know, I'll measure total steps per day  
6 or I'll measure, you know, the amount of time in  
7 vigorous activity -- and it's their concept that  
8 that's going to be important for the patients.

9 So it's refreshing to hear what, you  
10 know, Diane's describing in terms of the CPATH work,  
11 which is clearly going about this a very different way  
12 and the correct way in terms of involving the patient.

13 But I think, you know, what I'm  
14 interesting in really is just how we then do that.  
15 And, you know, going out to patients to understand, in  
16 this example, you know, what is meaningful to you as a  
17 patient in terms of your mobility. And, you know, it  
18 might be that a patient might say, as part of that  
19 research: Yeah, I'd like to walk, you know, without  
20 any motor function problems; I'd like to walk without  
21 freezing my gait; I'd like to be able to walk at an  
22 even pace for a number of minutes and I can't do that

1 at the moment, but that would make a big difference to  
2 me. And if that's the case, then measuring something  
3 like gait variability would sort of make sense.

4 And so, starting to develop a  
5 meaningful aspect of health, which is describing these  
6 important aspects of movement that the patients are  
7 describing; that's the first part. And so, we might  
8 then say, well, this reasonable that gait variability  
9 could be a meaningful aspect of health for this group  
10 of patients. And if that's the case, we can then  
11 develop a concept of interest in our studies to try  
12 and measure that.

13 And, you know, if gait variability is  
14 the meaningful aspect of health, what could the  
15 concept of interest be? Well, it might be something  
16 like, you know, the number of purposeful walking  
17 episodes that I'm able to perform without freezing, or  
18 it might be the stepping of all the time it takes  
19 between steps and having that, you know, constant, or  
20 the cadence, the stepping rate, and showing that  
21 that's a relatively constant thing; those might be  
22 reasonable measurements.

1           And so, as we start to think about then  
2     developing an endpoint around that, that's where we  
3     start to think, well, what's the best way to measure  
4     that. And it could well be that in this case an  
5     accelerometer is the best way to measure this. But  
6     it's only really when we've been through this process,  
7     starting with the patient voice, that we actually can  
8     then decide, well, what's the best measurement  
9     approach.

10           And as I started, again, thinking about  
11     this example, the gait variability, you know, there  
12     are different ways we could measure that. We could  
13     give somebody a diary or we could give an observer, or  
14     a carrier a diary for them to assess this for the  
15     patient, or we could put this accelerometer on the  
16     wrist and hope that we can measure this concept  
17     accurately.

18           And, you know, one of the things that's  
19     interesting about activity monitoring is that, you  
20     know, you collect all this data, but you rarely have  
21     context for the data. And so, you know, for example,  
22     if I'm looking at somebody walking and the variability

1 in their gait or maybe the freezing patterns in their  
2 gait, have they frozen or have they stopped moving  
3 because of a motor problem or did they simply stop  
4 moving because they were stopping to cross a road or  
5 they were doing something else.

6 And so, those are the sorts of things  
7 where this technology might not be ideal in this  
8 situation; whereas, a patient-reported outcome could  
9 actually be able to measure that even better. But I  
10 think those are the things we have to think about as  
11 we start to consider what is the best measurement  
12 approach for that endpoint.

13 EBONY DASHIELLE-AJE: Thank you so  
14 much, Bill. Now I'd like to call on Mark Frasier to  
15 just give us some highlights with regard to concept  
16 measurement from your personal experience with your  
17 work, just briefly highlighting things that you've  
18 encountered and best practices that should be  
19 highlighted in an example related to exploring what  
20 the best concepts are for measuring.

21 MARK FRASIER: Sure, yeah. So the Fox  
22 Foundation is supporting a study called Fox Insight,

1 which we're really excited about because it brings the  
2 patient voice into a study that is data centric and  
3 voice of the patient centric. It's an online study  
4 that can be -- that participants can take part of from  
5 the comfort of their own home; they just need a Wi-Fi  
6 connection.

7           And we have about 42,000 individuals  
8 enrolled in the study, so it's quite robust in terms  
9 of the data collection; 75 to 80 percent of those  
10 individuals are people with Parkinson's. And they  
11 enter information every three months, every quarter,  
12 and fill out validated questionnaires, as well as some  
13 more exploratory questionnaires that provides  
14 information about what they're experiencing as it  
15 relates to Parkinson's, what's bothersome, what's  
16 troublesome.

17           And what's been exciting to see is now  
18 we have this longitudinal data in some of the analyses  
19 that have been done. Particularly, I would highlight  
20 some by Dr. Ira Shoulson who is here in the room is  
21 that it's been reported what is bothersome, and that  
22 has led to concepts that have supported the initiative

1 that Diane mentioned in the critical path for  
2 Parkinson's. So we are marrying what's important to  
3 the patient, spoken by the patient in a data-driven  
4 way, with what to measure and how to measure it, so  
5 that's been really exciting.

6 EBONY DASHIELLE-AJE: Great. So next,  
7 we're going to move on to the concept of tool  
8 selection. So, you know, we discussed guiding  
9 principles for determining how to select the most  
10 appropriate DHT to measure the concept of interest.  
11 And, you know, you have to assess if the DHT meets  
12 performance specifications for the proposed intended  
13 use.

14 So for this question, I'd like to start  
15 off with Matthew Diamond from FDA to just talk about,  
16 you know, re-emphasizing what is most important for  
17 determining whether a DHT is the most appropriate  
18 approach, and then what aspects of DHT selection need  
19 to be considered.

20 MATTHEW DIAMOND: Thanks, Ebony. And I  
21 think it's important to first just acknowledge that  
22 for this example, I think it is very appropriate to

1 use a digital health technology because it does serve  
2 to illustrate the guiding principles. And just to go  
3 back for a moment to the first guiding principle of  
4 concept measurement, right, really understanding  
5 what's really important to patients.

6 I think that digital health  
7 technologies can be really well suited for that step  
8 and for this example. As a rehabilitation physician,  
9 part of my role is to really ask patients, understand  
10 how they're functioning and what their goals are and,  
11 you know, very concretely. It might be that a patient  
12 wants to walk up the stairs to their apartment. And I  
13 think here too it's important to really ask patients  
14 and understand very concretely what's important to  
15 them.

16 When patients talk about wanting to  
17 feel or function a certain way, it's really about  
18 doing that within the context of their daily lives,  
19 and digital health technologies allow measurements to  
20 occur in their native environment. Similarly, when  
21 patients talk about wanting to feel a certain way, it  
22 is over time, and digital health technology allow the

1 collection of information in between those punctuated  
2 measurements that might occur with more traditional  
3 measurements.

4 I think it's really helpful when the  
5 measurements fit seamlessly into peoples' lives. And  
6 if someone is using a wearable and maybe a watch that  
7 they've already -- that they would wear anyway, it  
8 doesn't add any additional burden and it doesn't make  
9 them feel sick because of the measurement now that's  
10 happening in their life.

11 Using digital technologies allows us to  
12 reach patients that might have difficulty coming in  
13 and participating in more traditional assessments.  
14 And what I think is very exciting is the opportunity  
15 to collect novel measurements to really get at what's  
16 important to people. I think that if you look at all  
17 the other guiding principles here for tools selection,  
18 in which I know is, Ebony, what you asked about.  
19 Using the digital health technology in this example  
20 allows us to go through and really evaluate all the  
21 different choices, because when it comes to digital  
22 health technologies, there are many. You talked about

1 it really spans a spectrum from both wellness products  
2 to medical devices.

3 In terms of usability testing, digital  
4 health technologies may raise novel questions about  
5 usability, especially when someone is using it at  
6 home. And for endpoint measurement, as we're talking  
7 about today, having data collected continuously by a  
8 digital health technology, you know, forces us to  
9 address some of the novel statistical questions  
10 involved in proposing an appropriate endpoint.

11 And in terms of study deployment;  
12 again, there are novel questions, but that also have  
13 applicability across clinical outcomes assessment most  
14 generally. So I think for this example, I think that  
15 digital health technologies, and specifically this  
16 one, is appropriate.

17 EBONY DASHIELLE-AJE: Andrew, can you  
18 speak to just with regard to the specifications for a  
19 DHT, not necessarily the detailed advice that we would  
20 normally give, but more so within the context of  
21 selecting something that can measure something  
22 accurately, the concept of interest accurately.

1                   ANDREW POTTER: Yeah. So as Matthew  
2 had mentioned, DHTs have an advantage where you can  
3 measure, you know, continuously, so you have -- and  
4 that's a little bit different than some of the stuff  
5 we've had. But when we go to take -- go to create an  
6 endpoint, we're going to take probably take those  
7 measurements, combine them, so we want to have a tool  
8 that can measure those.

9                   And the accuracy on our endpoint is  
10 going to depend on the accuracy of the measurement,  
11 maybe how frequently it's measured, and then is the  
12 person going to -- is the patient going to wear it.  
13 So if it's a -- you know, we may want to say we'll  
14 sacrifice, you know, so we want to consider these  
15 different things. So, for example, maybe we have a  
16 watch that a patient likes to wear; it's a little bit  
17 less accurate than maybe a hip worn DHT, but we can  
18 say, well, we get to measure more of their steps and  
19 that may be an advantage or more frequently and some  
20 of the tradeoffs will change.

21                   And then we can also go back and look  
22 at specifications that the manufacturer provides for

1 the tool and say, okay, we have very accurate  
2 measurement here. But as we go through to create our  
3 endpoint, our measurement may increase before we do  
4 our statistics, or maybe the other happens.

5 EBONY DASHIELLE-AJE: Thank you so  
6 much, guys. Now moving on to the next guiding  
7 principle of usability testing. We know that we want  
8 to make sure that stakeholders plan to conduct  
9 usability studies to ensure that the DHT is usable by  
10 patients in the proposed context to be used without  
11 serious errors or problems.

12 So, Andy, can you speak about just  
13 practical things that we should be outlining in an  
14 example related to usability testing?

15 ANDREA CORAVOS: Sure. So I think when  
16 you think about -- this factors back into the tool  
17 testing, as you just heard about with other groups, so  
18 if you're, like, figuring out which tool you want to  
19 use. So when you're thinking about a tool, I would  
20 say that you first want to make sure that these tools  
21 have more benefit than they do risk. And you heard  
22 that there might be some tradeoffs between accuracy,

1 usability and other components. I would say there are  
2 four things to think about, and I'll walk through each  
3 of them briefly.

4 One is accuracy and thinking about what  
5 that actually means. Some of that will be covered by  
6 this guidance and not. And so, I think some instances  
7 when we think about where this guidance plays, we  
8 should really think about how that ties to other  
9 pieces and make sure that this guidance links to that.  
10 So, for example, if you're testing the accuracy of  
11 ePRO, that looks different from a sensor, and that  
12 would be something to consider.

13 That then factors into things like  
14 usability, so the different type of tool would have  
15 different type of usability. I would say that you can  
16 think about this section broadly, whether or not the  
17 tool is useful, and useful is a combination of  
18 usability plus utility. So utility is whether or not  
19 the product has the features that you need, and then  
20 usability is whether or not those features are easy to  
21 use. Those are two things that matter, and we'll talk  
22 about this later in some of the deployment.

1           There are other things to also think  
2 about so. So digital tools have a number of different  
3 types of risks than other things than we've ever had.  
4 Most, if not all, are connected to the internet.  
5 Anything that's connected to the internet, it's not if  
6 it gets hacked, it when. And so, how do tools deal  
7 with their cybersecurity, and FDA has issued a number  
8 of different guidances around thinking about that.  
9 And then also data rights.

10           So these tools are collecting a whole  
11 bunch of different pieces of data. And so, as you  
12 think about whether or not it's useful and usable,  
13 it's really important to make sure that people  
14 understand how and when their data are used. And  
15 usability is not just for the patients and  
16 participants who are using the tools, but also the  
17 data engineers who are incorporating those tools  
18 afterwards. So if you're selecting a tool that has  
19 APIs that are not really well documented or you can't  
20 ingest them into your dataset, then the tool might be  
21 useful for the patient, but not actually for the  
22 people who have to do the statistical analysis of that

1 thing.

2                   So the four things are: accuracy  
3 centered around verification and validation; two,  
4 usefulness, which is a combination of utility and  
5 usability; three, cybersecurity considerations, in my  
6 opinion; and then four, around the data rights and  
7 management for it.

8                   EBONY DASHIELLE-AJE: Thank you so  
9 much. Diane, can you speak a little bit about the  
10 qualitative nature of usability testing?

11                   DIANE STEPHENSON: Certainly. The main  
12 misconception -- I've learned so much in leading this  
13 project over the past year -- is that it seems that  
14 there's a lot of confusion around what would be deemed  
15 appropriate for when you select a tool.

16                   So as you know, there is various  
17 definitions and terminologies for FDA acceptance. But  
18 I've been told many times that people think that if  
19 you use an FDA cleared device or an approved device --  
20 510(k) cleared device -- then that automatically means  
21 that that device will be accepted as an endpoint, a  
22 digital endpoint in a trial, so that's incorrect.

1           As we've heard today many times that  
2 definitions of how to define what would be achieved  
3 with an endpoint are quite unique. And it's also  
4 through the formal qualification process that's been  
5 discussed by FDA, that it's not required that you have  
6 a cleared device in order to qualify a digital measure  
7 through the formal qualification process.

8           So these are just some really important  
9 grounding that we try to continue to remind,  
10 especially sponsors who are selecting digital tools  
11 for use primarily as exploratory endpoints, but their  
12 goal really is a digital endpoint in a trial.

13           EBONY DASHIELLE-AJE: So in the  
14 interest of time, did you want to say something?

15           MATTHEW DIAMOND: Yeah, just to provide  
16 -- thank you very much -- just a little bit of  
17 additional clarity there from the Centers for Devices  
18 and Radiological Health. Clearance of a device or FDA  
19 approval of a device is clearance for marketing as a  
20 device to be used for treatment, prevention, cure, or  
21 the mitigation of a condition or disease, and you  
22 generally would not require clearance or approval of a

1 device by CDRH for use in a clinical trial. As we're  
2 discussing here, the most important thing is that that  
3 product -- be it a device, a medical device or not --  
4 is fit for the purpose in the trial.

5 EBONY DASHIELLE-AJE: Thank you so much  
6 for that clarification. In the interest of time, I  
7 just want to move on to endpoint measurement. And I'd  
8 like Abigail to speak about just different guiding  
9 principles related to endpoint derivation in analysis  
10 considerations.

11 ABIGAIL LUO: Thank you. So I think  
12 today, earlier today, we talked about an estimate of  
13 framework; basically, how you come up with a  
14 (indiscernible) question of interest and align your  
15 design counter analysis and interpretation of the  
16 clinical study so they can better align.

17 So I think it's very important you  
18 actually enable, very difficult but really necessary.  
19 And I think it's overdue interdisciplinary discussion  
20 at a desired stage. So I remember, I would like to  
21 tell -- so I remember when I first joined FDA as a  
22 statistician. So I was expecting the clinician would

1 just hand me an endpoint and a design, and then I  
2 would just calculate the simple science and do the  
3 analysis and check whether there was pre-specified and  
4 I would be done. So but (indiscernible) to be the  
5 case.

6 So I would like to give a couple of  
7 examples: so I remember a long time ago, I don't have  
8 the perfect memory of that situation, but it was an  
9 oncology indication. So our clinician told me that --  
10 I read the endpoint was very convoluted. So  
11 basically, (indiscernible) told me that I would like  
12 to look and compare the duration of response among the  
13 patients, but not all the patients would respond to  
14 the treatment. But they said, what's really important  
15 to us is I want to know the difference in the median  
16 duration of response. And then when I look at the  
17 endpoint, I said I can tell you that both median would  
18 be the median, both median would be zero because less  
19 than 50 percent of the patients would respond to the  
20 treatment in either the treatment arm or the control  
21 arm.

22 So actually, that was -- in that

1 situation, that we had a lot of discussion between us,  
2 the statistician and our clinical colleagues, and we  
3 actually realized that actually you have two groups of  
4 patients in there: one group of patient would enter  
5 the study without the disease and you actually watch  
6 for when the disease recur. And the other group of  
7 patients, actually they would have the disease, you  
8 would actually watch whether they respond and then the  
9 duration of response. So it was much more complicated  
10 than what a single endpoint can capture within those  
11 two groups.

12           And that started my fascinating journey  
13 that I constantly talk to my clinical arm. So just  
14 back up a little bit. I'm from the Central for  
15 Biologics. And some people ask me, what disease area  
16 do you work on, and we actually work on anything under  
17 the sun that you can think of that a gene therapy or a  
18 cell therapy may be indicated for.

19           So I think the (indiscernible) was very  
20 important. And actually, in terms of developing the  
21 endpoint, I think we would benefit to have more  
22 earlier involvement of the statistician. Just as the

1 (indiscernible) said, sometimes you may have a  
2 clinical meaningful question you would like to answer,  
3 but it may not be easily quantifiable, so you may not  
4 be able to have a good estimate of what you want.

5 And then you probably would need to  
6 have some compromise; your primary endpoint would be  
7 something that's more easily quantifiable, but also  
8 clinically meaningful. But then you will also have  
9 rigorous collection of secondary endpoints and have  
10 supplementary analysis that will give you a vast  
11 answer to the clinical questions of interest.

12 EBONY DASHIELLE-AJE: Thank you so  
13 much. Now with regard to, you know, endpoint  
14 measurement within the context of the DHTs, there have  
15 been some things that I've heard before regarding DHTs  
16 uniquely having such high volume, high frequency data;  
17 and having so much data that's generated through these  
18 tools that, you know, it's necessary to pre-specify  
19 the window of time and the methodology used to  
20 calculate the concept response to treatment for each  
21 patient, describe how missing data will be handled,  
22 and then describe how the data will be aggregated to

1 generate a score.

2           So in terms of those types of concepts,  
3 we would like to also make sure that we are describing  
4 those sufficiently in the example so that people can  
5 consider them when they are trying to think about all  
6 of the guiding principles across the guidances.

7           Now we are running low on time, so the  
8 last concept of deployment in clinical trials. I'd  
9 like to punt that to Diane and have her just talk  
10 about what it means to use it in a study and  
11 considerations, your top two considerations that you  
12 would like to see highlighted in an example.

13           DIANE STEPHENSON: So thank you, Ebony.  
14 No surprise I'll say data sharing is key to success.  
15 And in the area of digital health technologies, it  
16 took quite some time for individual sponsors who are  
17 using these as exploratory tools in their trials to  
18 understand that it is going to be much more  
19 informative for them to share information and learn  
20 from one another.

21           But one of the themes of this meeting  
22 obviously is the voice of the patient. And so, we've

1 heard today over and over again about engaging  
2 patients throughout all the steps is so key. One of  
3 the many valuable lessons learned: we heard from both  
4 FDA and EMA from the critical path innovation meetings  
5 was how important it is to conduct exit interviews.

6           And we're so fortunate to be working  
7 with our partners at the Fox Foundation who've done  
8 such a great job at engaging patients in all of their  
9 work and validation of novel tools such as digital  
10 technologies. But the more we can engage the patients  
11 and hear of their experience, the better off we're all  
12 going to be.

13           In the traditional industry sponsors  
14 studies using such tools as exploratory endpoints,  
15 that information usually would not be shared. But  
16 I'll just say a call to action is we need to share  
17 this information with one another so that we reduce  
18 the burden and optimize the chance for success. These  
19 patients are incredibly inspired and want to help, and  
20 we've bene very excited to see how much these patients  
21 really want to adopt this technology in their lives.

22           EBONY DASHIELLE-AJE: Thank you so

1 much. And all of our panelists have expertly woven in  
2 COAs in general, as well as DHTs. So this last  
3 question I'm going to punt to Michelle. And just  
4 briefly in one minute, how well do you think the  
5 guiding principles illustrate considerations for any  
6 type of COA?

7 MICHELLE CAMPBELL: I would say that  
8 (indiscernible) should try to time me on this one, but  
9 I'm not going to put him to that test. I think  
10 actually I was really glad to see your slides earlier  
11 that really set out specifically those guiding  
12 principles and kind of referenced to people as a  
13 reminder where to find that information.

14 I think what we see here in this  
15 example and the combination of this meeting from the  
16 entire PFDD guided series is how all these guidances  
17 have overlaid and are interwoven together and should  
18 be used as an entire series when we're looking at how  
19 to incorporate the patient voice into clinical trials  
20 and ultimately into what is at endpoint.

21 And so, I think the guiding principles  
22 I've listed are the critical ones that are needed, and

1 we must ultimately start with what was in the first  
2 guidance, which was talking to patients and talking to  
3 the key stakeholders and opinion leaders and  
4 understanding a disease, and building upon that what  
5 their next guidance in terms of how do we take that  
6 information and kind of put it into an informative  
7 way, which will then ultimately lead us to, how are  
8 you going to select a COA and what's that appropriate  
9 COA. Is it here in this example, the digital health  
10 technology, or is it a patient-reported outcome or a  
11 clinician-report outcome?

12           And so, we need those foundational  
13 early guidances that we've talked about over a year or  
14 a year plus ago in this same room. Those guiding  
15 principles are the starting pieces to get to this  
16 point and the end of how do we take that information  
17 from -- we collect it from a COA or, again, this  
18 example here of digital health technology, and  
19 ultimately convert it into an endpoint.

20           So I think the ones that were selected  
21 are the appropriate ones. All of them reporting  
22 principles, but I think we need to remember to use

1 this entire series collectively together moving  
2 forward when we're examining how to incorporate that  
3 patient voice.

4 EBONY DASHIELLE-AJE: Thank you so  
5 much, and thank you to all my panelists for their  
6 insights. Here's a slide for helpful links. And now  
7 I'm going to open up the floor to audience Q&A. So if  
8 anyone has any questions or comments related to what  
9 you would like to see in a working example that's  
10 supposed to be cross-cutting across the guidances,  
11 feel free to come to the mic.

12 MAN 1: (indiscernible) from ICON.  
13 I've got a question specifically about the  
14 incorporation of multiple facets of a specific domain.  
15 In the example that you gave, you talked about gait  
16 used in the study, but there's other elements to that.  
17 So in gait, there's also going to be a difference of  
18 seasonality and how that's going to affect the gait  
19 and how it's being measured, so that would be a  
20 companion facet to that DHT that would need to be  
21 collected. Or in the case of a band where you're  
22 talking about measuring sleep; there's a difference

1 between measured sleep using a DHT and perceived sleep  
2 as collected with an ECO or a COA solution.

3 How does that tie into what needs to be  
4 collected and how that ties to what we were talking  
5 about earlier today in answering the right questions.  
6 I'd like, Bill, since you published on that, you'd  
7 have some --

8 EBONY DASHIELLE-AJE: Yeah, so I will  
9 punt it to Bill first.

10 BILL BYROM: Good question. And, you  
11 know what, I think I'm certainly an advocate that we  
12 need to do both. So, you know, using a digital health  
13 technology, if I'm going to use that term, if we're  
14 measuring an activity monitor or something like that,  
15 we still want to understand how the patient feels.  
16 And, you know, there's been some quite interesting  
17 examples in the literature.

18 So things like when we measure fatigue  
19 or we measure pain, quite often, a patient can show an  
20 improvement on a pain scale. And because of that  
21 improvement, they become a little more active. And  
22 when they become a little more active, they actually

1 feel a bit more pain again. And so, actually  
2 measuring the two together provides a really  
3 insightful picture as to what's going on; whereas,  
4 just one on its own may give you the wrong answer.  
5 So, you know, again, I feel it's so important to  
6 measure both.

7 And equally, actually what matters to  
8 the patient is actually how they feel. And so, if we  
9 stop asking them through patient-reported outcome  
10 measures, we're missing such a vital component.

11 EBONY DASHIELLE-AJE: Andrew, can you  
12 also contribute to that answer?

13 ANDREW POTTER: Yes. I want to agree  
14 with what Bill said about you still have to ask the  
15 patient. But also, for example, with sleep, you know,  
16 using a band with perceived sleep, but the same  
17 problem exists with polysomnography. What the sleep -  
18 - what they say -- the perceived sleep from a patient  
19 versus polysomnography sleep, that may also not agree.  
20 So you have patients who complain of they aren't  
21 sleeping, yet they go in and they have normal sleep  
22 time on a polysomnography and vice versa. So this

1 problem isn't anything new; it just may be that we  
2 have, instead of intermittent visits where every few  
3 months, we have to deal with this problem every day.  
4 So we've taken the same problem, just a lot more  
5 frequently.

6 EBONY DASHIELLE-AJE: So it sounds like  
7 the answer is yes, both. You know, you can generate  
8 complementary information from multiple sources,  
9 including that collected through a DHT and those  
10 collected through traditional measures or other COAs.  
11 Next.

12 SONYA EREMENCO: I'm Sonya Eremenco  
13 from the ePRO and eCOA consortium and consortia, two  
14 separate ones, at Critical Path Institute. And first,  
15 I'd like to thank the panel for an excellent  
16 discussion around these guiding principles. And I  
17 think, to answer the question, I do think that there  
18 is something potentially missing from these guiding  
19 principles in the context of these digital health  
20 technologies, which is feasibility. You talked about  
21 usability.

22 But as many of us, especially from the

1 ePRO world know, there's a difference between  
2 usability and feasibility, and it's something that's  
3 been explored in the CITI recommendations for  
4 deploying mobile technology in clinical trials that  
5 was produced, I think it was maybe about a year ago.  
6 So there's recommendations out there, but it really is  
7 looking at how well does it actually work in the trial  
8 setting. And it does involve things like talking to  
9 the sites who are working with the patients to  
10 administer the technology and how are things  
11 integrating together.

12 So I think that I just want to  
13 encourage you all to think about that, of  
14 incorporating the feasibility aspect as well. And I  
15 don't know if anyone had any comments and wanted to  
16 respond to that.

17 ANDREA CORAVOS: I know this might be  
18 untraditional, but the next speaker was the project  
19 manager for the CITI clinical technology, and she  
20 might be better suited than all of us. Is that -- can  
21 Jen answer that question?

22 EBONY DASHIELLE-AJE: Jen can answer

1 the question.

2 MICHELLE CAMPBELL: I think I would  
3 just say real quick before Jen answers, is that I  
4 think feasibility is an important thing. I'm sure  
5 Bill has some thoughts from the eCOA perspective of  
6 that aspect of how well can we implement when it gets  
7 down to the site. And so, it is an important  
8 consideration I think that applies to all COAs, you  
9 know. For example, if you're using a performance  
10 measure and it's not being standardized or across your  
11 trial sites, you're going to have data issues there  
12 too.

13 So I thank Sonya for bringing that  
14 point up, and it is an important consideration no  
15 matter what type of COA that you select to help  
16 support your clinical trial endpoint.

17 MATTHEW DIAMOND: Yeah. And just to  
18 add, and thanks for highlighting the feasibility  
19 question. And I think that if you really do tool  
20 selection well and the appropriate usability testing  
21 and think through the clinical study deployment in the  
22 underlying principles, I guess it's 2, 3 and 5, that

1 is really what you're wrestling with, that theme of  
2 feasibility across those principles.

3 EBONY DASHIELLE-AJE: Jen, would you  
4 like to add to that, and then also ask your question?

5 JENNIFER GOLDSACK: Sure. So I agree  
6 completely. I think the feasibility is a really  
7 important component to add to that really nice list of  
8 four considerations that Andy proposed. I also think  
9 it would be valuable to really be clear in the  
10 definition of feasibility study.

11 I think that, as we deploy more and  
12 more of these technologies, the time is being used  
13 really broadly and perhaps outside the original sort  
14 of definition that it had before we entered this era  
15 of digital. I think a lot of the vendors are using  
16 feasibility studies in multiple ways, and it's hard to  
17 actually identify which studies are going to give you  
18 the information you need, so coming up with some kind  
19 of taxonomy there would be really useful.

20 JENNIFER GOLDSACK: And now my  
21 question. My name is Jen Goldsack. I'm at the  
22 Digital Medicine Society now, having formerly been at

1 CITI. I wanted to make a comment. Diane, I was so  
2 happy when you brought up the issue of whether these  
3 DHTs need to be cleared devices. I've heard FDA twice  
4 personally, it may have ben said far more often, but  
5 twice say that these technology do not have to be  
6 medical devices and both times, it was in this room.  
7 It was during the launch of the CITI recommendations  
8 in the Summer of 2018, and then again today.

9 To bring some perspective from the  
10 technology side. Diane, you mentioned that there's a  
11 lot of confusion on the sponsor side about the need  
12 for these things to be medical devices. I think that  
13 that confusion is seen on the vendor side as well.  
14 And I would love to see it actually stated in the  
15 guidance, if that's appropriate, that these DHTs do  
16 not have to be medical devices.

17 And I think what that does is the next  
18 obvious question is, so how do we identify those tools  
19 that are suitable, and I thank the panel today. Thank  
20 you, guys, you did a great job of identifying what  
21 those characteristics might be. And I think if we can  
22 get away from this idea of being a cleared technology

1 being a way to rubberstamp the use of the sensor and  
2 the tool, it will really help advance the field.

3 DIANE STEPHENSON: Jen, I want to thank  
4 you. You've done a fantastic job at CITI and now in  
5 the Digital Medicine Society with so many --  
6 addressing so many issues that everyone faced and also  
7 highlight the importance of standards, which your  
8 recent webinar tackled, so we all are very thankful to  
9 have you as part of our whole collaborative network.

10 MATTHEW DIAMOND: Yeah, and thanks very  
11 much, Jen, as well. And just to add one clarifying  
12 point. If the product that is intended to be used in  
13 a clinical study is one that is invasive and, you  
14 know, making measurements that are traditionally  
15 associated with a medical device, like a glucometer,  
16 it would be very surprising to see one used that is  
17 not a cleared medical device for that purpose. But if  
18 we're talking about accelerometers that, you know,  
19 would be used in a general-purpose environment, then  
20 it's really about, again, being fit for purpose. And  
21 being cleared in and of itself is not necessarily  
22 sufficient for being appropriate, certainly not.

1 EBONY DASHIELLE-AJE: Are there any  
2 other questions from the audience?

3 MICHELLE CAMPBELL: Can I just add one  
4 thing, Ebony?

5 EBONY DASHIELLE-AJE: Yes.

6 MICHELLE CAMPBELL: I think just taking  
7 Jen's point and the collective thing, and I guess it  
8 hasn't been said yet or maybe it has. But  
9 particularly as we emerge in this area with digital  
10 health as another option with digital health  
11 technologies, I do think this is somewhere where --  
12 this is where the encouragement of that early  
13 conversation is important. And Diane's experience  
14 shows how that early communication was really  
15 important and critical to how they plan their study  
16 and next steps.

17 As we continue to learn about the  
18 capabilities and what kind of data and endpoint can be  
19 created from digital health technologies, in  
20 complementary with our other COAs, I think those  
21 conversations should happen early with your respective  
22 medical product center and division to make sure

1 there's agreement and understanding from all sides of  
2 really what are we trying to accomplish in the end.  
3 So I would just encourage that if you're considering  
4 that, making sure you've had some early conversations.

5 EBONY DASHIELLE-AJE: Thank you all.  
6 Just as a quick high-level wrap-up. It appears that,  
7 you know, from our panelists that the scenario that  
8 we're using in Parkinson's disease is one that's  
9 appropriate for highlighting all of the different  
10 guiding principles that span all of the Guidances 1  
11 through 4.

12 And the guiding principles of concept  
13 measurement, tool selection, usability, testing  
14 endpoint measurement in clinical study deployment are  
15 all very important. But from our audience, we've  
16 heard that we're missing the key component of  
17 feasibility and, therefore, we should consider  
18 incorporating that into an example that we're going to  
19 be displaying.

20 And overall, we're thinking that all of  
21 these principles are not just applicable to DHTs, but  
22 across all COAs; and, therefore, it is useful for

1 highlighting the principles that we think span any  
2 type of COA that would be developed our used by our  
3 stakeholders.

4 So with that, I want to say thank you  
5 all for listening, and we are early a little bit.  
6 Right? I deliver, right? I overdeliver -- wait --  
7 under promise, overdeliver, yes. So we have two extra  
8 minutes to chat, chat, chat, and then our panelists  
9 for the next session will come up. Thank you all.

10 (Break)

11 MEGHANA CHALASANI: Hi, all. I'm going  
12 to ask you all to please be seated so we can get  
13 started with our closing session for the day. My name  
14 is Meghana Chalasani and I work in CDER's office as a  
15 center director on the patient-focused development  
16 program staff and I have the honor of being the  
17 moderator for our closing and final session today.

18 The purpose of this session is to wrap  
19 up on what we've heard throughout the day and hear  
20 from our panelists on the key takeaways from the  
21 workshop. But then we're also going to broaden the  
22 discussion a little bit and ask our panelists and, of

1 course, the audience to reflect on the overall  
2 methodological PFDD guidance series that the FDA has  
3 been working on.

4 Before we get started with our  
5 moderated discussion, I'd like to ask each of my  
6 panelists to please introduce themselves. Marc, if  
7 you'd like to get us started.

8 MARC BOUTIN: Sure. good afternoon,  
9 everyone. My name is Marc Boutin. I'm the CEO of the  
10 National Health Council which is an organization  
11 created by patient groups for patient groups 99 years  
12 ago and has many, if not all, health stakeholders'  
13 representative membership.

14 STEPHEN COONS: Hi, I'm Stephen Coons.  
15 I am the program officer for clinical Critical Path  
16 Institutes, Clinical Outcome Assessment Program and I  
17 am an executive director of the Patient-Reported  
18 Outcome Consortium at Critical Path Institute.

19 KATARINA HALLING: Hello. I'm Katarina  
20 Halling and I am the head of patient-centered science  
21 within AstraZeneca.

22 TELBA IRONY: And good afternoon. I'm

1 Telba Irony. I'm the deputy director of the Office of  
2 Biostatistics and Epidemiology at the Center for  
3 Biologist.

4 LAURA LEE JOHNSON: Good afternoon.  
5 I'm Laura Lee Johnson. I'm a division director in the  
6 Office of Biostatistics in the Center for Drugs and  
7 I'm also the office Patient-Focused Drug Development  
8 liaison.

9 PANDU KULKARNI: Hello. I'm Pandu  
10 Kulkarni. I'm the chief analytics officer and vice  
11 president of biometrics and advanced analytics at Eli  
12 Lilly which is also including the Real-World Analytics  
13 Group. Typically, the statistics group don't include  
14 that, but that's why I wanted to call it out as a  
15 specialty.

16 MICHELLE TARVER: Good afternoon. I'm  
17 Michelle Tarver. I'm the director of patient science  
18 and engagement at the Center for Devices and  
19 Radiological Health.

20 MEGHANA CHALASANI: Great. Thank you  
21 all. So to get us started, let's start with hearing  
22 one to two of the most important messages that we've

1 heard related to the methodologies presented in the  
2 discussion document for this workshop and whether they  
3 can be reasonably and rigorously implemented in  
4 medical product development.

5 To get us started, Stephen, would you  
6 mind chiming in?

7 STEPHEN COONS: Sure. Well, the first  
8 thing I just want to say is that the utility of this  
9 fourth guidance is truly predicated on the quality and  
10 comprehensiveness of Guidance 3, because based on  
11 today's discussion and the discussion document for  
12 Guidance 4, Guidance 4 will assume that the sponsor  
13 has a fit for purpose COA ready to deploy in a  
14 treatment trial for the derivation of a COA-based  
15 endpoint.

16 And so that connection is critically  
17 important and hence, it's kind of difficult to fully  
18 address the adequacy of the contents of what were in  
19 the discussion document and our discussion today and  
20 will ultimately be in Guidance 4.

21 But both Elektra and Michelle mentioned  
22 that there are so many connections and

1 interdependencies between all four guidance documents  
2 or there will be and I think that is particularly true  
3 for Guidance 3 and 4. So hence, there will really  
4 need to be sufficiently clear and explicit cross  
5 referencing among the guidance documents since they  
6 are separate guidance documents.

7           And I was glad to know that at least  
8 the glossary of this Guidance Document 4 will be  
9 comprehensive. It will be an aggregation of all the  
10 glossaries from the previous three as well as the  
11 fourth.

12           And the only other point I'll make is  
13 that in the first panel, Kevin alluded to lack of  
14 information in the discussion document dealing with  
15 the heterogeneity in symptom and functional  
16 manifestations of disease within and among patients.  
17 And my assumption is the content of the panel three  
18 discussion will lead to a much more robust content in  
19 the resulting draft guidance around this issue and  
20 that will be incredibly important.

21           And Larisa in panel one and Steve in  
22 panel three both mentioned the heterogeneity in

1 meaningful within patient change in addition to the  
2 heterogeneity of symptoms and functional disease  
3 manifestations. And like (indiscernible) said earlier  
4 in his comment that R.J. didn't necessarily view as a  
5 question, we need to be creative and think about  
6 nontraditional approaches that may enable us to get  
7 closer to individualizing or personalizing end points.

8           And as R.J. correctly stated, it is  
9 hard. It's hard to do that, but it doesn't need to be  
10 considered impossible and particularly as more  
11 individualized gene and cell-based therapies are  
12 emerging. So I think we really need to put a lot more  
13 time and effort into thinking about dealing  
14 effectively with heterogeneity and getting to the  
15 point where we do have more patient-focused and  
16 personalized end points. Thank you.

17           MEGHANA CHALASANI: -- Stephen. I do  
18 want to emphasize one of the points that you made  
19 about the PF, Patient-Focused Drug Development  
20 glossary that encompasses the entire series of  
21 guidances and just teeing it up nicely. It is  
22 something that we envision being a living document and

1 so forth, so if you have an opportunity to review all  
2 of the terms and provide comments through the docket,  
3 that would be very helpful for us as well.

4 Same question to Katarina, just  
5 reflecting on the themes and takeaways.

6 KATARINA HALLING: So I think it kind  
7 of nicely builds on what you said, Stephen. I think  
8 the key things that I've heard today is a couple of  
9 questions related to Guidance 4 and where is it  
10 relevant to also include patients. I think that is  
11 something that will be extremely important to make  
12 that very explicit that it's not only in the beginning  
13 of the drug development and the planning that we do  
14 listen to patients and engage with patients.

15 It's actually an iterative process and  
16 I think we need to ensure that that is crystal clear  
17 throughout all the guidances, so it's kind of building  
18 on what you said, Stephen, about a little disconnect  
19 between some of the guidances.

20 And I think specific examples in  
21 Guidance 4 where I'd like to see more examples is, for  
22 example, in the clinical meaningful. In the

1 meaningful change section, there is a huge component  
2 where we take what we heard from patients in  
3 qualitative interviews and build that together with  
4 the statistical and analytical approaches.

5 I think in the patient burden section,  
6 I'd like to see a positive framing of what actually  
7 drives what patients think is a burden to them. There  
8 is text around what happens if it's too much burden,  
9 which I agree to, that's not good. But I think the  
10 key thing is that if we do include things that are  
11 important and relevant for patients, which we have  
12 heard from talking to them, I mean, that is one of the  
13 critical aspects of patient burden.

14 So I'd like to see a little more of  
15 that. I think that the estimand discussion was good.  
16 I've heard some say this is what we're doing. I think  
17 we're partly doing it, but we can be more crystal  
18 clear and be more systematic in how we do it.

19 Again, I'd like to see more examples of  
20 how patient actually also are alive in that  
21 conversation and I think that the estimand structure  
22 will be a good thing also to drive home what was

1 mentioned in the first session which is early.

2           So if we're really thoughtful in that  
3 process, it'll be easier to make the right decisions  
4 and start the right design of our endpoints already  
5 that early, and secondly, it will also facilitate the  
6 interdisciplinary collaboration which is critical to  
7 make this right. So those would be some of my  
8 comments.

9           MEGHANA CHALASANI: Thank you,  
10 Katarina. Pandu, would you like to add to this from  
11 the industry perspective as well?

12           PANDU KULKARNI: Yes, thank you. Let  
13 me first start by recognizing that in every single  
14 discussion we heard today, there was tremendous  
15 passion for patient-focused drug development. I think  
16 that's key, right. Everybody's aligned on that.  
17 Challenges will be there, but first of all, whether  
18 you want this or not is the question and I think looks  
19 like we all want this and we want this really bad and  
20 therefore question is, how will we make it happen and  
21 whether the guidance allows us to make that happen and  
22 what needs to be there.

1           So we have a great foundation to start  
2 with. So there are challenges. As we have been  
3 dealing with clinical end points for 50 years -- and  
4 these are hard end points -- and even there we have a  
5 lot of issues. So it's not an easy road and we heard  
6 that panel after panel; there are a lot of challenges.  
7 Even in the clinical end points recently we've been  
8 dealing with estimands and value of P value and so on,  
9 so forth.

10           So there is a lot of issues there we're  
11 dealing with. Now, we're introducing COA which has  
12 lot more variability, lot more unknowns and so there  
13 are really a lot more challenges and we need to be  
14 ready for those challenges. And I think the guidance  
15 touches on all of the aspects from having learnt from  
16 the clinical hard end points, so therefore guidance  
17 has done a really good job of looking at all of the  
18 aspects that needs to be done or dealt with and that's  
19 where I think the glossary is complete.

20           But what's not complete is the details  
21 of how to deal with it, and I don't know that that  
22 will ever be complete because this is an ever-evolving

1 arena and especial when you introduce digital into it  
2 and I think at lunch somebody was mentioning when she  
3 goes on a horse riding, her Fitbit thinks she is doing  
4 all kinds of exercise.

5           So I think those are things that we  
6 have to learn to deal with and they're going to be  
7 there and when these things are collecting data all  
8 day long, aberrations happen. How do we deal with  
9 those aberrations, I think, is a really key point. We  
10 don't know how to deal with them. You can't just take  
11 a look at the summary data. You've got to look at the  
12 data in a more fundamental way and we've got to  
13 develop new methodologies and I think guidance will  
14 have to provide some of those boundaries as to how we  
15 deal with it.

16           And the heterogeneity, in every single  
17 panel came up as to how there's so much more  
18 heterogeneity than you would have in the clinical end  
19 points and how do we deal with those heterogeneity and  
20 how do you make this homogeneous. If you try to make  
21 it homogenous, it becomes harder and therefore you  
22 have to learn to deal with heterogeneity.

1           So I think there are a lot of things  
2           that we have to deal with as a community and the key  
3           point that I think I took away from several of the  
4           panels was how important it is to collaborate now with  
5           different groups: psychometricians and clinicians and  
6           the clinical statisticians and people who have been  
7           doing the drug development for a long time.

8           We need to get them excited about these  
9           so that they can bring that experience together with  
10          patient-reported outcomes and COAs and that will make  
11          this whole process a lot better and smoother instead  
12          of people dealing with it all of a sudden fresh.

13          So my plea and urge will be to all of  
14          us to work together from the clinical experience to  
15          patient-reported outcomes experience. Bring it all  
16          together and deal with the uncertainty and the  
17          heterogeneity in a way that is manageable.

18                 MEGHANA CHALASANI: Thanks, Pandu.  
19          Thank you for even the way you kicked it off by really  
20          recognizing and appreciating the patient-focused drug  
21          development or in this case medical product  
22          development, really, mission that we kind of have been

1 accomplishing through this guidance series.

2           Marc and I were just talking a little  
3 bit briefly earlier about how this was what we wanted  
4 when we were all at the table several years ago and  
5 how much we've really accomplished. One other theme  
6 that I heard through the day, a little bit throughout  
7 the different panels was some folks and some panelists  
8 were asking for a little bit more detail, some more  
9 technical details and other folks were thinking, we  
10 still need to understand the big picture a little bit  
11 more. We still need some high-level guidance and so  
12 forth.

13           And so really thinking and reflecting  
14 about who the audience is for this guidance and maybe  
15 getting some thoughts on, your thoughts on whether  
16 it's striking the right balance or how we could better  
17 strike the right balance, Marc, would you mind kicking  
18 us off?

19           MARC BOUTIN: Sure. Before I respond  
20 to the question, I just want to take a moment and say  
21 as a patient advocate that has been working in this  
22 space for more than 15 years and really sort of came

1 out of the concept of getting benefit/risk correct  
2 from a patient perspective, the patient community  
3 became really, really antagonized over the fact that  
4 critical decisions were being made for us without  
5 consulting or input from us.

6 And we pushed the FDA and then started  
7 to collaborate with the FDA and to be in an  
8 environment now where we have multiple guidances on  
9 device and drugs coming to the fourth one, I think we  
10 have to step back and recognize how far we've come.  
11 And so I'd love to get a round of applause for the FDA  
12 folks that have worked so hard on this for nearly a  
13 decade.

14 We in the patient community really  
15 appreciate the tremendous amount of work that's gone  
16 into this. From my perspective to your question, I  
17 think in this guidance we are getting at the right  
18 tone. We could certainly go more technical, but as  
19 you've heard from other speakers today, from a patient  
20 perspective, it's already a document that is very hard  
21 to understand.

22 And if you are what I call an average

1 patient, you're going to have a really, really hard  
2 time with it. So I think we need to think about how  
3 we present this to various stakeholders, how they  
4 understand it. My dream would be, we would have an  
5 infographic for each of the patient engagement  
6 guidances and we'd have a general infographic that  
7 would combine them together and explain how they work  
8 together.

9           Because we've had several comments  
10 already from this panel and previously that we need to  
11 think of them as a greater picture. And two things  
12 I'll share about that. One is, I don't want all of  
13 you researchers, scientists, statisticians developing  
14 the infographic. Want to be really clear about that.

15           Love you all to death. I do not want  
16 you to create those infographics. We have the  
17 contents, now we need to bring in experts that can do  
18 that and make them useful for what I would call real  
19 people.

20           And then second, we have all come  
21 together in this forum and I've heard a lot of  
22 comments where I listen to people and you get it. The

1 fundamental purpose of these guidances were to help us  
2 generate data and evidence that would inform us about  
3 representative samples and sub populations of people  
4 living and dying with disease. But I've also heard  
5 from some of you say, oh, we just need to do it the  
6 way we are. The core outcome assessment is something  
7 that's been new and ahead of the game for a long time.  
8 That's true, but at the end of the day, all of these  
9 concepts of engaging patients, codesigning, co-  
10 development, have to be front and center.

11 And just because you're in the business  
12 of developing core outcome assessments, doesn't mean  
13 that you're patient centered or getting it right. So  
14 it means we all have to bend. We all have to change  
15 if we're really going to get the impact we all want  
16 from this.

17 MEGHANA CHALASANI: Thanks, Marc. I'll  
18 turn to others on the panel to reflect on the theme  
19 about the right technical level and audience.  
20 Katarina, perhaps?

21 KATARINA HALLING: I just would like to  
22 start to say that I think you're absolutely right. I

1 think that we collaborate with different skills in  
2 this big endeavor and as you say, we're in a great  
3 place where we now are combining patient focused with  
4 good measurement properties and different ways of  
5 collecting that data including newer digital  
6 technologies. That's a huge step and we need great  
7 collaboration.

8 I think you're right. We should not  
9 explain this and be the ones that put those  
10 infographics together. I think there are people who  
11 can do that much better. I do agree with you that I  
12 think Gigi said it really nicely in the first session  
13 that it may be that it's not very accessible to  
14 patients and I'd love for this to come together and be  
15 understood by everybody which I know is one of the key  
16 things we set us up to do in the beginning.

17 And that will not only be good for  
18 patients. That'll be good for all of us in the  
19 collaboration to have a common understanding of  
20 actually what the little pieces are. Then, yes, we  
21 will need details for those of us who are doing this  
22 on a daily basis, but I do think we have most of the

1 details right, right now. If there's one thing I  
2 could wish for, it'd be, there's this summary of the  
3 guidance and recommendations of where we are today. I  
4 think we're recognizing we made a huge step forward to  
5 be where we are today, but also recognizing that we're  
6 continuing moving forward.

7           So just as I really like the guiding  
8 principles for digital health technologies, I'd love  
9 to see a framework for how do we continue to push for  
10 new innovations, how do we start tackle individualized  
11 measurement strategies. It is really hard. We need  
12 to continue to strive to make the complex easy and any  
13 frameworks that we could work together would be really  
14 helpful, I think.

15           MEGHANA CHALASANI: Thank you,  
16 Katarina. Pandu, would you like to chime in here as  
17 well?

18           PANDU KULKARNI: Yeah. Pretty much  
19 actually about the infographics, I think the  
20 infographics are extremely useful and they should be  
21 targeted. They shouldn't be just for patients. I  
22 think you also need it for other people. This

1 guidance is supposed to help everybody. Starts with  
2 the patients in mind and you do what the patients will  
3 get attracted to but you also need people who -- how  
4 to implement this thing.

5           And for them, you need to provide some  
6 details. Without those details, patients will get  
7 hurt in the end because it will take so long for the  
8 discussions to happen, you will never be able to  
9 develop anything fast enough. So I think you got to  
10 have, the infographics that I dream about, Marc, is if  
11 you are a patient, click on this. If you are a  
12 researcher, click on this. If you're a statistician,  
13 click on this.

14           And we have details for those roles and  
15 each of them can benefit from what they need to do.  
16 That way, you are not only having one in mind, all of  
17 us in mind because all of us have to do the work to  
18 get the patient benefitted. So I think this guidance  
19 is really good at the high level. It touches all of  
20 those, but it does lack those details.

21           Like I think the panelist said, I'm a  
22 psychometrician. I can see where it is going but I

1 don't know what to do on a practice basis. Guidance  
2 says, come talk to us. You can go talk to them, but  
3 it will take very long time to have that discussion  
4 without certain guidance. So I think it would be  
5 phenomenal to develop that infographic for different  
6 groups. They can click on them and get some more  
7 details that they need.

8           You don't need all the details, but you  
9 do need some more details for us to make this happen  
10 faster.

11           MEGHANA CHALASANI: Thanks, Pandu. I  
12 do want to turn to my FDA colleagues on the panel now  
13 and kind of reflect on what you may have heard so far  
14 already on the panel discussion but as well what we've  
15 heard throughout the day. Telba, if you'd like to get  
16 us started?

17           TELBA IRONY: Yeah. I will start with  
18 actually a point that's very dear to me and is the  
19 discussion that we had this morning on the meaningful  
20 improvement or meaningful difference for a patient in  
21 any treatment, and what I heard combined with what I  
22 previously thought is that what's clinically

1 meaningful, what's meaningful for the patient depends  
2 on the benefit/risk balance.

3 I think if you have a treatment with a  
4 high risk, a meaningful benefit will be higher than if  
5 you have a treatment with a lower risk. Of course,  
6 that depending on the context and depending on how  
7 much that benefit is needed and appreciated by the  
8 patient.

9 So we need to strike a benefit/risk  
10 balance to define what's clinically or patient  
11 meaningful, and also we need to consult the patients  
12 because what's clinically meaningful, what's  
13 meaningful for one patient, might not be meaningful  
14 for another one.

15 So how do we know what's meaningful for  
16 the patients? We talk about heterogeneity in disease  
17 responses and also in preferences. So I emphasize  
18 that's important to conduct patient preferences  
19 studies and obtain patient preference information, not  
20 only to determine what's clinically meaningful, what's  
21 a meaningful difference, but sometimes on choosing the  
22 end points and when you were talking about the

1 composite end points that have multiple components,  
2 even to give different weights to different  
3 components.

4           So patient preference information, it's  
5 very important and these studies are also very  
6 important. Now, going on the clinical outcome  
7 assessments, we all heard several times that they are  
8 not end points but they can be used to generate end  
9 points, and sometimes to generate several end points.

10           We also learned that we want end points  
11 that reflect patients' perspectives and also they are  
12 sufficiently robust to answer our clinical questions,  
13 our study questions and also to help us to make  
14 regulatory decisions and also to be included in  
15 labeling so the patients can make the decisions for  
16 themselves.

17           So it's important to align the end  
18 points with the study design and the scientific  
19 question that we want the study to answer and as  
20 Abigail mentioned in the previous session, sometimes  
21 one end point, one single end point, will not answer  
22 the questions. We might need more than one end point.

1                   Which brings me to the discussion that  
2 we had before about the responder rates and the  
3 continuous end points. In that cases, in my  
4 experience, a responder rate, it's easier to interpret  
5 and it's probably what the patient wants to know.  
6 What will be my improvement and what's the chance that  
7 I'm going to experience that improvement?

8                   For the statisticians, the averages,  
9 the continued end points and the (indiscernible) are  
10 more convenient and will be more powerful. In other  
11 words, we will require a smaller sample size for the  
12 study. So what's the solution for this dilemma? In  
13 my experience, it's to analyze both. We have one that  
14 will give us a better picture about benefit/risk per  
15 patient but also in respect to the overall patient  
16 population and sometimes for the public health.

17                   So in this case, two end points will be  
18 much better than one even if they require more  
19 analysis. Also with respect to the heterogeneity of  
20 patients along time and among patients. I'm a  
21 statistician and I'm claiming the statisticians have a  
22 tool box to deal with the heterogeneity and with the

1 uncertainty that comes from the heterogeneity.

2 So what's in the tool box?

3 Randomization. We'll fix a lot of these problems of  
4 reduced uncertainty. Stratification, modeling, and  
5 other statistical tricks. And I think that's what I  
6 would say. I also agree with you about the guidance  
7 and the accessibility of the guidance.

8 Someone also in one of the sessions  
9 gave a very good suggestion about making a patient  
10 summary for the guidance that maybe can be attached to  
11 the infographics and with all these things to patients  
12 will understand the content of the guidance but we  
13 actually need to be technically deep so that the  
14 professionals, the statisticians, the psychometricians  
15 will know what the FDA is expecting. And I'll  
16 finalize here.

17 MEGHANA CHALASANI: Thanks, Telba.

18 Laura Lee?

19 LAURA LEE JOHNSON: Sure. So I'll be  
20 brief because you're going to hear a little bit more  
21 from me later as well, and I think we always learn a  
22 lot at these meetings and an important few points or

1 to clarify the links between and across the guidances,  
2 really the communication, and to echo Pandu, the  
3 collaboration.

4 I think inside of FDA, in many ways, we  
5 have worked on this very strongly but we're hoping  
6 that this also is more encouraging for a lot of our  
7 other partners as well in that area, that we need to  
8 write down some things that we would think were self-  
9 evident and several of our colleagues, like, yeah, you  
10 know we didn't say that because we figured of course.  
11 And we need to be more explicit.

12 And also having more examples.  
13 Everybody always wants more examples, so you'll hear  
14 my plea right around 5:00 to say, write them and send  
15 them to us. Put them in the docket because also you  
16 all's examples and what you're currently struggling  
17 with is going to be really relevant. We see what we  
18 see, but you all have a lot more experience there as  
19 well, so part of those examples, please send them and  
20 be willing to share them with all of us.

21 But it is the details and we also, this  
22 tension, the good news is we've been feeling this

1 tension for a while and trying to figure out what we  
2 were going to write and how we were going to write it.  
3 I do worry a little bit that if we separate things too  
4 much, do the roles and do the different groups then  
5 fully collaborate? Do they only read their portion  
6 and not the whole?

7           So I do think we need to figure out how  
8 we have both focused information but also that people  
9 really understand that whole. And so, I've said to my  
10 colleagues, I won't put all the details in an appendix  
11 because then people don't read the appendix. They  
12 focus on that key.

13           So how are we going to balance? And if  
14 you tell me I'm wrong, a thousand people tell me I'm  
15 wrong, maybe I'll change my mind. But I think these  
16 are some of the things that we continue to look at and  
17 we're really thankful for the feedback.

18           MEGHANA CHALASANI: Thank you, Laura  
19 Lee. And Michelle?

20           MICHELLE TARVER: So I think one of the  
21 things that we clearly heard is that it's important to  
22 put the question first, understand what are you trying

1 to address. And the reason why I bring that up as an  
2 important issue is that we're not only using clinical  
3 trials as the way of generating evidence to support  
4 product development.

5 We're looking at real world data  
6 sources that can then, therefore, inform us. So  
7 understanding what the question would be really can  
8 help with planning for registries as well, registry  
9 platforms. Understanding how is that end point going  
10 to be operational-wise can then inform how often  
11 should the general public that's providing information  
12 in the registry, how often should they be taking those  
13 clinical outcome assessments or performing those.

14 And that is important because you can't  
15 go back and retrofit it if it's going to be a  
16 comparator arm in a clinical trial in the future or  
17 used to inform the medical product.

18 The other theme that I think I heard  
19 was the least burdensome principle, and for our  
20 center, that's a central principle. We really do look  
21 and strive to make things the least burdensome, not  
22 only on companies but on patients as well as the

1 review team. We want to make sure we officially  
2 create solutions that can land in the public realm and  
3 help our patients protect and promote their health.

4 And so to that end, I think it's  
5 important to start with first things first, which is  
6 not just the question but the patients, having them at  
7 the table, having them part of the conversation, not  
8 by just having focus groups but actually having them  
9 as advisors sitting side by side and helping to inform  
10 how we're approaching these conceptualization, not  
11 only of the tools but of how they're going to be  
12 analyzed and the clinical investigation.

13 Our center has a draft guidance that we  
14 posted that talks about the importance of including  
15 patients' advisors in the clinical development and  
16 conduct.

17 And the last thing I'd like to mention  
18 is the importance of making the information  
19 interpretable. I think we heard that in many of the  
20 different panels and as a healthcare provider and  
21 ophthalmologist, when I have a conversation with a  
22 patient I'm not looking at their score on a

1 questionnaire, but I need to be able to translate that  
2 into language they understand so they can make an  
3 informed decision about their health care.

4           And so while it is important to have  
5 strong and robust measurement properties, it doesn't  
6 mean anything if it's not communicatable and so we  
7 want to make sure that we can communicate very clearly  
8 to the patient population and to healthcare providers  
9 who may not be as familiar with some of the language  
10 that we've been using in this room, be able to  
11 communicate that information so that people can make  
12 informed decisions. And I'll stop there.

13           MEGHANA CHALASANI: Thanks, Michelle.  
14 And so I'll look at my panel and see if, based on some  
15 of the comments that we've heard from the panel if  
16 that spurred any additional thoughts or sparked  
17 anything else that you'd like to share or add on  
18 before we transition. No? Okay.

19           I gave them very strict warnings about  
20 the need to, like, stay on time and be succinct, and  
21 so now they're not even going close to the mic.

22           So moving on to our second primary

1 question, which we kind of already started teeing up  
2 which is taking a step back from specifically guidance  
3 for the discussion document for this workshop and  
4 looking at the breadth of the entire guidance series.

5 We've already started hearing about the  
6 need to perhaps cross reference and link a little bit  
7 more between the individual documents and so forth,  
8 but just getting an understanding from you all, if  
9 there is a big picture that you're starting to see or  
10 that you see and how the pieces kind of fit together.  
11 Marc, would you like to reflect on that for us a  
12 little bit?

13 MARC BOUTIN: I think seven or eight  
14 years ago, we hosted a meeting and we actually held it  
15 here at the FDA with participation from the FDA to  
16 look at how we might move the concept of patient  
17 engagement along and we identified a number of  
18 barriers and the first and probably the most difficult  
19 was changing culture.

20 And if you think about how challenging  
21 that is, there's so many parties that have vested  
22 interest in the status quo. Even within your own

1 organizations and companies there are so many people  
2 with a vested interest in the status quo. And at the  
3 end of the day, changing culture is tough, but it  
4 really takes three things.

5 It's inspiration, information, and  
6 intimidation. And we have done a lot on the  
7 inspiration side. And it's not just the patient  
8 community. It's representatives of the regulator  
9 industry, researchers, all the folks here stepping up  
10 and explaining why we need to do better, why it needs  
11 to be different.

12 Well, one of the key reasons were so  
13 excited to partner with the FDA as it started to look  
14 towards guidance was that it would create the  
15 information, the how-to. And in all my years as a  
16 patient advocate, I've never heard industry say to FDA  
17 or any other regulator, give me more guidance, tell me  
18 what to do.

19 And we have set forth a whole lot of  
20 information. Is there more that can be done?  
21 Probably. Is there more clarification, can we get  
22 more technical? But I'll tell you, the roadmap is

1 there. The information is there. But most culture  
2 change, whether it's in society, in an organization,  
3 falls because we forget about the intimidation.

4 We're not hotwired to coerce people and  
5 nobody's asking the FDA to coerce you. But for all of  
6 us in our organizations, whether it's a nonprofit  
7 patient group or a company, we're going to have to  
8 coerce in order to change the culture and make this a  
9 reality. And that's going to be critical.

10 And for the people here who drank the  
11 Kool-Aid and are on board with this, you know when you  
12 go back to your organization, there are hundreds if  
13 not thousands of people who have no idea that this  
14 meetings' even taking place. And yet, you've still  
15 got to help move your organization to make this an  
16 integrated cultural reality.

17 Where FDA can help -- and again, I'm  
18 not asking FDA to coerce -- but this point about the  
19 integration of the guidances, this point about how and  
20 whether there's a clear understanding, I think for us  
21 in the room, the answer is yes.

22 But when I look at large companies,

1 this is going to be handed off into a very specific  
2 silo within a company and they're probably not going  
3 to look at the other guidances and they're not going  
4 to get the big picture. And if you do the COA work  
5 without the engagement from the very beginning, which  
6 has been said a number of times, you're going to get  
7 interesting results but it may not be relevant to the  
8 people you're trying to serve.

9           So anything we can do to drive home the  
10 fact that these guidances are connected, that there's  
11 a function that needs to be systematic, consistent,  
12 and integrated into the work that we do, is key. And  
13 I think we have to drive that message over and over  
14 and over again so that you can go back as leaders  
15 within your organizations and strategically move us to  
16 the next level where we put in those coercive  
17 components, where this gets written into all  
18 stakeholders' or all staff goals and objectives.

19           It becomes part of retention,  
20 recruitment, salaries, bonuses. That's going to be  
21 key to make this shift lasting and not have us revert  
22 back to the old culture where this becomes just a tick

1 the box and not truly meaningful.

2 MEGHANA CHALASANI: thank you, Marc.  
3 Stephen, would you like to...

4 STEPHEN COONS: Well, I do think there  
5 is a clear understanding of how they fit all together  
6 and I think -- and I addressed this to some extent  
7 earlier -- in theory, absolutely and I'm not being  
8 critical at all, but again, we haven't seen draft  
9 Guidance 3 yet, but in theory, we really start where  
10 we need to start in Guidance 1 and move to this point  
11 of having clinical outcome assessment tools that can  
12 then appropriately be deployed in clinical trials and  
13 analyzed and made into something that is interpretable  
14 and will be able to be put into labels that can help  
15 patients and clinicians make these important decisions  
16 regarding therapy.

17 So I do believe that there truly is an  
18 overall package here that is potentially very cohesive  
19 and comprehensive.

20 MEGHANA CHALASANI: Thanks, Stephen.  
21 Would anyone else on the panel like to comment on  
22 this? Pandu?

1 PANDU KULKARNI: I agree, Marc, the  
2 culture part I think is the critical part. I've been  
3 in the industry for 19 years and for the most of those  
4 years, PROs were an afterthought and they were just  
5 put in there just as other end point and nobody really  
6 thought through them very much and because there were  
7 not that many validated ones and very little chance of  
8 getting them on the label and so there was no  
9 motivation.

10 So my thought is still true motivation,  
11 inspiration rather than coercing. So the motivation  
12 and inspiration would come from having this guidance  
13 aligned with others to say, yes, if you did this, you  
14 would get it on the label. If you get it on the  
15 label, payer would pay for it. And if payer is paying  
16 for it, patients will benefit from it.

17 I think if we can get all of those  
18 elements aligned, I think industry is prime part of  
19 this. In every industry, if you look at every  
20 pharmaceutical company's website, they say patient is  
21 the number one. That's what we drive for. We go to  
22 work every day because we want to help the patients.

1           I think it is just that motivation to  
2 say, we can get this on the label, needs to be there,  
3 and I think this guidance is bringing that forward and  
4 then I think the payer groups also have to come along  
5 to say, if we have functional improvements, we will  
6 pay for this drug or device or whatever. I think it's  
7 those kind of motivation we need to drive and, of  
8 course, the culture change has to happen that we do  
9 need to think about these at the very beginning of the  
10 trial and even before that to say what is the patient  
11 journey and how can we take that into account in  
12 making up end points that are really useful and not an  
13 afterthought, and I think that would be very  
14 fundamental.

15           And having the discussion with the FDA,  
16 even to begin with to say, what can we be doing here  
17 to benefit the patient and can get it on the label, I  
18 think those discussions will really motivate people to  
19 do a lot more than they have done before.

20           MEGHANA CHALASANI: Thanks, Pandu and  
21 Marc. I've got a very excited panel. Very thought-  
22 provoking comments. Stephen and then I'll turn to

1 you, Katarina.

2           STEPHEN COONS: Well, I just wanted to  
3 recognize that we have use patient-reported outcome  
4 measures for years in terms of, there are certain  
5 symptoms, there are certain clinical outcomes that  
6 only the patient has been able to tell us for years.  
7 So I don't want to lose site of the fact that patient-  
8 reported outcomes have been very important. Pain,  
9 erectile dysfunction, all sorts of drugs have been  
10 approved based on patient-reported outcomes.

11           I don't think they were all necessarily  
12 as patient focused as we would like them to be, so I  
13 think that's what part of this whole effort is to make  
14 sure whatever we do in terms of clinical outcome  
15 assessments, whether they be clinician reported or  
16 patient reported or observer reported, that they are  
17 more patient focused and take into consideration what  
18 is meaningful to patients. So, just some clarity  
19 there.

20           MEGHANA CHALASANI: Thanks, Stephen.  
21 Katarina?

22           KATARINA HALLING: I do think that

1 we've started to see the culture change inside of  
2 companies as well and I do think that the effort with  
3 these guidance documents is helping us to put the  
4 patient at the heart of drug development so that will  
5 clearly help. That's also why it's so critical that  
6 we have a cohesive summary that we will all be able to  
7 use as a common framework.

8           And then just to comment on what you  
9 said with the labels, I also think that yes, labels is  
10 important. But I'd also encourage us to look for  
11 better ways of also incorporating the broader patient  
12 experience, even if that cannot make it into the label  
13 because we pre-specify one or two or three COAs, but  
14 there's a sea of information. I think we also can do  
15 better in representing the patient perspective more  
16 holistically as well, outside of the label.

17           MEGHANA CHALASANI: Thanks, Katarina.  
18 Michelle, did you want to comment?

19           MICHELLE TARVER: I was just going to  
20 say that there's a lot of development work that  
21 happens outside of companies, too. There's a lot of  
22 academic centers and other places where novel ideas

1 are being generated and having a nice layout of  
2 different ways to look, develop, and analyze clinical  
3 outcome assessments, I think, helps to facilitate some  
4 of those solutions that we're looking for for a lot of  
5 our health conditions.

6 I know that a lot of clinicians are  
7 doing research and when we can all sit at the table  
8 and understand what each other is talking about, I  
9 really do think that allow a generation of novel ideas  
10 and new methodologic approaches, then, can potentially  
11 be explored.

12 MEGHANA CHALASANI: Thank you,  
13 Michelle. I do want to touch upon whether there are  
14 any gaps, methodologically, approach-wise, for  
15 example. Are there any gaps, something that you  
16 thought you would see in this series, perhaps? Pandu?  
17 I see Stephen and Pando going.

18 PANDU KULKARNI: Go ahead.

19 STEPHEN COONS: Well, I do think that  
20 there are some of us here in the room that would like  
21 to see a little more on the analysis side and there's  
22 obviously a couple of examples in the appendix. And

1 again, this was mentioned earlier in terms of the  
2 first example, uses the estimand framework but it is  
3 more theoretical and doesn't have a complete sort of  
4 analysis plan laid out and it's not an actual  
5 approval; whereas, the second is a CBER approval,  
6 Luxturna.

7           And it is more concrete but it is not  
8 sort of laid out in the estimand framework and Kevin  
9 Weinfurt mentioned this this morning that he liked the  
10 example in Appendix 1 because it did have that  
11 framework and the example in Appendix 2 was less  
12 organized. But I think there could be a happy medium  
13 or both of those could be brought to the point where  
14 they really provide much more detail in terms of,  
15 particularly in the first one, how a concrete example  
16 could be provided that actually ended up with a label  
17 claim for a drug.

18           And then the other issue is just that  
19 there are many examples or several examples in terms  
20 of what FDA doesn't want to see like responder indexes  
21 and, essentially, percent change from baseline. But  
22 it would be nice to have just some more detail about

1 really what are the ones that FDA would expect to see  
2 and prefer to see, and I just think a little more  
3 detail there would be helpful.

4 MEGHANA CHALASANI: Thanks, Stephen.  
5 Pandu, did you still want to chime in?

6 PANDU KULKARNI: Yeah, so just one of  
7 the key things that would happen as we go into COA and  
8 then the digital is going to be tremendous amount of  
9 variation and missing data. Missing data. You look  
10 at the audience now. At the beginning of the trial  
11 was full. Now, it's about 50 percent missing. So the  
12 question is, how do I deal with that 50 percent  
13 missing and how do I motivate them to stick around in  
14 a clinical trial to the end of the trial? If not, how  
15 do I deal with it?

16 I think that part is really critical  
17 for us, and I think here in this example, it's going  
18 to be more and more critical, so I think we should head  
19 on, address some of that in the guidance because other  
20 ones, you can take into account and do what we have  
21 been doing in the clinical outcomes, but this, I  
22 think, is going to just be very, very tough to deal

1 with if we don't address it from the beginning.

2 So guidance should probably start to  
3 think about, how do I deal with the missing data, what  
4 kind of importation should I do, not do, and how do I  
5 deal with aberrations in the data if people are  
6 wearing Fitbits, it can go off for some reason wacko.  
7 What do I do with that data? There is no  
8 (indiscernible) on that data and therefore, what do I  
9 do with it?

10 I think those methodologies we haven't  
11 really developed them for big data, so I think that is  
12 something that we should figure out how to do that as  
13 a community and address some of the technical issues.

14 MEGHANA CHALASANI: Thanks, Pandu.

15 Telba, did you want to --

16 TELBA IRONY: Yeah. I suggest it's  
17 part being participating in something that occurred to  
18 me as a gap when we're talking about end points making  
19 into the labeling, the guidance that is currently  
20 useful, the document emphasizes the hierarchy and  
21 hypothesis testing and always talking about making it  
22 to the labeling because you have to have several end

1 points and make it to hierarchy and it doesn't address  
2 a (indiscernible) framework in which you not  
3 necessarily testing hypothesis but you're talking  
4 about joint distributions of several end points.

5 So I think that will be helpful  
6 particularly when we are talking about strict control  
7 type one error which is very hard when we're talking  
8 about rare diseases in which the populations are small  
9 and the samples are small. So have to deal with more  
10 uncertainty in the strict hypothesis testing won't  
11 work as well. So that's one gap that we might want to  
12 address and the other one relates to what I said  
13 before, maybe we have to think about the another  
14 guidance on patient input and patient preferences, how  
15 to address benefit/risk, but maybe this is a big  
16 undertaking and we'll have to think more broadly about  
17 how to collect patient preferences to address  
18 benefit/risk determinations.

19 MEGHANA CHALASANI: Thanks, Telba.

20 Laura Lee?

21 LAURA LEE JOHNSON: Sure. So I wanted  
22 to go back to this idea of thinking about, like, the

1     intercurrent events or missing data and things like  
2     that and part of what we need your feedback on is  
3     thinking about, like, some elements of missing data,  
4     like, this is bread and butter. It doesn't matter  
5     what your end point is. You got to deal with missing  
6     data in certain ways.

7                     One part of what we tried to focus on  
8     in the discussion document is what are the weird parts  
9     of those COA-based end points? So like you mentioned,  
10    Pandu, like all right, now I have this accelerometer.  
11    What do I do with this as I'm trying to combine it and  
12    I'm trying to measure their walking or something like  
13    that? So these are the types of things that, you'll  
14    notice there are a lot of cross references in the  
15    document and we would like feedback because we can't  
16    kind of address everything-everything, but to the  
17    point we also don't want folks to kind of miss that  
18    they need to attend to something as well.

19                    So just thinking about, again, that  
20    balance, but this is a big element of saying for a  
21    COA-specific end point, different than other types of  
22    end points, what do we really need to attend to,

1 because as you said, people haven't been thinking  
2 about it, so what are the reminders we need to give  
3 them, specifically because what they're trying to work  
4 from is that clinical outcome assessment?

5 MEGHANA CHALASANI: Thanks, Laura Lee.  
6 Katarina?

7 KATARINA HALLING: So just a quick  
8 comment on one of the things I think would be really  
9 helpful and that is, as much as we want, we would  
10 always like to move into our Phase 3 with perfectly  
11 fit for purpose COAs, but we all know that that's not  
12 always the case.

13 With the speed of drug development, in  
14 order to get new medicines to patients as quickly as  
15 possible, there are sometimes things that we can do in  
16 parallel to Phage 3 and I think it'd be great if we  
17 could have some commentary from the FDA on some of the  
18 acceptable things that you would be open to there,  
19 both statistically but then also in terms of  
20 confirming qualitatively in parallel to Phase 3 in  
21 order to have all the evidence when we need to look at  
22 the results together.

1 MEGHANA CHALASANI: Thank you. Does  
2 anyone else from the panel -- Stephen?

3 STEPHEN COONS: I just wanted to say  
4 that I was so glad to see a section -- and it's a  
5 placeholder for now -- on computerized adaptive  
6 testing because I think that is something, and I'm  
7 hoping that there are people in this room or people  
8 that are hearing this that will provide content to the  
9 docket that can be put into that section because I  
10 think it's incredibly important in the future because  
11 we are, through computerized adaptive testing, we  
12 would be able to have essentially short forms that are  
13 more personalized for the respondent.

14 And so I think that would help us in  
15 many ways and I'm glad to see through this document  
16 that the FDA is at least receptive to hearing more  
17 about the use of that in clinical trials.

18 MEGHANA CHALASANI: Thank you, Stephen.  
19 I do want to start asking folks if you have questions  
20 in the audience, please feel free to make your way to  
21 a microphone. I do want to leave ample time for  
22 folks. In the meantime, I do have one additional

1 question for our panelists. I mean, I have several,  
2 but start with one.

3 One of the more, beyond methodological  
4 aspects that the guidance series was tasked with kind  
5 of including was more procedural or process related  
6 which was getting at considerations for formatting and  
7 submitting the data as part of an application. And so  
8 I wanted to look to, primarily, our industry  
9 colleagues, the ones kind of putting applications  
10 together and submitting them, if those considerations  
11 are coming across clear in the guidance documents or  
12 if there's any gaps or any additional feedback that  
13 you have in that regard.

14 I don't know if, Katarina, you want to  
15 provide feedback or if Pandu wants to go first.

16 KATARINA HALLING: I think they're  
17 there. Again, I'd like to see even more clarity  
18 around where patient input actually influenced a  
19 decision. I think the patient experience table is  
20 very useful, but I think that's one of the things that  
21 we could probably improve more to be more clear on how  
22 patient focused we actually were throughout the

1 process.

2 MEGHANA CHALASANI: Thanks, Katarina.  
3 Pandu, anything to add? Oh, we have folks at the mic.  
4 Kim? Question?

5 KIM MCCLEARY: Hi, all. Kim McCleary.  
6 Marc and I haven't had the chance to tag team  
7 recently, so I'm going to take advantage of the  
8 opportunity to do that and just echo some of his  
9 thanks and congratulations to FDA for not only this  
10 series of documents but the tremendous progress that I  
11 think is very palpable in the room today.

12 Just a few observations of seven or  
13 eight years ago when we started down this road, you  
14 had CDER with the Patient-Focused Drug Development and  
15 CDRH with patient preference initiative and now look,  
16 all three product centers at the same table talking  
17 about these topics. Like, woohoo.

18 And thinking about kind of this higher  
19 level of what's the narrative, what's the story line,  
20 like, let's not lose sight of the fact now there are  
21 eight guidances, I think, total -- three from CDRH,  
22 and if you add the one about the guidance for

1 guidances to the four, that's a lot of information, as  
2 Marc said, a lot of direction and a clear signal to  
3 sponsors and industry and academia that you guys mean  
4 business as a whole agency.

5           This isn't some narrow little thing.  
6 What else have you written eight guidances on in the  
7 last seven or eight years as a package? And I think  
8 there's kind of a higher-level story that could be  
9 told about just this transformative process. I've  
10 heard Janet talk about it and Jeff talk about, it's  
11 changed the way you think about things. It's not only  
12 changing sort of SOPs and maps and your internal  
13 documentation, but it was really powerful today to  
14 kind of sit and hear the dialog and I had to go back  
15 to my agenda to figure out that comment that eight  
16 years ago would've only come out of a patient  
17 advocate's mouth is now coming from Michelle Campbell  
18 or it's coming from somebody from industry or it's  
19 coming from an academic.

20           Like, we've all put on different hats  
21 and switched roles and I think that's a powerful sign  
22 of change and the culture, and maybe it is a little

1 concentrated here in this room and a little more  
2 diffuse out in the other parts of the ecosystems we  
3 travel in, but it's meaningful and I think it is a  
4 sign of how to get the rest of our colleagues to move  
5 along with us.

6 So those are just come comments on  
7 maybe --

8 MEGHANA CHALASANI: Thank you.

9 KIM MCCLEARY: -- a little amplified of  
10 your (indiscernible).

11 MEGHANA CHALASANI: Thank you, Kim.  
12 Anyone want to -- no? Okay. We have one question in  
13 the middle.

14 CAROL MANSFIELD: This is more of a  
15 comment than a question. I'm Carol Mansfield from RTI  
16 Health Solutions and I wanted to echo what Telba said.  
17 The guidance documents cover a lot of ground, but one  
18 big hole is patient preference studies and I hope that  
19 that's on the list of things you're developing for the  
20 future.

21 MEGHANA CHALASANI: Thank you. R.J.?

22 R.J. WIRTH: Hello. First, I want to

1 echo what Stephen said about including computerized  
2 adaptive testing. I think it's great that it's a  
3 discussion and that it's in there and that we can  
4 provide more information, which leads to my question.  
5 It's been around for a long time. We know a lot about  
6 it, so with regards to what type of information would  
7 be most beneficial, if we can comment on that, to be  
8 submitted as part of the docket. Is there anything in  
9 particular that FDA might be looking for or is it just  
10 sort of, flood you with information?

11 MEGHANA CHALASANI: I'll turn to my  
12 panelists. Laura Lee?

13 LAURA LEE JOHNSON: I beg of you not to  
14 flood us with information. What I do want, though,  
15 information that can be copy and pasted is good, so  
16 think brevity, but usefulness. Not a thousand pages.  
17 But there's a difference between, you can have a lot  
18 of data and no information or a whole lot of  
19 information, right. What's key here and I think what  
20 the struggles are that we hear actually from industry  
21 more than just ourselves is how to implement in a  
22 clinical trial.

1           So as you're thinking about what to put  
2     in there, think about if you have a multiregional --  
3     so this is an international, to use a less crazy terms  
4     -- you have an international trial. I got rare  
5     disease patients. I might have people, all sorts of  
6     different groups. I might have issues with  
7     connectivity. I might have all these other things.

8           How do you pull it off? So think  
9     about, and we hear concern about this, and also for  
10    most of you, like this is FDA guidance but I also want  
11    you all to think about what you've heard from other  
12    regulatory authorities or payers, et cetera, because  
13    as many people have mentioned, this information is  
14    going to move forward and the type of feedback we  
15    sometimes hear is, they know -- although, as you all  
16    mentioned, the point is not to stay where we've been  
17    but where we should move forward -- but they know  
18    they're going to be okay with this five-item short  
19    form.

20           So they're just going to go with that.  
21    And so to really understand and also when we're  
22    thinking about the real-world evidence, so now I've

1 got the tool but then we've got people that are  
2 collecting data in medical records and so it's part of  
3 a registry and a natural history study and now they  
4 want to use that as an external control or they're  
5 borrowing part of the information or they're trying to  
6 design their clinical trial, so how do we really  
7 implement it from a logistic standpoint, just like a  
8 lot of the DHT part, the digital health tools that we  
9 were talking about, but also think about the trial  
10 designs it could be used in and how we can also reuse  
11 data.

12           It's the reduce, reuse, recycle  
13 phenomenon. But it's in there because we don't want  
14 to say no, and too many people think the answer is  
15 just no and the answer's not just no. What we want to  
16 hear from you all is, what are the details, what are  
17 the struggles, what are the considerations, because a  
18 lot of what this document really is going to be in  
19 order for it to have a shelf life past the date of  
20 publication is to really say these are the processes  
21 and considerations.

22           So go forth and think and plan with

1 this in mind. Does that help?

2 R.J. WIRTH: A little bit. I mean,  
3 obviously, I will --

4 LAURA LEE JOHNSON: Yeah.

5 R.J. WIRTH: I won't send a thousand  
6 pages, half that maybe. All right, but it's curious  
7 and to hear about issues with connectivity and such, I  
8 mean, given that everything be app based now, that  
9 essentially ePRO, right, it's just either you get all  
10 the items or some of the items, but outside of that  
11 it's just ePRO. But I think in terms of just  
12 understanding sort of design and working that in, that  
13 will help sort of focus our submission.

14 LAURA LEE JOHNSON: And I'll also say,  
15 again back to the Guidance 3 and Guidance 4 part, a  
16 lot of the basis of computerized adaptive testing is  
17 item response theory and so thinking about all the  
18 different elements of that, if you want to write  
19 something that you think may be more Guidance 3 than  
20 Guidance 4, that's fine. We're open to that. Go  
21 ahead and send it in. Just tell us where you think it  
22 goes.

1 R.J. WIRTH: Thank you.

2 MEGHANA CHALASANI: Thanks, Laura Lee.

3 Did anyone else from the panel want to add to that?

4 Okay. We had one question up here.

5 KATY BENJAMIN: Hi, Katy Benjamin from  
6 AbbVie. There are a couple places where I'd really  
7 like to see more information. I was really hoping  
8 that there may be some additional guidance  
9 methodologically for the use and validation of other  
10 types of COAs besides PROs, especially  
11 (indiscernible).

12 I think that there are some real  
13 differences and challenges in validating these kinds  
14 of measures for use in clinical trials as patient-  
15 centered end points and how we go about proving that  
16 the kinds of things that are measured in these types  
17 of instruments actually are relevant and important to  
18 the patient. I don't think it's straightforward and  
19 I'd really like to see more work on that.

20 The other thing that I'd really like to  
21 see more on, because I think we're all struggling, is,  
22 as the panel has just acknowledged, the label is not

1 really sufficient to give patients a good idea as to  
2 the risks and benefits of a specific treatment. And  
3 we were talking about how else we can provide that  
4 information. Well, we now know how to collect all  
5 this PFDD stuff.

6 How do we actually present it to the  
7 regulators? How will it make it into the label or  
8 some other public format so that people can have this  
9 additional information?

10 MEGHANA CHALASANI: Thank you for that  
11 comment. Did anyone on the panel want to respond?  
12 Laura Lee?

13 LAURA LEE JOHNSON: So I do think a lot  
14 of the details you talked about in your first part of  
15 the comment really go more towards Guidance 2 and  
16 Guidance 3, but we note that and we'll try to make  
17 sure as we're getting those out the door -- and I  
18 can't remember if the docket for the draft of Guidance  
19 2 is still open or not --

20 MEGHANA CHALASANI: It's open until the  
21 end of the year.

22 LAURA LEE JOHNSON: It's open until the

1 end of the year. This is why we love Meghana, because  
2 she remembers all these --

3 MEGHANA CHALASANI: One of the reasons.

4 LAURA LEE JOHNSON: But I would  
5 encourage you to put that in there because that, to  
6 look back through the draft of Guidance 2 to also see,  
7 especially if it's, like, do patients really find this  
8 important and are we gathering that for the non-PRO  
9 COAs, take a look and see kind of if that is tied in  
10 there well enough, and if not, give us your thoughts  
11 on how we could do it and put that in the docket, too.  
12 Thanks.

13 MEGHANA CHALASANI: And Marc?

14 MARC BOUTIN: Just very quickly to your  
15 last point, I don't know what the answer is but I  
16 think it is critical that we not only make sure that  
17 the information that is useful for other stakeholders  
18 -- payers, providers, patients -- makes its way into  
19 the public domain. One of the things that's so  
20 exciting about the work that has been done here at FDA  
21 is it has global ramifications, not just in drug  
22 development but in how we think about the health

1 ecosystem, how we deliver care.

2           And if we're ever going to get to the  
3 place where we really need to be, we need that  
4 information that is the foundation of all health  
5 interventions and it's the clinical research, and it  
6 needs to make it into the delivery system. And that  
7 doesn't all belong to FDA by any stretch of the  
8 imagination, but there's a key linkage to the entire  
9 ecosystem that is critical and it goes back to that  
10 intimidation piece.

11           If that information is there and it  
12 makes a difference to who is paying for care and who  
13 is delivering care and who is receiving care, and it's  
14 ultimately paid for, your companies are going to make  
15 sure that you do this in a systematic way from front  
16 to end in research. That's how intimidation gets in  
17 and shifts culture.

18           So I think this is a key element and I  
19 think we have to think carefully how we do it and I  
20 think it goes beyond the FDA.

21           MEGHANA CHALASANI: Thank you, Marc.  
22 We had one question up here.

1                   MAN: Hello. This (indiscernible) from  
2 Gilead Medical Affairs Outcome Research Department.  
3 Actually I was trained 15 years ago as a Bell  
4 statistician, so here, I actually have two questions  
5 regarding in the current events here. And the first  
6 thing I think I would also acknowledge that several  
7 panelists already mentioned that these guidelines  
8 pretty much focus more on randomized clinical trials  
9 instead of real-world studies, right?

10                   And I think after reading through these  
11 guidelines, I think one thing probably is currently  
12 missing is loss followup in real-world studies, like  
13 observational studies, especially for these patient-  
14 reported outcomes or COAs simply because of lack of  
15 motivation of the patients because in randomized  
16 control trials, it could be like a compulsory  
17 (indiscernible) driven procedure, but in such kind of  
18 a real world observational studies, it is not.

19                   But it's also sometimes not part of the  
20 daily, normal clinical practice so here, my question  
21 is to the panelists. It's how we can mitigate such  
22 kind of thing in, like loss followup because of lack

1 of motivation from the patients and I mean, sometimes  
2 according to our experience, I mean the response rate  
3 from patients could be as low as, like, 10 percent, 20  
4 percent from such kind of real-world observational  
5 studies. I mean, how low that the FDA or the  
6 panelists think that is it acceptable as such kind of  
7 COA studies? Thank you.

8 MEGHANA CHALASANI: Thank you. Laura  
9 Lee?

10 LAURA LEE JOHNSON: So, everything is  
11 situational dependent, so you're not going to see a  
12 line of how low can you go. But I do think we can do  
13 somewhat of a FAQ with some of us, the frequently  
14 asked questions or something like that. I would say  
15 that nothing is ever compulsory, really. One of the  
16 first trials I worked on, and we had a lot of COAs in  
17 there, so there was a huge burden.

18 This was an observational study and  
19 it's a huge burden on the people that were involved in  
20 it. And what we found, actually, was as people got  
21 better, they didn't have time to sit down and fill out  
22 all that stuff. They went back to work. So people,

1 like, oh, you're missing data must be the sicker  
2 people. And as we dug into it, I was like, no.

3 So this, though, gets back to also  
4 thinking about trial procedure, so regardless of what  
5 data you're missing, is thinking about talking and  
6 engaging all of these patients throughout the entire  
7 development of the trial, is this what they want to  
8 answer. Can they do it? How are we facilitating  
9 their being able to continue their participation?

10 So a lot of these issues, they're not  
11 like statistics. We're the dead end time. Like, now  
12 we don't have a choice. We've got to figure out how  
13 to fix it. The best time to do that is way earlier in  
14 that trial planning and having the consistent  
15 engagement and realizing also, like, hey, we're  
16 starting to see a problem.

17 Let's talk to our patients, do those  
18 exit interviews, do other things, and figure out,  
19 okay, we thought we planned well enough but now we see  
20 a problem. How can we redo it? And that's, in some  
21 ways, beyond the scope of this but in some ways it's  
22 tied. But thank you for your comments.

1 MEGHANA CHALASANI: I did speak with  
2 Mary Jo who's the moderator for the open public  
3 session after this and she gave me permission to go a  
4 few minutes over. So Pandu, did you want to add here?  
5 Oh, okay. Michelle, go ahead.

6 MICHELLE TARVER: So I think my point  
7 is going to be very short. I think it's important to  
8 measure what patients care about and we've talked  
9 about that already and you heard Telba already allude  
10 to ways that you can potentially approach that with  
11 patient preference information to inform those  
12 outcomes if you have to prioritize, then you can  
13 prioritize with what's most meaningful to them.

14 CDRH and CDER put out a guidance  
15 document on patient preference information. I  
16 encourage you to look at that if you're looking for  
17 some information on what that's about and how it could  
18 potentially be used in a regulatory context.

19 MEGHANA CHALASANI: Okay. Marc?

20 MARC BOUTIN: Just super quickly  
21 because I think you guys nailed that response. When  
22 you have a situation and you want to interpret it, you

1 always have to bring in the patient community or  
2 you're going to make mistakes. One of the classic  
3 examples I hear from the AI folks is, we can tell you  
4 when the child puts a wearable on the dog. That's  
5 great. Can you tell me why the child put it on the  
6 dog? No. But if you engage the children and their  
7 family caregivers, you can figure that out.

8 So bring us in to help you interpret  
9 those issues. We can make a big difference.

10 MEGHANA CHALASANI: Thank you. And  
11 Pandu, you wanted to jump in?

12 PANDU KULKARNI: Yeah, so I was going  
13 to just say the best missing data is no missing data,  
14 and so we got to start, as Laura Lee said, from the  
15 beginning itself. I think we don't spend enough time  
16 and research this on making sure that we get all of  
17 the data. Having said that, I actually, Marc, I think  
18 we could use patient advocacy groups and other groups  
19 that can help us with motivating the patient to stick  
20 around and provide the data so that it is useful.

21 Sometimes, it is not lack of  
22 motivation. It is because they got better and they

1 didn't fill out and sometimes it is because they are  
2 just terribly feeling bad and therefore they leave.  
3 So there's a reason why they're leaving. We just  
4 don't know many times why they're leaving. And  
5 sometimes, it is just they're losing, leaving out  
6 somehow.

7                   So I think utilizing some of the  
8 patient advocacy groups, we have not, I think,  
9 typically done that but probably we should start doing  
10 that to see how we can motivate the patients, although  
11 the patients are very hard to reach throughout the  
12 globe when we are doing a global study, but we should  
13 do something about it.

14                   MARC BOUTIN: Cocreate and we'll help  
15 you motivate.

16                   MEGHANA CHALASANI: Laura Lee?

17                   LAURA LEE JOHNSON: And I know we have  
18 one more person, but I want to add into this, thinking  
19 back to that estimand discussion, which is to also go  
20 aback as you're doing this because systematically  
21 collecting and following up and understanding where  
22 people ended up, you may be missing that particular

1 score but I have a whole lot of information and now  
2 you can turn that and say, okay, what's really that  
3 research question that we need to address. What  
4 really should the end point and the summary be.

5 And especially if you've done that  
6 prework, a lot of times, we know what could happen in  
7 advance, but did you actually work that into your  
8 estimand? Are you sure you can really address the  
9 right research question, the one you're going to end  
10 up with in the end? A lot of times, we can pre-think  
11 this and we should, but it's when that information  
12 isn't collected, it's not worked into there, because  
13 it takes money, it takes time. But that's something  
14 that if you want to do it robustly, sometimes we get  
15 that, we use it, and we can do that.

16 MEGHANA CHALASANI: Thanks, Laura Lee.  
17 And so for our last question, I'll just go to the  
18 middle right here.

19 MAN: Yes.

20 MEGHANA CHALASANI: And after that,  
21 we'll have to --

22 MAN: Yes. (indiscernible), Clinical

1 Survey Outcomes. Just like to follow up on Katarina's  
2 points in terms of the qualitative research and how  
3 that activity can support the drug development, not  
4 only in terms of meaningfulness but also to get a  
5 better understanding on the PRO responses and to  
6 challenge the product profile as well, because when  
7 you are in drug development, in the early stage of the  
8 drug development, there are great uncertainties around  
9 the product profile and the confidence intervals are  
10 very large and then, which PRO instruments should you  
11 then include.

12           And that is very often a challenge and  
13 are there additional benefits that are not seen on the  
14 product profile that you do not know. What you do  
15 when you're in this situation, I've been there several  
16 times, well, then you include some quality of life  
17 measure and treatment impact measure that has been  
18 validated already and then you hope that that will  
19 capture what you hope that the product actually will  
20 have a benefit.

21           But then, it's included in the early  
22 trials, these safety trials and they are conducted in

1 small samples, so the struggle continues. You  
2 actually sit there with PRO results once these result  
3 comes out and because of low sample size, you can  
4 only, at best, see trends in some of the scores. And  
5 for lack of better knowledge, what do you do? Well,  
6 then you include the same PROs in the following large  
7 clinical trials.

8           And then you may actually hear that  
9 patients come back and say, well, we have a struggle  
10 understanding the questions in the generic messages  
11 because we cannot relate to them. And then you  
12 actually then get the results. You may actually have  
13 (indiscernible) coming over and saying, oh, we're very  
14 excited. We have scoring, SF-36, moderate physical  
15 pain by 0.2. What does it mean?

16           I don't know. Is it less pain in the  
17 joints, less pain in the heads or stomach? Cannot  
18 tell. And then the product comes on the market and  
19 then only to realize that oh, there was an additional  
20 benefit that the standardized PRO instrument did not  
21 measure. Oh, we found out there was, the population  
22 that we thought would appreciate the product actually

1 turned out to be completely different and all because  
2 we didn't listen to the patients at some point.

3 And that's why to encourage you to put  
4 more emphasis on listening to the patients actively in  
5 the drug development, not only just using PROs. Thank  
6 you.

7 MEGHANA CHALASANI: Thank you for that  
8 comment. (indiscernible). I think with that, I think  
9 since I've taken enough of Mary Jo's time, I would  
10 like to wrap up our session. I want to thank all of  
11 my panelists. Thank you all so much for your  
12 participation and to the audience for being so  
13 engaging. And in case you have not heard, we have a  
14 public docket associated with this workshop and it's  
15 open until February 4th of 2020, so we encourage you  
16 to submit additional comments to the docket.

17 And with that, I'd like to invite Mary  
18 Jo.

19 MARY JO SALERNO: Good afternoon,  
20 everyone. As Meghana just stated, my name is Mary Jo  
21 Salerno and I work in CDER Office of Biostatistics. I  
22 have the honor of moderating the public comment

1 session and the tail end of this workshop. So for  
2 those of you that are not aware, the purpose of the  
3 public comment session is to allow an opportunity for  
4 those who have not had a chance to speak on issues  
5 that are not related to our main discussion topics of  
6 the workshop.

7           Please keep in mind we will not be  
8 responding to the comments, but they will be  
9 transcribed and be part of the public record. We'd  
10 like this to be a transparent process, so we encourage  
11 you to note any financial interests that you have  
12 related to your comment. If you do not have such  
13 interests, please state that for the record and if you  
14 prefer not to provide this information, you may still  
15 provide your comments.

16           We've collected sign-up before the  
17 meeting and during the break. We have four  
18 participants signed up and about 20 minutes for the  
19 sessions, so that'll be approximately four-minute time  
20 limit for each. We'll be keeping track of time. I'm  
21 not sure if it's really necessary, but -- two minutes?  
22 Okay, all right. I stand corrected. I was just

1 dividing 20 by four, so I guess this will just be a  
2 shorter comment period, so thank you for clarifying.

3 I'll ask you to wrap up, and as we've  
4 stated numerous time, the public docket is available  
5 for further comment and we encourage you to comment  
6 through the public docket. The public docket closes  
7 on February 4th, 2020.

8 So we're going to take our comments  
9 from the microphone in the middle aisle and if someone  
10 is not able to get to the middle aisle for mobility  
11 reasons or other reasons, we'll hand you the  
12 microphone. I'll run through the order of the  
13 commenters. Please note the name of the commenter  
14 before you and be prepared to line up at the  
15 microphone when he or she begins commenting.

16 So we have Andrew Trigg, Carrie  
17 Barnhart, Danielle Meyer, and David Reasner. So if  
18 Andrew Trigg can please go to the microphone?

19 ANDREW TRIGG: Yep, thanks. Yes, so I  
20 have no financial interests, first of all, but yeah as  
21 a bit of a disclaimer, I think I signed up to this  
22 this morning, but with hindsight it's something that's

1 been discussed quite a lot already today, so I'll keep  
2 it brief.

3           Yeah, so I'm a statistician working in  
4 consultancy and I think one kind of challenge we face  
5 and the challenge quite kind of linked to what's in  
6 the guidances is convincing pharmaceutical clients  
7 that it's okay to have kind of mean-based between  
8 group difference kind of end points in terms of your  
9 actual kind of hypothesis testing.

10           And I think based on what people have  
11 said today, it seems that there is agreement that it's  
12 okay to do that and your within patient stuff can just  
13 be, I suppose, supplementary, like you want to have  
14 it. But really, when looking at a guidance and when I  
15 think a lot of people we speak to read the guidance,  
16 you've got about a quarter of it is within patient  
17 meaningful change and it can seem, I think, that that  
18 is the only thing that the FDA are interested in  
19 looking at.

20           So I think a recommendation from really  
21 the statisticians in my team is to kind of make the  
22 discussion between the differences a bit more

1 prominent in the main body. I think at the moment,  
2 it's a bit kind of hidden in the appendix or in little  
3 areas and to tie in with that, really thinking about  
4 clinical relevance in terms of between group  
5 differences.

6           Again, there's so much focus on what is  
7 meaningful with patient change, but also tying that  
8 back and saying, ultimately, we will sometimes want to  
9 look at between group differences and means, but we  
10 also need a threshold for that as well. But we'll put  
11 that in the docket. Thanks.

12           MARY JO SALERNO: Thank you for your  
13 comment. Next, we have Carrie Barnhart. Carrie, are  
14 you here? I don't see anyone at the microphone.  
15 Okay. It looks like Carrie is not here. Danielle  
16 Meyer? Yeah, I don't think that Danielle is here,  
17 either. So we'll just have one more comment and that  
18 is David Reasner.

19           DAVID REASNER: Well, I'm laughing  
20 because actually my comment was covered in one of the  
21 more recent panel sessions, but not because there was  
22 a vacuum, but in response to the other comment, I'll

1 make a short comment, and I don't have any marketed  
2 products or affiliations other than I work at Imbria  
3 Pharma.

4           The comment, a number of panelists  
5 commented on this dichotomy between testing for mean  
6 differences and testing responder end points, and I  
7 actually think we muddied the waters today, so maybe  
8 it is worth making a comment. It makes sense to study  
9 mean difference if you're hypothesis testing and you  
10 need a primary end point. And I'm glad to see that  
11 that's represented in the discussion document because  
12 that's usually my recommendation to teams.

13           But that said, we do a lot of work to  
14 come up with a clinically meaningful improvement  
15 talking to patients, so we should use that in  
16 interpreting that mean difference. And in fact, in  
17 explaining these topics to folks, I've come to believe  
18 that the easiest thing to say is, there's no such  
19 thing as a clinically meaningful difference at the  
20 group level.

21           It only matters if an important number  
22 of patients get dragged over the threshold of an

1 important threshold clinically. So in that sense, put  
2 that end point wherever you want, but you won't  
3 understand your trial until you look at a range of  
4 response that's been endorsed by patients. So I guess  
5 that's the two cents.

6 It's really just one set of data. They  
7 aren't different data. In fact, there's pseudo  
8 specific. So it's two faces of the same coin and you  
9 can test the mean difference, but please look at a  
10 responder definition prior, preferably a declared a  
11 priori. Thanks.

12 MARY JO SALERNO: Thank you for your  
13 comment. Okay, so brief public comment session, I am  
14 going to now turn over the microphone to Laura Lee  
15 Johnson for our closing remarks of the day.

16 LAURA LEE JOHNSON: So thank you all  
17 for sticking around this late, I will say. And I want  
18 to give first a little bit on process because as we've  
19 mentioned many times, please send us your comments.  
20 This is what that page looks like and so for you or  
21 anyone who wants to provide comments either on the  
22 meeting itself, so what you're heard here today, on

1 the discussion document, send the details.

2 Please list things like the section of  
3 the document if that's what you're talking about, the  
4 line number so we can more quickly work to combine the  
5 comments and address them as we work on draft  
6 guidance. And if you think that your comment might be  
7 relevant to other guidances in the series, just let us  
8 know that, too, or other guidances in general.

9 Now, just to give you a little bit of  
10 feedback, when the draft guidance also publishes,  
11 there will be a docket for public comment there as  
12 well, so this is not the one and only time to give  
13 comment. There will be multiple opportunities to give  
14 comment. You can also look at our Patient-Focused  
15 Drug Development web page for more details on the  
16 process.

17 So I do want you all to remember we  
18 have questions for you. And the guidance format's an  
19 important one. We also want to hear your  
20 recommendations on the content in addition to the  
21 style and format. If you have a great, plain language  
22 way to express something, a good example from any type

1 of medical product, especially examples of  
2 communications and patient input and involvement,  
3 we've heard a lot about that today, please submit  
4 those.

5           And it might be a device, drug or  
6 biologic product, but we also have a lot of consults  
7 and do a lot of work with our friends and food safety  
8 and veterinary medicine, so it is open to lots of  
9 different products. But please send it to us. And  
10 your experiences and thoughts. That's what's really  
11 helpful and moves us forward and it helps shape the  
12 guidance that, not only we need right now, but that's  
13 going to help it remain relevant as we're moving  
14 forward.

15           So let us know, but I also want to take  
16 this as the opportunity to thank the village that got  
17 us to this moment. Usually this is when everyone  
18 starts packing up, but I want you all to pause as some  
19 folks in the last session mentioned to consider how  
20 broad and deep the commitment to this effort goes.

21           Across the FDA, it's not just a couple  
22 of pockets here and there, across the entire FDA,

1 people lent us their best scientists but also their  
2 best process people and contractors and a lot of  
3 times, we're asked, like, are the clinical review  
4 divisions really bought in. And we hope that today  
5 you'll have seen that we're at the leadership meetings  
6 on a lot of different levels at the primary reviewer  
7 meetings that we are all together in patient-focused  
8 drug development. It's a key part of our FDA mission.

9           And while hiring and pay continue to  
10 always be concerns, FDA employees are 100 percent  
11 mission. So I want to give a few thank yous to Mary  
12 Jo Salerno who was just up here who's our project  
13 manager who oversees all these different moving parts,  
14 the CDER Office of the Center Director, especially,  
15 Mina and Meghana, you all have provided so much in the  
16 terms of the logistics and policy oversight and  
17 getting us and all these documents here today. And  
18 that's true especially for Meghana for this entire  
19 series that she's worked on.

20           The Office of Translational Sciences,  
21 where I live, our Office of Administrative Operations  
22 Travel Team, the Office of New Drugs has the public

1 meetings team, so you saw them running around all here  
2 today and when you signed in, they were there. And a  
3 lot of people across a lot of different offices and  
4 FDA have supported these guidance efforts. We've had  
5 contract supports now for copy editors and technical  
6 writings including Rick Turner who's sitting here and  
7 helping us edit and shape the workshop document.

8 CDRH said, here's our digital health  
9 team. Here's our patient science and engagement lead.  
10 Like, we're going to spend our time doing this and  
11 CBER. We have our Science of Patient Engagement leads  
12 and other comments and other information from other  
13 centers keep coming in because the basis of the  
14 document that we had for today's workshop came from  
15 the comments FDA's given to sponsors and patient  
16 groups.

17 Over a hundred different reviewers  
18 across statisticians and social scientists and data  
19 standards experts, clinicians, psychometricians, and  
20 more, across all these different therapeutic areas and  
21 product types contributed comments that have been  
22 written over the last few years and also what they saw

1 on the horizon.

2           Several leaders at FDA read all of  
3 that, gave a lot of feedback on that. We had a seven-  
4 person writing team that took the charge, over a  
5 hundred pages of lots of different information and  
6 their own expertise to try to put this together with  
7 20-plus people across three centers and a lot of  
8 different offices editing and making additional  
9 comments to make the document a reality, and we  
10 couldn't sustain this effort without the feedback and  
11 support of our FDA center directors.

12           And that also is the feedback and  
13 support we've gotten both from patients, industry,  
14 academics, and others, many of those organizations  
15 that you saw here today. But there are other people  
16 that I also want to thank: Michelle Tarver at CDRH,  
17 Telba Irony at CBER, and my special thanks to Theresa  
18 Mullin at CDER because over 10 years ago, she took  
19 this charge and she took the voices of many,  
20 internally and externally moved this forward.

21           And I also want to give my special  
22 thanks to Scott Komo. So none of this work would've

1 happened without his leadership, his staff mentoring,  
2 and dedication, the countless hours of public service.  
3 And I can fully express the gratitude. Sorry, I told  
4 myself I wouldn't cry, but I knew I would. The people  
5 who know me, know that. But I can never really  
6 express the gratitude he's due because he's been and  
7 remains the scientific leader helping the public get  
8 that accurate and science-based information they need.

9           And it's also, I have to thank our  
10 families because they put up with a lot of long hours  
11 for us to make this happen. But back to what we need  
12 from you.

13           We need you with all the time and care  
14 that you can, that means we know what we've done is  
15 not perfection and we need help. So we want to hear  
16 from you by 11:59 p.m. Eastern. I say that because I  
17 was once on the Pacific time zone and didn't get my  
18 stuff in on time. So now, I remind people. But we do  
19 want, value, and need your input.

20           So on behalf of the thousands of  
21 employees at FDA, thank you for coming today. Send us  
22 your comments to the docket. We read them. We want

1     them written down so we can prepare the best draft  
2     guidance possible.  And thank you for your continued  
3     effort and work in this area.  Have a good evening.

4                     (Whereupon, at 6:08 p.m., the  
5                     proceeding was concluded.)

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## CERTIFICATE OF NOTARY PUBLIC

I, MICHAEL FARKAS, the officer before whom the foregoing proceedings were taken, do hereby certify that any witness(es) in the foregoing proceedings, prior to testifying, were duly sworn; that the proceedings were recorded by me and thereafter reduced to typewriting by a qualified transcriptionist; that said digital audio recording of said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.



MICHAEL FARKAS

Notary Public in and for the

STATE OF MARYLAND

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I, SONYA LEDANSKI HYDE, do hereby certify that this transcript was prepared from the digital audio recording of the foregoing proceeding, that said transcript is a true and accurate record of the proceedings to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.



SONYA LEDANSKI HYDE

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