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

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

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

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

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

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

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

9 I do want to mention that in addition to this
10 meeting a docket will remain open until December 14,
11 2018. You will also be hearing that multiple times
12 today and tomorrow. To which the public may submit
13 general or detailed comments or examples regarding
14 specific aspects of the discussion documents or topics
15 raised in the two-day meeting.

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

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

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

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

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

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

22 Tomorrow we will continue our panel session on

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

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

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

1 25 speakers, although we do hope you're able to ask
2 your questions during the question and answer period in
3 each session.

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

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

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

22 DR. MULLIN: Thank you, Michelle. If whoever

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

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

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

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

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

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

1 based on our laws and regulations.

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

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

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

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

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

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

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

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

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

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

22 We weren't sure how we were going to approach

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 reliable for many uses, quite frankly.

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

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

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

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

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

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

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

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

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

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

22 And there are a few other areas that we're

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

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

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

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

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

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

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

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

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

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

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

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

1 shorter name.

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

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

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

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

1 product lifecycle.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 questions and adequate response options in that survey.

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

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

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

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

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

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

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

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

1 Seattle.

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

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

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

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

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

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

1 experience data.

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

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

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

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

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

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

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

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

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

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

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

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

22 For example, some folks might look at social

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

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

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

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

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

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

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

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

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

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

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

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

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

22 The other piece that I think is missing is,

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

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

16 DR. DASHIELL-AJE: Thank you so much.

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

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

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

10 DR. FREEMAN: We are working on that.

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

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

17 DR. DASHIELL-AJE: Mm-hmm.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

17 (No audible response.)

18 DR. DASHIELL-AJE: Okay.

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

20 DR. DASHIELL-AJE: Oh, yes.

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

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

4 DR. DASHIELL-AJE: Mm-hmm.

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

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

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

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

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

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

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

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

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

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

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

13 DR. DASHIELL-AJE: Mm-hmm.

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

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

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

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

10 DR. DASHIELL-AJE: Right.

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

14 DR. DASHIELL-AJE: Okay. Great example.

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

17 DR. DASHIELL-AJE: Right. Great example.

18 Diane, do you have anything to add?

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

1 selection, you know, bias, right.

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

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

19 DR. DASHIELL-AJE: Great. Emily?

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

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

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

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

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

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

3 DR. AMTMANN: Is it on?

4 DR. DASHIELL-AJE: It is on.

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

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

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

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

1 and I agree with Emily, as far as triangulation.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 DR. DASHIELL-AJE: Mm-hmm.

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

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

13 DR. DASHIELL-AJE: Exactly.

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

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

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

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

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

1 their actual diagnosis might be.

2 DR. DASHIELL-AJE: Mm-hmm.

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

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

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

1 materials, like interview guides, etcetera.

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

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

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

19 (No audible response.)

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

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

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

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

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

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

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

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

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

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

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

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

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

19 DR. DASHIELL-AJE: Mm-hmm.

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

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

1 do you have anything to add?

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

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

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

22 MS. BUSH: Yeah. I think that transparency

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

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

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

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

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

1 any other panelists?

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

7 DR. DASHIELL-AJE: Okay.

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

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

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

5 DR. DASHIELL-AJE: Great points.

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

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

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

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

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

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

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

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

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

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

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

22 DR. DASHIELL-AJE: Okay.

1 DR. AMTMANN: Can I make one more point?

2 DR. DASHIELL-AJE: Sure.

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

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

13 DR. DASHIELL-AJE: Mm-hmm.

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

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

1 session.

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

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

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

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

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

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

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

22 And unfortunately I don't think there are too

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

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

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

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

19 DR. DASHIELL-AJE: Okay. Dagmar?

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

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

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

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

22 It has nothing to do with statistical

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

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

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

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

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

3 DR. DASHIELL-AJE: Mm-hmm.

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

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

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

22 And so for every disease I think there's a

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

7 DR. DASHIELL-AJE: Okay.

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

9 DR. DASHIELL-AJE: Diane?

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

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

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

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

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

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

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

1 about concept elicitation.

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

9 Yeah.

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

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

22 Feel free, since you all are experts, to

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

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

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

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

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

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

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

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

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

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

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

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

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

13 DR. DASHIELL-AJE: That's wonderful.
14 Wonderful. Thank you, all, so much for your insights.
15 I'm now going to open the floor to audience Q and A.
16 We have about 11 minutes left. So if you all could --
17 18 minutes, oh 18 minutes. I am early. Oh, yay,
18 wonderful. I'm looking at this timer. Okay. Well, we
19 have 18 minutes, which is great. So if you could line
20 up -- are we doing the passing the mic, or are we doing
21 the lining up in the middle? Mic's in the middle,
22 right?

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

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

12 MS. DEAL: Hello.

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

14 MS. DEAL: Linda Deal, Pfizer.

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

17 MS. DEAL: Linda Deal, Pfizer.

18 DR. DASHIELL-AJE: Perfect.

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

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

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

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

20 DR. DASHIELL-AJE: Great point. Next.

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

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

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

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

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

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

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

11 So I was just wondering that any advice on
12 that.

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

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

20 DR. DASHIELL-AJE: Thank you. Emily?

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

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

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

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

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

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

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

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

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

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

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

8 DR. DASHIELL-AJE: Okay.

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

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

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

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

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

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

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

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

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

11 DR. DASHIELL-AJE: Diane?

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

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

1 from other sources, the existing data or literature.

2 And then exit interviews are, you know, they're
3 logistical issues. I don't think it needs to be at the
4 exit, right.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 populations to get that input from.

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

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

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

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

22 DR. DASHIELL-AJE: One more minute. Anyone

1 want to take a stab at that?

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

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

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

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

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

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

7 MS. SPEARS: Yes.

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

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

1 docket by December 14.

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

7 (Applause.)

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

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

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

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

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

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

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

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

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

9 And at this time I'm going to have them
10 introduce themselves. And I'm going to start from my
11 left side, and we'll move right down the line. And if
12 you can just speak directly into the mic, 'cause I know
13 we have some hard hearing in the back, and also we have
14 300 individuals on the web that would love to hear your
15 guys' voice.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

18 Could you say, you know, as a starting point
19 20 to 30 would be a good starting point? 'Cause that
20 will generally give you representativeness. That will
21 generally give you enough to work out whether you've
22 got saturation.

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

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

16 So interview guides, you've got, you've fully
17 open, you've fully structured, and you've semi-
18 structured interview guides. We know that generally
19 semi-structured interview guides are probably the best
20 way to start.

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

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

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

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

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

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

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

3 MS. EREMENCO: Yes, I do. And I want to echo
4 what Tara was saying and what the panel earlier was
5 saying about the need for more detail around the sample
6 size. I just want to quote something that was actually
7 stated in Guidance 3, which I think belongs in Guidance
8 2, which is that generally the number of patients is
9 not as critical as the interview quality and the
10 patient diversity included in the sample in relation to
11 intended clinical trial population characteristics.

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

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

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

8 So that's one thing on saturation. I won't
9 repeat the quote, but there's actually a really
10 definition of concept saturation in Guidance 3, line
11 732, 736 that I want to see in Guidance 2. Because,
12 again, that's part of the key decision point of do you
13 have enough, enough interviews or enough data
14 collected. So those are two points.

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

1 giving the wrong impression.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4 (No audible response.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 appendix was referenced because of that.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 anything additional to add to what Bill has already
2 stated?

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

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

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

1 as they plan their project.

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

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

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

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

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

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

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

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

3 DR. DANIELS: Is that all, Antonia?

4 DR. BENNETT: Yes.

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

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

14 (No audible response.)

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

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

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

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

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

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

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

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

1 experience on an online survey. They type that in.

2 You give them some -- that could be the primary
3 endpoint ClinRo or a PRO. They filled that in.

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

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

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

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

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

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

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

16 (No audible response.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 able to do that.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 I think just as often as we discover in

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

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

13 DR. DANIELS: Any other panelists or ...

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

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

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

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

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

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

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

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

11 (No audible response.)

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

17 DR. SYMONDS: Yes.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 DR. DANIELS: Yeah, that's an excellent point.

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

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

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

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

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

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

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

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

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

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

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

1 ahead.

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

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

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

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

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

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

10 DR. DANIELS:

11 MS. LASCH: But that's okay.

12 DR. DANIELS: Okay.

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

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

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

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

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

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

1 in different results.

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

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

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

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

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

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

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

11 DR. DANIELS: Okay.

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

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

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

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

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

15 (Applause.)

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

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

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

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

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

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

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

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

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

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

1 probably essentially iterative and not sequential.

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

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

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

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

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

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

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

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

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

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

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

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

11 (Applause.)

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

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

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

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

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

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

22 So there are different ways of classifying

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 tested specifically for each disease in context of use.

2 And so we often look to use existing COAs.

3 And a decision that we grapple with frequently is
4 whether an existing tool is fit-for-purpose as is for a
5 context of use. Whether it could be modified for a new
6 context of use, and whether a tool should be developed
7 from scratch. In other words, there is nothing that we
8 can employ that's existing.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 This is a copy of the wheel and spokes figure.

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

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

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

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

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

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

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

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

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

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

3 And importantly FDA is open to considering
4 alternative methods and approaches in this setting to
5 meet the challenges of measurement. Now, in rare
6 diseases we also see a lot of the same challenges
7 because, of course, rare diseases will frequently
8 affect people across the lifespan.

9 And here we see some challenges related to,
10 perhaps, incomplete understanding of the disease, such
11 as its natural history or important subsets. Of
12 course, by definition there are small patient
13 populations that we can include in our instrument
14 development, as well as clinical trials. And we heard
15 some about that this morning.

16 There are cognitive and linguistic differences
17 and developmental differences and several other
18 considerations similar to that in pediatrics. But also
19 there's limited availability of disease experts. And
20 there's wide geographic dispersion of patients. And so
21 we have to carefully consider, you know, the cultural
22 and linguistic validation of any clinical outcome

1 assessment that we use.

2 So what are some of the recommendations to
3 help approach some of these challenges? Well, of
4 course, we should use fit-for-purpose clinical outcome
5 assessments in natural history studies that will inform
6 clinical benefit in future drug development. And so
7 this is very important consideration.

8 We should also carefully consider the
9 measurement strategy, leveraging existing COAs where
10 appropriate. Measurement property is also critical
11 because any noise in an instrument can interfere with
12 our ability to pick up a treatment effect, in
13 particular, when there are small populations.

14 So we recommend consulting with the FDA with
15 patients and other experts early in medical product
16 development. And I'd also like to stress that pretty
17 competitive collaboration is also extremely important
18 in rare diseases as with other diseases, and that the
19 FDA's open to considering multiple approaches.

20 Another area that we often struggle with is
21 how to interpret clinically meaningful change in a
22 measure score. And that, again, will be another topic

1 for the panel discussion tomorrow. So why is this
2 important? Well, it's imperative for understanding
3 whether a medical product has provided clinical benefit
4 or, perhaps, harm. And we know that statistical
5 significance alone doesn't indicate whether an
6 individual has experienced a meaningful clinical
7 benefit.

8 And so I've shown some of the specific methods
9 on this slide, including anchor-based methods, which we
10 see quite commonly, again, and distribution, cumulative
11 distribution displays. Again, we see that quite
12 commonly.

13 Cognitive interviews are very useful. We can
14 ask patients or caregivers whether the differences
15 among response options are important. Study exit
16 interviews might be employed. In addition, surveys and
17 perhaps, and there are also other emerging methods.
18 But typically we use multiple methods in combination.
19 And this provides us with greater confidence in that we
20 have a meaningful change threshold.

21 Tomorrow afternoon we also have a session on
22 digital health technology. Again, this is an emerging

1 area of research, and we are continually learning about
2 how we can leverage this technology in clinical trials.

3 So first I wanted to say that this term,
4 digital health technology is a very broad term and
5 includes categories such as mobile health, health
6 information technology, wearable devices, telehealth,
7 telemedicine, and personalized medicine. So it's quite
8 broad.

9 For the purposes of this workshop we're using
10 this in the sense, in the context of clinical trials to
11 capture clinical outcomes. So, for example, mobility,
12 sleep, falls, and just wanted to say a few additional
13 words about the technology. It can be used to collect
14 -- it can rely on either active or passive patient
15 participation. So an example of active participation
16 is where a patient is asked to perform a task. So it
17 could be, say, a memory test. And in that case it's
18 basically a performance outcome assessment.

19 Digital health technology also very commonly,
20 as we've heard about this morning, is used for passive
21 data collection, such as through wearable activity
22 monitors. But importantly, I think, you know, the

1 value of this and why I think this area is so important
2 is that it can provide us with a window into patients'
3 lives that may not be accessible any other way. And it
4 can also provide us very useful complementary
5 information to patient-reported outcomes or other types
6 of outcomes.

7 So, again, digital health technology is being
8 assessed in many venues and actively discussed in many
9 venues, both within the agency and outside the FDA.
10 And why is that? Well, it affords many potential
11 opportunities. And some of these are shown here in
12 this slide.

13 We can assess patient functioning in a real
14 world setting. It could streamline clinical
15 investigations, including areas, such as rare diseases,
16 pediatrics, and sleep. And it can capture offsite and
17 remote data directly from study participants. And this
18 allows us to access patients in distant locations and
19 potentially enable broader participation and inclusion
20 in clinical trials. And there are other potential
21 opportunities, I'm sure, that are expressed here.

22 There are also many elements that need to be

1 factored in when planning for digital health
2 technology. So, you know, importantly is how do we
3 select the appropriate tool for the concept and the
4 context of use. So what performance characteristics in
5 the specific technology are we looking for? And are
6 they appropriate for that patient population? What
7 aspect are we measuring?

8 So maybe we're interested in mobility. Well,
9 are we looking at walking speed, walking distance, you
10 know, what are we exactly, what's the most appropriate
11 aspect that will give us meaningful information in a
12 particular population?

13 Another consideration is how do we develop the
14 endpoint and the analysis plan? So what data are we
15 aggregating, and how are we analyzing the data in a
16 meaningful way? Because, as you can imagine, we can
17 get massive amounts of data from using this technology.
18 And we want to be able to analyze it in a meaningful
19 way so that we can interpret the results.

20 Also we need to think about compliance so that
21 we avoid missing data. So is the patient, is the
22 patient willing to wear a sensor? Are they going to

1 forget to wear a sensor? Those are things we need to
2 consider. And among other factors, such as safety,
3 comfort of wearing a, say a wearable device, and
4 privacy concerns. And I'm sure there are others.

5 So in closing, I hope I've reinforced that any
6 COA should be fit-for-purpose in medical product
7 development. And FDA has developed tools to help
8 stakeholders select and use fit-for-purpose COAs, which
9 include the roadmap for patient-focused outcome
10 assessment, and a proposed framework for decision
11 making for COA selection, modification or development.

12 And finally, I want to stress that the agency
13 recognizes that multiple approaches to clinical outcome
14 assessment and instrument development may be
15 appropriate.

16 Okay. Thank you for your attention. And now
17 we're going to transition to our FDA panel discussion.
18 So I'd like the panelists to -- I'd like to invite you
19 to the table, and we can get started. So if everyone
20 on our panel could please introduce yourselves. We'll
21 start with Michelle.

22 DR. TARVER: Good afternoon. I'm Michelle

1 Targer. I'm the Director of Patient Science and
2 Engagement at the Center for Devices and Radiological
3 Health.

4 DR. HO: Good afternoon. My name is Martin
5 Ho. I am Associate Director for Quantitative
6 Innovations at Center for Devices and Radiological
7 Health.

8 DR. IRONY: Hi, my name is Telba Irony. And
9 I'm a Deputy Office Director at the Office of
10 Biostatistics and Epidemiology at the Center for
11 Biologics.

12 DR. JOHNSON: I'm Laura Lee Johnson. I'm the
13 Division Director for Biometrics III in the Office of
14 Biostatistics and the Center for Drug Evaluation and
15 Research. I'm also our Clinical Outcome Assessment
16 Liaison and our Rare Disease Lead for the office.

17 DR. KLUETZ: My name is Paul Kluetz. I'm a
18 medical oncologist working in the Oncology Center of
19 Excellence, and I'm leading a patient-focused drug
20 development program as an associate director.

21 DR. LAPTEVA: I'm Larissa Lapteva. I'm the
22 Associate Director in the Division of Clinical

1 Evaluation Pharmacology and Toxicology in the Office of
2 Tissues and Advanced Therapies in the Center for
3 Biologics.

4 DR. MULLIN: Hi. Theresa Mullin, Associate
5 Director for Strategic Initiatives -- oh, there's my
6 title -- in the Center for Drugs. And I lead the
7 patient-focused drug development effort in CDER.

8 DR. PAPADOPOULOS: Thank you, all. And Dr.
9 Billy Dunn, who is the Division Director for the
10 Division of Neurology Products will be joining us a
11 little bit late from another meeting.

12 So I'd like to just start with, you know, the
13 general principles that we hope to emphasize in
14 Guidance Number 3 as shown here in this slide and
15 invite anyone on the panel to comment on whether these
16 are the appropriate principles to emphasize if they
17 would emphasize any other principles. And perhaps, you
18 know, from your perspective, what are some of the
19 activities, some of the policies or practices in your
20 respective areas that could speak to some of these.

21 So I'll just open it up. Yes, Martin?

22 DR. HO: Thank you. I would to speak on

1 number one and number two. I think they are -- goes
2 well with each other. Mostly because in devices we are
3 -- our regulation is a bit different from drugs. And
4 when we're talking about COAs mostly, the focus we --
5 would be on using them as an endpoint, which would
6 result in labeling claims.

7 But in devices we not only are using them for
8 labeling claims, but we are also using them to inform
9 us to make the benefit risk assessments when we are
10 conducting clinical trials or when we are evaluating
11 clinical trials. And, therefore, definitely the COA
12 should be fit-for-purpose and also that specific
13 purposes should be well understood before we are
14 committing resources to, you know, to study them or
15 perhaps to use them in clinical trials.

16 And I also wanted to say that the good
17 measurement principle is not only relevant to all COA
18 types, but I would say that to all the measurements
19 being used and studied in clinical trials for us so
20 that we can learn from this experiment.

21 But I would say also that validity is a
22 spectrum to me. So yes or no -- it's not yes or no,

1 but rather is a combination of different types of
2 evidence that gather, and we are using them as a whole
3 to consider for us to make our regulatory decisions.

4 Thank you.

5 DR. PAPADOPOULOS: That's a great point. Yes,
6 Laura Lee.

7 DR. JOHNSON: So I'll mention a little bit
8 about number four kind of with my rare disease hat on.
9 And it was mentioned in the morning as well. And one
10 element that I like about much of what Elektra just
11 presented out of these documents is to really clarify
12 the ability to leverage the existing COAs where
13 appropriate.

14 And we have gotten feedback over time where it
15 appeared that sponsors were concerned about not -- they
16 thought they had to create de novo. And I think we've
17 spent considerable time trying to say, no, that's not
18 the case.

19 So what I'm hoping, and I'm sure probably
20 others agree with me, is that this will encourage use,
21 and to steal the phrase, reduce, reuse, recycle, to
22 think about that. And especially when you're thinking

1 in the rare disease realm where we do have precious few
2 patients, and patients are your most important resource
3 everywhere, regardless of actually the group that
4 you're working with and the patient population.

5 But to be able to leverage something,
6 especially if you're measuring a common concept, such
7 as physical function. Others say, okay, does this
8 really apply to my patient group. And if it does, can
9 I get a little bit of information and move forward.
10 And that's not always going to be the case, you know.

11 For example, if you're worried about
12 ambulation and the tool is talking a lot about your
13 upper extremities, that may not be the case. But that
14 general principle of can we leverage what we know
15 because we know a lot. And that reduces burden on
16 patients and allows us to spend the energy and all the
17 other resources in many of the other areas where it's
18 necessary.

19 DR. KLUETZ: I'll make a couple points to
20 Elektra's slides. I guess from the oncology standpoint
21 we typically don't have a patient-reported outcome as a
22 primary endpoint in our clinical trials. And yet we

1 have patient-reported outcomes collected and assessed
2 in most every commercial randomized clinical trial
3 that's submitted to the agency. And so they're
4 important.

5 And it's important in our context for obvious
6 reasons. Our diseases can be symptomatic. Our
7 diseases have therapies that can also be symptomatic,
8 and those that net benefit from the improvement in
9 disease symptoms. And unfortunately the symptomatic
10 toxicities will feed into physical function.

11 So we've taken a look at patient-reported
12 outcomes within our area, and while not a primary
13 endpoint, looking to find ways that it can discriminate
14 between drugs. We see a lot more drugs than we have
15 ever seen, thankfully, in the oncology setting right
16 now. And so we have an opportunity now to have two or
17 three drugs in the same actual space, when that's never
18 happened before.

19 And so how can we help patients and providers
20 understand and differentiate between these therapies.
21 So we've created a framework of core outcomes, and if I
22 could make one comment, it would be that in each

1 disease area it would be nice, and I believe Theresa
2 has, is also looking to do this, to identify core
3 outcomes that would make sense for your disease-
4 specific area. And for us, we've looked at disease
5 symptoms, symptomatic toxicities, and overall side
6 effect impact in physical function and your ability to
7 work and do your activities as important.

8 And with a regulatory hat we try to ensure
9 that we are isolating the effect of the drugs. So
10 these concepts are close to the effect of the drug,
11 potentially less affected by non-drug influences.

12 So just to also mention on leveraging existing
13 COAs, we have these concepts that we're interested in.
14 There are many COA tools or patient-reported outcome
15 tools available for physical function, as well as
16 particularly symptomatic adverse events. And I think
17 it's really important that we leverage existing tools
18 where possible.

19 I think we spent a lot of time developing new
20 PRO tools. And I think the next three to four years is
21 going to be focused on identifying a very good research
22 question for these tools and the analytics and

1 interpretation to be able to use them effectively in
2 whatever disease area that you have.

3 Also to Martin's point, 'cause Martin does a
4 lot of this, digital health, I don't see digital health
5 wearable devices as replacing, for instance, patient-
6 reported outcomes. I think that they can be used in
7 concert.

8 I can imagine where a wearable device, for
9 instance, would give you great activity data that could
10 be further complemented by a patient-reported outcome
11 to give you an idea of the quality of that increased
12 activity and also the meaningfulness of that. And
13 it'll give your trial some internal validity. So you
14 should see things going the right way. Because there
15 is uncertainty in patient-reported outcomes, and
16 there's also uncertainty in how new the wearable
17 devices are.

18 It's a very exciting time technologically, and
19 I think we can do them both.

20 DR. PAPADOPOULOS: So -- I'm sorry, go ahead
21 Theresa.

22 DR. MULLIN: All right. Well, just quickly,

1 and I, you know, the methodological experts are to my
2 right. But I think that to me the first statement just
3 sounds -- it may sound so obvious, but how could you
4 use COAs that are not fit-for-purpose? But if you
5 think about what was said earlier today, like you have
6 to start, Patty Spears, for example, I believe was said
7 earlier, you know, you've got to remember to start with
8 asking people what matters the most. Don't skip the
9 step of finding out, listening to patients and hearing
10 what really mattered to them.

11 And having done that early work, and that sort
12 of sets the scene, I think, to me, before you go into
13 the little flow diagram that Elektra showed. But
14 imagine if you had that, you had talked to people about
15 what really mattered, you had identified those things,
16 your product actually, you think, effects that.

17 What if you don't have a clinical outcome --
18 if you don't have a COA that's actually going to
19 measure those things, your product is not -- you're not
20 going to have the evidence you want to present at the
21 end of the day to the regulatory. You've done all that
22 work. You've invested all that money, but you used a

1 tool that actually wasn't going to really effectively
2 or wasn't relevant to the concerns that people told you
3 about. It may not be valid or reliably measure that.
4 And so, you know, you don't want to blow it in that
5 sense.

6 I mean, I think in terms of investment you
7 really want to be careful to connect what you hear
8 early to the characteristics of that tool that you use.
9 And not to say anything that's not consistent with what
10 everyone has said in terms of if you can find an
11 instrument to use that's already out there that does
12 that, great. If you can adapt something that's already
13 out there, great. But it's tied to those things that
14 you heard mattered the most.

15 DR. LAPTEVA: Well, I would like to add that
16 in addition to agreeing with everything that's been
17 said before, I think we should not be losing sight that
18 when we're talking about methodologies of clinical
19 outcome assessment development, we should really
20 remember to view COA development from the perspective
21 of finding new treatments, because that's what really
22 important to patients.

1 In the draft guidances we've described more or
2 less classic psychometric approach to how to develop a
3 scale. You have a number of items. You would select
4 them. You would reformulate them. They're supposed to
5 reflect on the domains of interest and concepts of
6 interest. And then with application of the appropriate
7 statistical methodology you would have an outcome
8 measure through an iterative process.

9 And I think that this is really a proper way
10 of doing it, and a sound methodological way. And I
11 would like to really commend COA team and Elektra and
12 Laurie Burke before her for advocating for this
13 approach and really for bringing up in the quality the
14 outcomes assessments that we see in development
15 programs.

16 I also would like to say that inherently any
17 outcome measure in drug development would be connected
18 with the molecular pathway or pathways that a
19 particular investigational drug or biologic is supposed
20 to influence. And there are also realities of R and D
21 and R and D productivity metrics where one of the
22 initial steps in drug development would be target

1 identification and validation.

2 And we all know that oftentimes this is done
3 through automated searches of chemical compounds and
4 receptors and proteins, gene libraries nowadays. And
5 as we focus more and more on the clinical
6 meaningfulness of the patient-centered outcomes, I
7 think what we will probably be collectively doing, and
8 we hope to do that, would be to nudge the R and D a
9 little bit away from the combinatorial chemistry and
10 high throughput screening types of approaches towards
11 the systems biology in rational drug design.

12 Where we could potentially influence, really
13 target the focused places on the pathways of diseases.
14 Where it could be targeted specific disease
15 modifications and specific symptoms and signs that are
16 truly important to patients. So I think this is really
17 in the long run going to be a good thing. And
18 hopefully will increase the number of compounds that
19 are identified and then make it through the development
20 process to the market.

21 I do have a couple of comments about the
22 roadmap and the framework, but I think that should be

1 later, right?

2 DR. PAPADOPOULOS: Yes.

3 DR. LAPTEVA: Okay, thanks.

4 DR. PAPADOPOULOS: And after this one.

5 DR. TARVER: So just to make a couple of quick
6 remarks. In the Center for Devices we've seen an
7 exponential increase in the number of patient-reported
8 outcome measures being included in the submissions.
9 And we're seeing the use, not just in the effectiveness
10 component, but also in safety and inclusion and
11 exclusion criteria as composite endpoints.

12 So these measures are extremely important.
13 And being able to measure things that are important to
14 patients, we zoom out. What we're really trying to do
15 is help people make good decisions about how to take
16 care of themselves and how to make good healthcare
17 decisions. And so what we're measuring should reflect
18 those concepts.

19 So I think the fit-for-purpose concept is
20 something we've really focused on quite a bit in our
21 center to ensure that the measures that we are seeing
22 are actually measuring the concepts of interest that

1 are important to the patient's and the providers.

2 And also in terms of the leveraging existing
3 COAs, I think we all are echoing a similar sentiment,
4 which is that we really want to make this most
5 efficient. And in our center we have regulation that
6 says least burdensome approach so that we get the
7 answer that's meaningful to the providers and to the
8 patients.

9 So I think that these principles all reflect
10 what sentiments we are saying in our centers and across
11 the agency.

12 DR. IRONY: And finally I would like to
13 comment the principles of fit-for-purpose and the
14 leveraging the existing COAs and see how they might fit
15 together. And I think the great idea in that is when
16 you are leveraging an existing COA for a different
17 condition or a different patient population. The
18 difference might be on the clinically meaningful
19 benefit.

20 Because that will basically depend on the
21 condition you are treating, the patients in that
22 population and what the patients prefer, and the level

1 of risk. So if you have more risk, let's say, in a
2 certain treatment or for a certain patient population
3 because the disease or the condition is riskier, you
4 would probably require a higher benefit.

5 So the clinically meaningful benefit might be
6 not the same, even if you are using the same COA. That
7 will depend on the condition, will depend on the
8 patient. And that's an important comment that I would
9 like to make and emphasize, given everybody said a lot
10 of things about the principles.

11 DR. PAPADOPOULOS: Thank you. And I, I guess
12 I also wanted to highlight an example of, you know,
13 where we've actively tried to encourage the use of
14 existing outcomes. And this was discussed a few weeks
15 ago at a meeting on transplantation. And this meeting
16 was -- one of the key topics discussed there was how
17 can we do a better job of assessing symptomatic
18 toxicities in patients who are on immunosuppressive
19 drugs in the transplant setting.

20 And so what we, what we did was we brought in
21 other disease experts, Paul and others, and we -- and
22 also people from the NCI, looking to see how we could

1 leverage a tool that the NCI developed in the cancer
2 population that measures symptomatic toxicities in the
3 transplant population because a lot of the toxicities
4 are the same, fatigue and others. And it could be that
5 we can leverage these.

6 And so that's very exciting. That's what
7 we're looking to do. And, you know, of course there
8 may need to be some more specific items unique to the
9 transplant population and the drugs that are commonly
10 used. But certainly there -- nobody thought there was
11 a need to reinvent the wheel and start from scratch.
12 So I just wanted to highlight that example.

13 Yes, Larissa?

14 DR. LAPTEVA: So I would like to also bring up
15 an example. I speak for the Center for Biologics. And
16 one of the products we approved recently was a product
17 which contained autologous, meaning patient's own,
18 cells, chondrocytes, chondrocytes constitute cartilage
19 that is inside our joints. The chondrocytes were
20 harvested from a patient and then expanded en vivo and
21 then put on a membrane and then re-transplanted into
22 the knee joint where the product is currently used for

1 symptomatic defects of knee cartilage.

2 And so when that program came to us and we
3 were discussing a primary endpoint that would be used
4 as fit-for-purpose and in the desired context of use,
5 to then in the clinical trials demonstrate the primary
6 evidence of effectiveness, there was an instrument that
7 was developed years ago. And we looked at it and it
8 clearly covered the important concepts that we were
9 looking for.

10 It covered the symptoms, the signs, the
11 functioning, the activities of daily living, the
12 quality of life that was body-part related. And so we
13 adapted that instrument, and the program ended up being
14 a successful program.

15 And this is just one of many examples where we
16 don't necessarily worry about whether it's a new
17 instrument or an old instrument, whether it was
18 developed in the specific population -- we do worry
19 whether it was developed in the population for whom it
20 is important to really measure the concepts as we're
21 interested in. But it doesn't matter whether it's an
22 existing tool or a tool that's developed from scratch.

1 It's important whether it measures the concepts that
2 are important for that disease.

3 DR. PAPADOPOULOS: That's true. And I think
4 we've seen many examples where, you know, you have
5 tools that are, primarily have been developed in the
6 clinical setting that include items that aren't
7 expected to be modified with a treatment. They might
8 be -- you know, patients might have some impairment
9 which is fixed and cannot be changed with the treatment
10 under investigation. And so we will then want to not
11 include those items when we're developing, when we're
12 applying that COA because the concern there is that it
13 might interfere with the sensitivity of the measure.

14 So that's one common scenario that we've seen
15 when using existing instruments. Okay. Yes, Paul?

16 DR. KLUETZ: I would just also say as far as
17 the fitness for purpose, like one of the things that
18 we've been running into a lot in oncology is the
19 research question. And, again, I think there's so much
20 heterogeneity and lack of clarity on what the research
21 question is that it can hamper the utility.

22 And so one example would be you may be

1 interested in showing that you're add-on trial design
2 fails to decrease, or is about the same physical
3 function as the comparative arm. So there's no
4 meaningful difference. Or you're trying to show that
5 there's not a lot of difference between the arms. So
6 you can say we're adding some toxicity, but in general
7 patients are functioning the same.

8 This is a pretty common thing to do in
9 oncology because, of course with an add-on trial you're
10 adding another therapy that has more side effects, and
11 the side effect profile is usually a little bit worse.
12 So if you're trying to show that there's no difference,
13 suddenly the sensitivity of your tool becomes really
14 important.

15 And so we really look now to say how, we need
16 a sensitive tool. You're not going to ask a single
17 question, a single item about function in that
18 scenario. And then conversely, if you're looking to
19 show that you have a superior function between the arms
20 for a product, a new product, well, now in that sense,
21 geeze, if you use an insensitive instrument, it's at
22 your risk. And if you show a big benefit, wow, that's

1 even better. And in some cases a single item is even
2 more interpretable because you have categorical changes
3 rather than a transformed score of a small difference
4 that you're into the clinical meaningfulness question.

5 So I guess my point is the research question
6 is so critical, and that's why -- shameless plug coming
7 up -- the 2019 Clinical Outcome Assessment Workshop for
8 Cancer is going to be July 12, 2019. And we're going
9 to actually put people to task and say, here's two
10 research questions for physical function.

11 Number one, how does function -- describe
12 function while the patient is taking their therapy.
13 'Cause patients want to know, how am I going to
14 function while I'm taking my therapy. That's sort of a
15 tolerability question. And then, and it implies a
16 different population that you're going to study.

17 And then the second question is, you think
18 your drug is superior to the alternative in function,
19 how would you show a superiority that you improve
20 function or that function at some later time is better
21 on arm A versus arm B. That's more of an intention to
22 treat analysis. And that's more of an efficacy

1 question or a net benefit question.

2 And so those are very different, and we'll
3 create trials based on that. So I think we have to get
4 a little bit more specific about our questions, and the
5 tools may be slightly different to answer those.

6 DR. PAPADOPOULOS: I just, you know, this
7 brings up a really important point about context of
8 use. And how are you looking to use your COA. Is it a
9 primary endpoint? Is it, you know, secondary
10 exploratory? You know, in the case of a lot of
11 oncology it's not the primary endpoint. It's
12 secondary. And so, you know, there may be a little bit
13 more willingness to tolerate risk.

14 But say you have a scenario where you're
15 developing a drug for a rare disease, and there you --
16 and it's a primary endpoint, and there you only have
17 one shot, okay. Then it's really to everybody's, it's
18 everybody's risk, really, if you fail on that. So I
19 think that's an important consideration when we're
20 talking about fit-for-purpose. Laura Lee?

21 DR. JOHNSON: Yes, building on that, you know,
22 sometimes, and I'm going to say this in a very

1 colloquial way, it almost seems like folks want it to
2 matter a little bit less early in development. So why
3 do I have to be so rigorous early. But with my
4 biostatistician hat on, then becomes the problem that
5 you are getting ready for these later trials, and
6 you've realized, oh, well now I've had to tinker with
7 the COA, or I finally went and talked to the patient's
8 and figured out what mattered. So now I have to change
9 what tool I'm using.

10 And so now you're asking your statistical unit
11 to design and power a trial using a tool they basically
12 have no data on. And that is a huge risk. And
13 shockingly, as someone said, we shouldn't necessarily
14 have to put COA should be fit-for-purpose as number
15 one, but shockingly we see a lot of things that come in
16 that may be have been taking higher risks than other
17 sponsors would be willing to take.

18 And but sometimes you're in a situation where
19 you've got one shot. And so they're just, you know,
20 there really hasn't been that opportunity otherwise.
21 So you're doing the best that you can. But there is
22 this consistent risk in really talking to patients

1 early, even before starting your molecular development
2 of understanding where should we even be targeting.
3 What is important to them, and how are we going to
4 figure out how to measure it.

5 And this is something that is so key and can
6 really help development. Because as Elektra mentioned
7 earlier, you know, it cost a lot more money to fail in
8 the trials that you want to send to regulators for
9 registration and marketing. So it is about, as I think
10 everybody in this room and listening online probably
11 gets that, but feel free to go back and tell folks and
12 remind them of that.

13 DR. PAPADOPOULOS: Okay. Now I'm going to
14 transition to the roadmap. And I'll show the
15 schematic, but the question is whether it includes the
16 appropriate elements to help with the measurement
17 strategy. If not, if there's anything missing, what's
18 missing and where should it be positioned in the
19 diagram.

20 And so to review, here is the diagram. First
21 of all, I hope everybody can read it. But I just
22 wanted to get the perspectives from the panel, you

1 know, how they -- what do you think about the roadmap.

2 DR. LAPTEVA: Well, I promised to comment
3 about it earlier. So in the place where we're talking
4 about reliability and the ability to detect change, I
5 think it may be also useful to think about resistance
6 to bias. Because not even from the perspective of a,
7 say, an endpoint in the clinical trial, but from the
8 perspective of the tool itself.

9 It may be particularly helpful for, say,
10 instruments that are supposed to or anticipated to be
11 administered over time, where learning as well as the
12 knowledge that gets accumulated about how to compensate
13 for the stable performance on the parts of the
14 respondent whether they're doing a physical task or a
15 cognitive task, you know, may interfere with this
16 exactability to detect change. And this is just one
17 example.

18 So I think emphasizing the resistant to bias
19 and the particular context of use for specific
20 instruments, at least some preliminary look should be
21 taken when an instrument is being developed.

22 DR. TARVER: I think another important point

1 is the endpoint definition in the trial. We often see
2 sponsors tell us that the PRO measure is the endpoint,
3 when it's really not the endpoint. We want to know
4 what concept are you really trying to capture, what
5 change has to be seen in that concept in order for it
6 to be the endpoint that we're going to be looking at in
7 the trial.

8 So that, I think, is very clearly laid out in
9 the roadmap. And I think it's very important to
10 highlight that issue.

11 DR. KLUETZ: Can I just add to that. I think
12 it's important to come up with an endpoint if you're
13 going to statistically test it obviously. So you're
14 going to need to have an endpoint. But it is not
15 likely to be the only analytic test that you do on that
16 endpoint. And, in fact, we really do want to see
17 prespecified -- at least in oncology -- prespecified
18 sensitivity analyses on these sorts of endpoints,
19 especially for scales where you're picking a threshold
20 and you're doing your best you can because you don't
21 exactly have that threshold.

22 But we really want to see what the result

1 looks like at different thresholds. And also,
2 particularly for oncology there can be a missing data
3 issue. So stressing different sorts of analyses
4 looking at missing data.

5 The other issue I -- I guess I have a question
6 for some of the other panelists. And this is probably
7 more important for therapeutic areas where it's the
8 primary endpoint or whether you're -- where you're
9 trying to make a claim of treatment benefit. You know,
10 is there ever a drawback to adding an anchor in a
11 study?

12 I mean, to me it seems like it's just -- it
13 creates one more piece of data that gives you, you
14 know, some more certainty that you're having an effect.
15 And then if where you have a scale where you're unclear
16 about the meaningful difference it gives you that
17 anchor-based method to allow you to do that in addition
18 to distributional methods.

19 DR. PAPADOPOULOS: Yes.

20 DR. JOHNSON: So, I will answer your question
21 with what I've been told. And I'm -- go into my
22 target, which is we've been told sometimes is it's the

1 cost. And so when we've asked to add an additional
2 anchor, now one might say, why hadn't they worked it in
3 there in the first place. But think it was the
4 hundreds of thousands of dollars that it is going to
5 take them sometimes more to change their electronic
6 data capture system to make all these other changes.
7 But in general could you preplan it a bit more, yes.

8 But, and I see it's a few people nodding, like
9 yeah. But I do think that, again, gets back to
10 thinking about the bigger picture and the encouragement
11 of bringing all these different parties in early. So
12 what we don't have on here, but you eluded to, Paul,
13 and I've gone back and forth.

14 And I guess we'll talk a little bit more about
15 this when we get to Guidance 4 in the series. And that
16 is really thinking about the endpoint analysis. And
17 sometimes people also forget to bring in, again, those
18 statistical colleagues and your data colleagues as if
19 thinking about this to have an endpoint definition, but
20 to also think about it and tie us to that trial design
21 as well.

22 So I'm in 2B going through those little

1 bullets. The design of the endpoint definition I'm
2 really thinking about how am I going to analyze the
3 data and the interpretation of it. And that's
4 something that's hard for us to write in guidance
5 because this could be very particular to the study in
6 front of you. But gathering all of your daily diary
7 information, but not knowing really how we are going to
8 bring this together and then how I can come up with
9 great statistical techniques, but can I write it in
10 labeling.

11 So early on in my career at FDA I had a
12 division director who sat down and said, okay, just
13 tell me how to write in the label so your grandmother
14 understands it. I was like, well, okay. And but
15 that's my gut check. Every time that I think about it,
16 it's like, okay, how am I going to write it, because at
17 the end of the day all the people on this panel, that's
18 where we have to go. We have to make a regulatory
19 decision, and then we have to figure out how to
20 communicate that information. But so does everybody
21 else in this audience as well.

22 DR. PAPADOPOULOS: So I have a comment on the

1 roadmap. And that is, I think, the digital health is
2 conspicuously absent. And that's part of why we're
3 here because we want to get people's input. But that's
4 something, I think we need to consider as including
5 digital health. Yes, Paul?

6 DR. KLUETZ: Can I make a, in the not
7 reinventing the wheel vein, I think that, let's take
8 wearables for instance, and let's take steps for
9 instance. I don't think that the important lessons
10 from this will be lost to wearables either. I think
11 when you get a stream of wearable device data you're
12 going to run into the exact same issues that we're
13 running into with patient-reported outcomes.

14 We're going to have maybe very sensitive -- it
15 could be very sensitive with very small effects. And
16 now you're looking at a 20-step difference between two
17 arms in a cancer trial. Is that meaningful to
18 patients? I don't know. And so you're going to need
19 to integrate, again, a patient-reported outcome
20 question that says, you know, what is being -- and I
21 see some people smiling because we're doing this right
22 now.

1 We have -- we are collecting wearable device
2 data. It can be challenging. So as I said before, I
3 think we should look at both streams contemporaneously
4 and try to learn from each other. This would be a
5 great example of that there's no difference between the
6 arms functioning thing. It will be nice to have the
7 sensitivity of a wearable in that setting. And that
8 might give you that ceiling that you need for some of
9 the existing PRO measures. Then you could have the PRO
10 physical function data to also inform the
11 meaningfulness.

12 DR. PAPADOPOULOS: I think that's a great
13 point. And I think, you know, there's been a lot of
14 interest in use of wearables to supplement patient-
15 reported outcomes. So for example, one project that's
16 going on is looking at pain as, you know, patient-
17 reported pain as well as the activity. And the reason
18 is that oftentimes patient's will increase their
19 activity as they improve, even though their pain may
20 stay constant.

21 And so by having both measures we can really
22 have a fuller picture of what's going on with the

1 patient. And, Paul, I am -- oh, yes, please, Laura
2 Lee?

3 DR. JOHNSON: And I guess this is something
4 folks can tell us during the open session or into the
5 docket, which is where would it go here. I mean we
6 also -- we don't separate out other types of data
7 collection on here. And maybe we don't need to. And
8 so I think we need to think very carefully about where
9 it goes. Because I do think a lot of this applies. I
10 also worry about, kind of, false precision, but that's
11 a different conversation at a different time.

12 But I do, I think we need to be cognizant of
13 making sure that these documents appear to be very
14 open. And as somebody put it, kept almost timeless in
15 certain ways, but allowing that flexibility. And so
16 that's something that we do need to hear from folks is,
17 you know, does it go in the roadmap? Does it go
18 somewhere else? Kind of, what should be wear in order
19 to make everybody -- we don't want to stall
20 development. We want to make sure that good work
21 happens.

22 DR. PAPADOPOULOS: Yes, thank you.

1 DR. MULLIN: So one comment that I have as I
2 look at the stage two or phase two of the roadmap, the
3 second, B, it seems to me, I mean, and this is where --
4 it looks to me like this is just your basic good
5 practice for any kind of -- I mean we're -- it's not
6 special to patient-centered kind of work. You always
7 have to -- and back to points Paul and others have
8 made, you know, what's the objective of your study?

9 I mean there's an ICH E9 guidance still in
10 development on the importance of the S demand or as
11 they put it, knowing what your objectives are before
12 you start a study. And, you know, the fact that we're
13 now here in 2018 writing an international guidance on
14 this suggests that sometimes people proceed without
15 that. And it causes lots of problems.

16 But so I think the other thing to me is these
17 are all clinically important to any good program,
18 right, and definitions of endpoints. And it's
19 certainly true, and as you're integrating the patient's
20 perspective and through the instrumentation and your
21 plans for your trial design driven by your objectives
22 and so on, that that's pulled right in.

1 So if anything, I think we might even want to
2 unpack that term, context of use a bit to make sure
3 people know just kind of what are the considerations
4 we've been talking up here not to miss it. But it
5 seems not special just to this kind of information
6 source.

7 DR. PAPADOPOULOS: Agreed. That's a great
8 point. Okay. Any other comments on the roadmap? Then
9 we're going to go to the next figure, the decision tree
10 diagram. And question is does it adequately describe,
11 you know, how to go about selecting, developing, or
12 modifying a COA. And if not, what else should we be
13 considering.

14 And then also, you know, is this something
15 that we should replace the wheel and spokes with, or
16 should we retain the wheel and spokes figure and modify
17 that figure? So this is the decision tree. Can you
18 see the decision tree well, or do you want me to go
19 back to the other slides that I have?

20 (No audible response.)

21 DR. PAPADOPOULOS: Okay. I'm going to go
22 back. Okay. So this is the decision tree, and then

1 this is the steps of development. So I'll put it on
2 the decision tree first.

3 DR. KLUETZ: I have to say, I love the fact
4 that the first thing that you run into is, is there an
5 existing COA tool? Do you actually need to go down the
6 road of creating another one? And it does force people
7 to say, is it fit-for-purpose. What's my context? Is
8 it the same exact context? I like that thought
9 process.

10 I think this does really show that -- I think
11 the COA staff has become more okay with a modification
12 of an existing instrument. I think that's a very
13 critical point that I think a lot of -- could save a
14 lot of time. And I think we should leverage what's
15 been done in the past. So I think this is reasonable.

16 DR. PAPADOPOULOS: I also wanted to backtrack
17 a little bit and just remind people that this is
18 supposed to be used with the roadmap. So, you know,
19 you still need to go through columns one and two, and
20 then decide on, okay, what type of COA, is it PRO or
21 whatever, before you can even begin to search for an
22 existing tool. So I just wanted to remind people of

1 that. Okay. Any other input?

2 DR. LAPTEVA: I just want to make a comment
3 that would probably continue Theresa's earlier comment
4 about clinical trial endpoint and the endpoint
5 positioning in the objectives. When looking at the
6 steps for COA development, there are four steps here.
7 And then the first one includes a number of bullets in
8 there. And I guess you could potentially apply it to
9 both developing a COA from scratch as well as
10 considering an existing COA and modifying that existing
11 COA.

12 And in that aspect the sub-bullet that talks
13 about endpoint positioning, when we're talking about an
14 originally de novo generated clinical outcomes
15 assessment, at the same time when the context and the
16 concepts of interest in the domains are still being
17 identified, it may sometimes be a bit too early to
18 actually talk about endpoint positioning in the
19 clinical trial. It may not be too early to talk about
20 endpoint positioning for an existing COA, but with
21 something that is just being developed from scratch it
22 may just be not, perhaps, the right place for that

1 particular sub-bullet, or maybe we should also place it
2 somewhere towards the later stages.

3 Because realistically speaking when you're
4 just trying to figure out what's important to patients,
5 immediately thinking about positioning an endpoint in
6 the clinical trial may be just a bit too early.

7 DR. PAPADOPOULOS: And that's actually a
8 really important point, and one that I should have also
9 made earlier. And that is, you know, this, this is a
10 framework for things to consider. And it doesn't mean
11 that we know all of the answers. And it just -- it's
12 sort of a reminder to think about these things.

13 But oftentimes we have to move forward with
14 incomplete information and do the best we can. So, but
15 I think that's a really good point. And thank you for
16 bringing that up. Okay. Michelle?

17 DR. TARVER: I think as I look at the
18 framework on the next -- maybe it's the previous slide
19 or the next slide. The important first step is to
20 identify the context of use and the concept of
21 interest. So I think a lot of times we see a shotgun
22 where there's not a clear idea of what you're trying to

1 capture.

2 And by starting at that step, I really do
3 think that it helps to set the case for what do I
4 really need to ask patients. It's not an easy task for
5 patients to take hundreds and hundreds of items of
6 questions and answer them visit after visit after
7 visit. And we're trying to get the highest quality of
8 data to make a good decision.

9 So I think really starting at that point,
10 figuring out what do I really need to ask, what do I
11 really need to know to help make a decision about this
12 product is critical.

13 I like the fact that it clearly lays out the
14 modifiable instruments, that's a possible pathway.
15 Everything doesn't have to start from scratch. We have
16 literature. There's a lot of things we can start with
17 to better inform clinical outcome assessment
18 development. So I like that it opens the door.
19 Whereas the prior wheel and spoke kind of closed the
20 door. It eluded to the fact that maybe you have to
21 start from scratch every time.

22 So I do like the openness, the flexibility

1 that's reflected in this. And the fit-for-purpose
2 that's very clearly laid out.

3 DR. PAPADOPOULOS: Yes, martin?

4 DR. HO: Yes. I would like to second what
5 Michelle has said. I also wanted to say that sometimes
6 when I talk to sponsors, most of the time, even though
7 they understand the important of pinpointing, you know,
8 the endpoint or have a, you know, a concept as specific
9 as possible, but sometimes they may not really firmly
10 grip the concept of concepts.

11 In other words, what does it even mean to
12 them, a concept. So I think, therefore, I think it
13 would be extremely important that the core concept
14 measurements or the core common sets, that kind of, you
15 know, exercise can really help to firm up our examples
16 of what the concept's referring to. And therefore the
17 sponsors can have a better understanding or context as
18 to what exactly concepts they are referring to when
19 they are developing medical product.

20 DR. PAPADOPOULOS: So I have a question. One
21 regret that I do have is we can't put it all one slide.
22 So you have to keep moving back and forth. But the

1 question I have is what do you think about the layout?
2 So this is the -- excuse me. This is the wheel and
3 spokes, which is a circular figure. And we took it and
4 we put it in a line. And but, however, it isn't an
5 iterative process. So, does that raise any concern for
6 anyone? Would you change how it's laid out?

7 DR. JOHNSON: I guess it -- I kind of like it
8 this way. But I could see -- I'm interested to see
9 what we hear on the docket because I think even when it
10 was in the wheels and spokes and in a circle, people
11 felt like they had to go in a very prescribed format
12 and that also that they were done.

13 What I like about more of the flow diagram is
14 they keep saying, and don't forget you got to recheck
15 steps two to through four. And don't forget you got to
16 recheck. And like I've gotten questions when we use
17 the wheel and spokes. They're like, oh, but I'm
18 skipping to this part, is that okay? And it's like,
19 yes, it's fine, you're good.

20 So but, you know, some people may think they
21 literally have to finish everything in one before they
22 move to two, before they move in. So I don't know,

1 other than continuing to use the word iterative, what
2 we can say.

3 DR. PAPADOPOULOS: And we also paid careful
4 attention to this, so. We say as appropriate. So the
5 type of evidence that you gather would depend on the
6 modification, the extent and the nature of the
7 modification. So it doesn't necessarily mean you have
8 to do everything on this. Yes?

9 DR. KLUETZ: Can I just see from a show of
10 hands who is either a clinician or from the clinical
11 development group of their industry? So some, but not
12 the majority. So one of the things that I really want
13 to focus on over the next year or two or couple years
14 is to make sure we pull the clinical groups in much
15 more into this process. Because I guarantee you if I
16 stuck this up in front of one of my clinical reviewers,
17 they would be like, context of use, concept of
18 interest, content validity, iterative -- what is
19 iterative? I mean that's -- no, I'm just kidding. I
20 think they'd probably know that.

21 But literally, there's a lot of terminology in
22 there that is going to really blow clinical folks away.

1 So A, I would recommend that we do a very good job at
2 marketing very good glossaries that Theresa and her
3 group have put out in the PFDD Guidance to glossary
4 there, the best guidance from the NIH and FDA on what
5 is a biomarker, what is content validity, what are the
6 different COA instruments.

7 And then B, really loop our clinical
8 colleagues in. I'll do my part, but you, you know, you
9 need to get your clinical teams together so that we can
10 actually come up with those research questions and
11 those endpoints.

12 DR. PAPADOPOULOS: Yes, Theresa.

13 DR. MULLIN: Elektra, I don't have the, I
14 don't know the answer, but I can imagine that if you --
15 I mean, we say iterative, but I think we also want to
16 not scare people off with this idea of endless
17 iteration. So I think it has to be when are we close
18 enough to the asymptote that we're good.

19 And so when is it good enough. And a little
20 bit to Paul's point, and maybe it's the New Jersey
21 perspective, I don't know. But I think I'd even like
22 to see what this would -- if we translated it into here

1 are questions you need to ask yourself at each of these
2 stages. And so the question might be, for example,
3 what's the research question you're trying to answer?
4 Somewhere that comes in. How good, how sensitive does
5 that tool have to be to really be able to address the
6 research question you're trying to -- so some of it
7 might be we can even flip it a little bit to a
8 different way to think about the same concepts, the
9 same considerations.

10 But I think we'll want to give people a sense
11 of, you know, I've done some iterations on this, and
12 I'm -- it's at a good usable place now for the purposes
13 of my study and what I found out about, you know, the
14 patient population or something.

15 DR. IRONY: Let me just suggest, you know, one
16 approach would be to come up with examples that
17 illustrate the process. So if we could get a couple of
18 examples as we went through the iterations in the
19 guidance, that will be helpful, you know, it could say
20 some that have very few iterations and some that are
21 very, you know, took more iterations because of one
22 issue or another one.

1 Another thing I would suggest, I wouldn't call
2 steps because steps have the connotation of, you know,
3 you're going in one direction, but maybe points or
4 items to consider or, but steps, you know, they look
5 like you're going up somehow.

6 DR. PAPADOPOULOS: Thank you. Thank you.
7 That's extremely helpful.

8 DR. TARVER: I was going to say, it's not just
9 Jersey, it's California, too. But I would say that
10 creating a similar lexicon really does help empower
11 everyone to know that we're talking about the same
12 thing. I'm a clinician by training as well, and when I
13 came to that -- before I came to the FDA, some of the
14 terminology that's used here was just not familiar to
15 me.

16 And so when you're talking about the clinical
17 sites, when you're talking about the chief medical
18 officers that are helping to organize and design and
19 put these studies into action, we all have to speak the
20 same language. And so that what comes in resonates
21 with everyone. And so I do think that that's really a
22 very important point, figuring out a way to translate,

1 create that dictionary that -- not just the glossary,
2 but a dictionary. Because we -- action, we make these
3 words into actions, not just words that just exist on
4 paper. And so how do we make them actionable.

5 And maybe, as you all already eluded to me,
6 the examples will help or the questions or something
7 that makes it more tangible so that we are getting what
8 we need to get out of it.

9 DR. PAPADOPOULOS: And I think getting back to
10 Paul's point about, you know, the terminology that may
11 not be familiar to the audience and, you know, we're
12 trying to make it for a broader audience. So I think
13 that's a very good point. Martin?

14 DR. HO: Yes. One last thing. Even though I
15 am a statistician, and of course I would love these,
16 you know, the statistician can also use the same set of
17 languages. But I'm also now pitching for our
18 regulatory affairs colleagues, since they are the one
19 who are budgeting for these studies and lining up all
20 these timelines and making sure that things get done.

21 They are extremely important for them to get
22 them on the same page so that everybody is talking on

1 the same thing and move this forward. Thank you.

2 DR. JOHNSON: So I'm going to ask for another
3 case study. I know there are folks out in this
4 audience who have had to explain this to their clinical
5 colleagues and the reg folks and figured out how to
6 word it. So as we're thinking about case studies, let
7 us know, how should we reword these and to those, you
8 know, four or five simple questions. Or how is it that
9 you all convince folks to get things funded or started
10 earlier, etcetera?

11 DR. PAPADOPOULOS: And maybe you can also do
12 some focus groups on this document understanding. But
13 to that point, I think that if you could send examples
14 that you would like to see, something that you've had
15 practical experience, anything concrete that would
16 really help us that we could potentially adopt or
17 adapt, that would be great.

18 And we are joined by Billy. Welcome, Billy.
19 We only have about five -- anything else on the figure?
20 And then I might -- I'll just go back.

21 So the question, the first question I wanted
22 to bring up is -- so the first question was this,

1 whether the -- so these are the principles that we aim
2 to emphasize in Guidance 3, the guidance that's going
3 to be replacing the PRO Guidance. And so the question,
4 initial one, was, you know, are these appropriate
5 principles to emphasize, and if not, are there any
6 others, and if you could speak to some of these from
7 your perspective. And I know you have extensive
8 perspective. So I'll open it up to you. And not to
9 put you on the spot, but, yes.

10 DR. DUNN: Yeah, I'm going to pay, right,
11 yeah. I shouldn't have been chatting with you 'cause I
12 didn't hear everything. I'm so sorry. I apologize to
13 the group.

14 DR. MULLIN: Let's catch him up on what
15 happened.

16 DR. DUNN: Yeah, I apologize to the group for
17 being late. I was with a sponsor in an independent
18 meeting that was co-scheduled that we didn't really
19 have control over. Sorry about that.

20 Was there a particular area, Elektra, you
21 wanted me to focus on, or do you want me just to give
22 general comments?

1 DR. PAPADOPOULOS: So these are the principle,
2 kind of the general principles that we hope to
3 emphasize in this upcoming guidance, Guidance 3, to
4 replace the PRO Guidance. And so the first one is
5 around the concept of fit-for-purpose that the COA
6 should be appropriate for the research question, the
7 population, study design and such.

8 And the second one is, you know, the certain
9 good measurement principles, validity, reliability,
10 ability to change, that are common across all COA types
11 and not only that, other types of outcome assessments.
12 And that we want to emphasize flexibility alternative
13 methods and approaches may be appropriate to those
14 described in the guidance.

15 DR. DUNN: Right.

16 DR. PAPADOPOULOS: And then a big topic is
17 leveraging existing COAs where appropriate. And I know
18 that's something that we've had some really good
19 discussions about as, you know, how do we take a COA
20 and utilize the things that are fit-for-purpose and
21 maybe leave behind some of the other things.

22 DR. DUNN: Right. Right. Without making the

1 people that do this work too angry in the process as we
2 pare things away. You know, I think those topics are
3 great. You know, some of the thinking that I was doing
4 about this topic in discussions with you and the panel
5 in advance, I think, you know, dovetail with this quite
6 well. And, again, my apologies for being late.

7 But one of the things I really like about this
8 guidance is that I agree that documenting the optimal
9 approach is really the right way to go. But I think
10 there's an awful lot of room for flexibility and
11 judgement when you apply this, these principles. And
12 so having a repository of something that's optimized or
13 idealized is very, very important.

14 It doesn't necessarily mean it's going to be
15 attained in all situations, and I don't think it will
16 be in most times. But it's very reasonable, I think,
17 for us to write our guidance in a way that gets that
18 out there up front. And then we kind of know what the
19 playing field's like. So I'm very glad to see that
20 being emphasized.

21 You know, often we talk about the importance
22 of assessing how patients function in their daily lives

1 in their natural environments as opposed to a lab or a
2 clinic setting. That gets a lot of, pardon me, that
3 gets a lot of play here. But we don't want to be too
4 extreme about that.

5 You know, obviously a measure in a trial will
6 of necessity be assessed in that trial, and that may
7 and probably will involve structured assessment in a
8 clinic setting. You know, such assessments take a wide
9 variety of forms. And they can provide important and
10 often adequate evidence of a drug's effectiveness that
11 we can rely upon for a regulatory decision.

12 But the closer that we can come to the
13 function people experience in their daily lives and
14 their natural environment, the more informative we can
15 be about what patients might experience on a day to day
16 basis when being treated. And so trying to bridge that
17 gap, not losing the practicality of conducting our
18 trials, but trying to be as in touch with the daily
19 experience as we can is very important.

20 As Elektra just mentioned, we have extensive
21 experience and success with modification of existing
22 scales. Sometimes that's all we can do. I really like

1 what we do in this space, and we do it a lot. This can
2 be particularly important with some of the diseases
3 that we're responsible for in neuroscience where
4 specific tools and scales may not exist for the
5 condition being studied, you know. And the resources
6 of those responsible for the investigation may also be
7 limited, perhaps in time or perhaps in resources or
8 often both.

9 So leveraging existing knowledge and
10 experience can really enhance in efficiency. And we
11 try to do that very aggressively. We work with our
12 sponsors. And we work very hard to accomplish that.
13 That can tremendously enhance the efficiency of the
14 program if we can take advantage of what's already out
15 there.

16 Relevant tools from related conditions or
17 disease independent measurements are something we
18 emphasize a lot as well. Things that are not specific
19 to the condition being considered, but may nevertheless
20 be appropriate for evaluating effects in the population
21 under study.

22 I think this new guidance is going to ideally

1 present a fairly comprehensive and optimized approach,
2 which, as I already said, is very important to strive
3 for. I already mentioned flexibility as well. This is
4 very important, as various constraints may ask us to
5 make do with something that's less than perfect.
6 That's often the case, and that's often okay. It's
7 very much okay to do that. We try to do the best with
8 what we have.

9 A key point with regard to the roadmap, and
10 one that I think is reflected in the roadmap that I'm
11 assuming you presented earlier, is the staged approach
12 outcome development. I think that's very important
13 that you have this staged approach. And it emphasizes
14 that the more that you can frontload your work on the
15 understanding -- there it is right there. The more you
16 can frontload the work on understanding the disease or
17 condition you're considering, the more you can minimize
18 or insulate yourself against the risk inherent and
19 having the later stages of development be something
20 other than optimized, as will be reflected in the
21 guidance. So really, doing that heavy work early can
22 really pay off when it's time for the rubber to meet

1 the road down the road.

2 I'm not so sure if we want to talk about
3 digital health assessments. Have we gone there at all?
4 I can leave that alone. But talking about efficacy,
5 you know, I kind of have two laws of outcome measures
6 that I try to, you know, convey to the staff when they
7 arrive here at the FDA. And these are things I really
8 believe in that makes it very easy in some ways, is
9 that you want to assess meaningful concepts or domains.
10 And you want to ensure that measured changes in those
11 domains are meaningful.

12 If you do those two things, if you're
13 assessing something meaningful and you're scoring it
14 meaningfully, you're in really good shape to rely upon
15 any change that you find persuasive between the groups.
16 And that really covers a lot of the clinical
17 meaningfulness basis. So that's something we work very
18 hard for.

19 And that really is relevant to the question
20 about altering scales. That's commonly how we modify a
21 scale. We'll have a scale come in. It'll have 20
22 items, let's say, and we'll see that, you know, 15 of

1 those items look very appropriate, maybe a couple
2 tweaks here or there. But five of them are clearly
3 just not meaningful. There's something appropriate for
4 following a symptom in clinic or a physical sign in
5 clinic, and so we take those away.

6 And, again, that drives the psychometricians
7 nuts. They wonder what have you done to the
8 performance of my scale. But it doesn't decrease the
9 fact that if you do detect a change, you can interpret
10 it. And I think we've done very well there. And,
11 again, the constraints we have upon our situations
12 where that's all that you can do, pardon me, make that
13 a really good effort for that particular situation. So
14 I would really encourage people to keep that in mind.

15 I have a few other thoughts, but I can stop
16 there. I've been talking for a few minutes.

17 DR. PAPADOPOULOS: Maybe a couple of minutes
18 we have. We're a little bit over. But I, I really
19 want to hear your thoughts.

20 DR. DUNN: Oh, you want more?

21 DR. PAPADOPOULOS: Yeah.

22 DR. DUNN: Okay. So I see a good movie lately

1 -- no, digital health assessments. I mentioned I
2 wouldn't talk about those. So I know there's been some
3 discussion about whether that's a fifth COA, a fifth
4 type of COA or not.

5 You know, I don't really think so, but we may
6 end up doing that. But I'm not too troubled by that.
7 Call it what you want. You know, I think it's an
8 artifact of the definition to some degree. They really
9 aren't that far, if you think about it, from
10 performance outcomes or observer-reported outcomes.
11 It's just how we define who's doing the reporting in
12 those situations.

13 And they can even play a role in an augment
14 traditionally-defined clinician-reported outcomes and
15 patient-reported outcomes. What we do, do when folks
16 want to use these is that we pay an awful lot of
17 attention that the devices do what they say and that we
18 know what the output means. It's very common for these
19 enthusiasts in this space to just say, it's going to
20 give you an output, and it's going to work, and trust
21 us. And we have a lot of real good experts here, both
22 on CDER and especially with our device colleagues who

1 really do a great job thinking about what are these
2 devices doing, how are they working, and is the
3 information we're going to get from them going to be
4 what it is advertised to be.

5 But I tend to have a pretty simple view of
6 these things. As long as we get those technical
7 aspects right, I have to tenets about applying digital
8 health technology into trials. Let's do something more
9 accurately or better with regard to efficacy endpoints
10 or another endpoint that we traditionally do. Or let's
11 allow it to measure a meaningful endpoint that weren't
12 previously feasible or easy to assess.

13 So let's not just do it because it's cool and
14 it's the new thing, and everybody wants to strap
15 something to their wrist or their head or, you know,
16 whatever it is. But let's do it better. Let's do
17 something better or find things that were previously
18 undetectable.

19 And so I try to make sure our discussions with
20 our sponsors are guided in that direction to ensure
21 that we're accomplishing something there.

22 Another thing that I wanted to point out, just

1 'cause I had made some notes to myself is the, is the
2 real importance of precompetitive work in this space.
3 I already spoke to the fact that we often have resource
4 limitations for the folks who are working, particularly
5 with small populations. But we need to succeed, we
6 need to get there.

7 And I think people are really starting to buy
8 in. People know I sing this song a lot, but people are
9 starting to buy into the fact that when situations are
10 under-resourced on an individual basis, the advances
11 that we can get from pre-competitive sharing and
12 knowledge benefit all. They'll benefit the patients,
13 and they'll benefit the individual contributors to that
14 data base.

15 So that's something that we work really,
16 really hard on. We're highly engaged with the Critical
17 Path Institute on multiple fronts, as well as with a
18 number of typically smaller private consortia that are
19 working on this as to provide maximum benefit to our
20 incremental increases in scientific knowledge. So
21 that's something that I just can't emphasize strongly
22 enough as we think about developing new measures is the

1 fact that we can really work together pre-
2 competitively, which the FDA will participate in, as we
3 all know, and help ourselves get there.

4 I want to try a second time to stop and see
5 what you think.

6 DR. PAPADOPOULOS: And, yes, with that I'd
7 like to thank all of the panelists for a very
8 informative session.

9 (Applause.)

10 DR. CAMPBELL: Thanks, Elektra. So we went a
11 little over. So what we propose is maybe combining the
12 Q and A time from this session with the next session,
13 'cause the next sessions also going to focus on the
14 similar presentation. And so we'll just do Q and A all
15 at once if that's okay. So we'll just go ahead and
16 take our break now, and we'll try to come back around
17 3:30, 3:35. Is that reasonable? 3:35. Thank you,
18 all.

19 And this is going to be somewhat similar to
20 what we just had, except this time we've brought in
21 some of our external stakeholders. So I think it's
22 going to be a really great complementary session that

1 we're about to have.

2 So today we have a really great panel ahead of
3 us, and I'm going to have them first introduce
4 themselves and then I'll set up how we're going to run
5 this session. So Robin, can we start with you?

6 MS. CARSON: Sure. Good afternoon. Robin
7 Carson, I'm head of Patient Center and Outcomes
8 Research at Allergan.

9 MS. ALICYN CAMPBELL: Hi, I'm Alicyn Campbell.
10 I'm the global head of Patient-Centered Outcomes
11 Research for Oncology at Genentech and Roche.

12 MR. COONS: Stephen Coons, I am the executive
13 director of the Patient-Reported Outcome Consortium at
14 the Critical Path Institute.

15 MS. FOXWORTH: Phyllis Foxworth, I'm the
16 advocacy vice president for the Depression and Bipolar
17 Support Alliance.

18 DR. KLINE LEIDY: Good afternoon, my name is
19 Nancy Kline Leidy. I'm the senior vice president of
20 Scientific Affairs and Patient-Centered Research at
21 Evidera.

22 DR. WEINFURT: Hi, I'm Kevin Weinfurt. I'm a

1 professor in the Population Sciences Department at Duke
2 and a member of the Center for Health Measurement.

3 DR. CAMPBELL: Thank you. And so how I want
4 to start this session first is really to get some
5 instantaneous reaction from our panel, from our
6 panelists on what they just heard from Elektra's
7 presentation, and some of the discussion we heard from
8 our cross-center panel.

9 So if we could just ask, if I could ask you
10 guys just to give a couple minute's thoughts of what
11 you just heard. And then we're going to segue into our
12 questions about the roadmap and the decision tree
13 figure. But was your initial reactions to what you
14 heard? So we'll start with Stephen with that.

15 MR. COONS: Thanks a lot, Michelle. Well, I
16 think I was very appreciative of the fact that we did
17 have the FDA folks weigh in on this and give us their
18 perspective, and I think that's critically important.

19 One of the things, and Elektra brought this up
20 in terms of mobile devices, or mobile technology, and I
21 -- in terms of potentially adding it to the roadmap,
22 and I think that that is an important question. I

1 don't think it needs to be added to the roadmap, 'cause
2 I think as -- I think Paul mentioned that it's really
3 just another mechanism for collecting data and
4 particularly clinical outcome assessment data.

5 And I, but I think what I've seen here in
6 terms -- and what I've heard here, in terms of the
7 documents that were prepared and the things that we're
8 talking about, we're making some important steps from
9 the original PRO Guidance and providing a lot more
10 information that's going to be incredibly useful for
11 all of us, all the stakeholders that are in this area.

12 So I guess that's it from me for now.

13 DR. CAMPBELL: Thank you, Stephen. Phyllis?

14 MS. FOXWORTH: Thank you. I, too, appreciated
15 the FDA being here and giving their perspective, as
16 well as having the opportunity to have read the
17 guidance beforehand as part of my homework.

18 And one of the things I would say, share from
19 the patient perspective, I think it's a great start.
20 It's a good document. It's accessible to patients. I
21 mean the language is accessible. I will admit that it
22 is very overwhelming from a patient perspective, and

1 also very intimidating. But I like the fact that the
2 language -- it was clear to me that the language was
3 intended to make it accessible to someone who's not a
4 data scientist or part of the regulatory community.

5 But having said that, one of the things that
6 throughout when reading the document, as well as
7 through the comments today, one of the things that I
8 found missing that I would like to see is that it does
9 a great job of explaining the what, but for me, as a
10 patient, not necessarily the how.

11 And so what I mean by that is, you know, how
12 was the patient input gathered for the, just drafting
13 the document. One of the things that I heard in the
14 panels this morning was the need for a patient advisory
15 committee in developing tools. And I would just love
16 to be able to comment, you know, into the docket on the
17 process of how we got the patient input into the
18 overall process of creating this in the first place.

19 DR. CAMPBELL: Thank you, Phyllis. Nancy?

20 DR. KLINE LEIDY: General comments, the
21 document is a good start, and the panel discussion
22 earlier today was an excellent foray into the FDA's

1 consideration for how we can improve upon the document
2 as it's been drafted.

3 Couple of things came to my mind throughout
4 the day, actually. The first is I agree with the
5 comment in the previous panel that digital health seems
6 to be a method rather than a type of outcome per se,
7 and we really need to think about how can that method
8 be applied in order to develop endpoints that are
9 meaningful.

10 Right now I think we're restricted to steps
11 and activity, which is an important outcome, but then
12 how is that translated into endpoints, and could it fit
13 into one of the other categories so that we don't
14 overcomplicate our lives.

15 The second thing that I hope this panel
16 especially discusses is my radar are up on the use of
17 existing measures. I think it's a great idea to use
18 existing measures. The question is, how do you modify
19 an existing measure and what constitutes modification
20 and why.

21 As a developer of instruments, I can tell you
22 that modifications are recommended by almost everyone,

1 and slight little improvements can really create
2 problems in standardizing outcome measures. So we
3 really need to think about the rationale for
4 modification, the process for modification and making
5 sure that that process is systematic. And that we
6 actually take some of the documents and figures that
7 are in the guidance document that we have now and truly
8 make them applicable to the modification process so
9 that we can really formalize that process rather than
10 saying, oh, you can use an existing measure, just
11 modify it.

12 Let's make it systematic and then make sure
13 that the application then is standardized in a modified
14 way so that it can be used, you know, continually in
15 that new context of use. So let's really address the
16 modification issue. It's extremely important.

17 And then I think we're going to have an
18 opportunity to talk about what exactly does context of
19 use mean and how do we apply that across the board, so.

20 DR. CAMPBELL: Thanks, Nancy. And I think,
21 hopefully in our next part when we start talking about
22 the roadmap we can get into some of those questions and

1 discussion, and our panelists can start thinking about
2 that, about what is modification and what would it look
3 like. I think it's a really great point. Kevin?

4 DR. WEINFURT: Just a quick high-level
5 reaction. First of all, I was very grateful to be a
6 part of this and to get a chance to review the
7 materials. And the thing that I was struck with, both
8 in the materials and in the discussions today so far
9 was just the thoughtfulness that has gone into this.
10 It's clear in reading the documents and hearing the
11 discussions from FDA that there is an appreciation of
12 the types of challenges that people have been facing
13 both outside and inside FDA with respect to these
14 issues.

15 And all throughout the guidances, especially
16 Guidance 3, there are repeated commitments to
17 thoughtfulness and flexibility, which I think is just
18 terrific. I think some of the challenges, then, will
19 be translating the sentiment of flexibility and
20 thoughtfulness into more of a, what does that mean.
21 What does that thoughtful process look like. What's an
22 example of a reasonable argument to be made in a

1 particular case, so.

2 DR. CAMPBELL: Thank you, Kevin. And I do
3 think that's a really important question about what
4 does flexibility look like. And perhaps we can touch
5 on that a little bit when we talk about what would
6 modification look like. Robin?

7 MS. CARSON: Yeah, just to echo something that
8 Kevin had stated. You know, first I just want to
9 acknowledge both the panel's efforts and all of the
10 efforts at the FDA that have gone into the discussion
11 document. It's truly appreciated. It's clear you're
12 listening to the challenges that everyone is facing in
13 the multi-stakeholder environment.

14 With respect to directory actions to the
15 panel, I think the one thing that really resonated with
16 me is that an endpoint is an endpoint, right? And so I
17 think if we can reiterate that to our cross-functional
18 colleagues. It's not just the PRO people, right. What
19 are you bugging me about now, is sometimes the reaction
20 we get. And why is the quality here or the methods
21 different. And I think the quality is not different.
22 The level of rigor is not different. Sometimes the

1 methodology to get there and the skillset needed is
2 different.

3 But if we can emphasize that, as well as
4 better define, you know, concept versus measure versus
5 endpoint, to get us all talking the same language and
6 help them understand the benefits. Just so we were
7 talking earlier, I think Tara mentioned it. It's not
8 just about better quality endpoints, it's about better
9 precision and an ability to detect treatment benefit.

10 So I think if we speak in the terms and
11 incentivize on the aspects of trial design and clinical
12 development that apply to a broader stakeholder group,
13 they'll begin to feel some accountability. And we can
14 talk more about that in the roadmap. I think there are
15 aspects of application and implementation that we can
16 bring in that will make them feel and identify more
17 with the roadmap as opposed to this is just instrument
18 development. It's something different than what I do.

19 DR. CAMPBELL: Thank you, Robin. And Alicyn?

20 MS. ALICYN CAMPBELL: Thank you. I really
21 enjoyed the last session. I thought it was really
22 helpful to hear the different directors at the FDA's

1 perspective, and I really appreciate their time.

2 What really resonated with me was what brought
3 us back to why we're here, which is we really need to
4 start with the outcome of interest and the concept of
5 interest that's relevant to patients. We then need to
6 think about how that can be measured in an endpoint and
7 we construct an endpoint to measure that concept or
8 outcome of interest. And then we choose the right tool
9 that will measure it in the most rigorous and reliable
10 way.

11 And I really appreciated Dr. Dunn's comments
12 that digital health is just another tool we have to
13 measure what's most relevant to patients. And I do
14 think it's important, then, instead of focusing on
15 technology, we remind ourselves as measurement experts
16 that we're here to understand what's most relevant to
17 patients, measure that in a rigorous and reliable way.
18 Because if we don't as researchers, we're all doing a
19 disservice to the patients we have the honor to serve
20 with the work we do.

21 DR. CAMPBELL: Thank you, Alicyn. I thank
22 everyone for those opening remarks. It seems to all

1 resonate on the themes that we continue to hear, even
2 from this morning's session about some great advances
3 that were seeing. We see some challenges that we may
4 need to continue to address in our guidance documents,
5 but it's a great start. And definitely some more
6 examples on what is flexibility and what does that look
7 like.

8 So I want to transition to our panel to our
9 question that we've been charged with answering, which
10 was about the roadmap that was presented. There was
11 some lengthy discussion in our cross-center panel about
12 this. But from your perspective, does the roadmap
13 capture the appropriate elements and strategies to
14 select and/or develop and/or modify back to Nancy's
15 point for COAs for use in clinical trials. And if not,
16 what is missing? So I'm going to pull up this slide so
17 we can see it. It's on the screen for everyone. And I
18 want to turn this discussion over to what are your
19 thoughts about this? Are we heading in the right
20 direction? Are we missing something fundamental? So
21 I'm going to start with Kevin with this.

22 DR. WEINFURT: I think that one and two were

1 reasonably clear. It felt a bit like 3, 3B and 3C,
2 especially 3C, I wondered how applicable those were
3 going to be across all COA types. The language is very
4 much taken from psychometrics. And one general theme
5 I'll have is that there are alternative measurement
6 models that might be appropriate for other types of
7 measures. So we ought to perhaps look for places where
8 we're inadvertently dictating that people use one
9 particular type of measurement approach.

10 DR. CAMPBELL: Okay. We'll just work our way
11 right up there. So, Nancy, what are your -- some
12 thoughts you have?

13 DR. KLINE LEIDY: I thought the comment in the
14 last session about be careful about the use of the word
15 steps and how do we communicate the iterative process
16 was a very good one. The other piece of it is I think
17 the title of this is steps in development. So we kind
18 of, it's development and modification. So perhaps we
19 need to think about this as a process of readying.
20 It's really a process that you're using to ready a
21 measure either through the development or the
22 modification process so that it is ready to be used in

1 a pivotal trial for evaluation purposes.

2 So we might want to think a little bit more
3 about the title of it so that it adequately addresses
4 the process that's being used. Yeah, I think -- other
5 than that I think it's applied nicely from the, I mean
6 it's a nice slight modification from the original
7 version of this table.

8 DR. CAMPBELL: Okay. Phyllis?

9 MS. FOXWORTH: So I'm going to take a slightly
10 different direction than the rest of my panelists here.
11 I'll be speaking to the, addressing that question as
12 far as the elements and does it contain all the
13 appropriate elements, speaking as a patient
14 representative from a patient population that lives
15 with a progressive and a chronic condition.

16 And some of the things that I guess I would
17 just like for the agency to take under consideration,
18 just some suggestions on elements that I think are
19 missing, especially when I look at understanding the
20 disease or condition, the natural history.

21 One of the things that I think that is
22 important is to understand the important of relapse and

1 the environmental factors of relapse on that condition.
2 So, for example, is it cyclical. Someone living with a
3 mental health condition of depression or bipolar
4 disorder, they may find that the environmental factors
5 of, or external factors could be the reason for the
6 relapse. So understanding the natural history and how
7 that affects relapse, I think is an important
8 consideration.

9 Another important consideration when thinking
10 about clinical trials, and understanding the natural
11 history is a past experience, especially for someone
12 who's living with a condition that has -- while there
13 might be multiple alternative options for a therapeutic
14 intervention, none of them are working. Well, why is
15 that? And is there an opportunity for understanding
16 what -- in the clinical trials what has been the past
17 history and what bearing that has on that particular
18 clinical trial.

19 Tied in with that, I would suggest looking at
20 genetic testing. I mean just in the condition in which
21 I represent, two-thirds of individuals will go through
22 multiple therapeutic options before they find one that

1 works. Other people, a full one-third of them will
2 never find an option that works.

3 And genetic testing is proving promising in
4 being able to identify for people, especially those
5 living with depression, there are genetic tests that
6 can identify which classes of medications would be
7 optimal for you. What the metabolism rate is. Those
8 are all things that would be an important aspect from
9 our population that I represent in the clinical trial.

10 The other thing that I would like to touch on
11 around elements that I think that -- make some
12 suggestions for elements that could be included under
13 the patient and caregiver perspectives is under the
14 clinical definition of benefit. And I think that if
15 you talk to most of the peers within my community, that
16 the clinical definition of benefit probably doesn't
17 resonate with them. It's probably not the same
18 definition.

19 So when we're looking at clinical trials, it's
20 extremely important that we have good definitions of
21 what a clinical benefit is, and make sure that also we
22 have a, that we're representing what is the patient

1 benefit, because as I said, they are typically, at
2 least in my community, not the same thing.

3 Another area that we should be looking at is
4 on impact of change. And I would respectfully ask that
5 we consider whole health considerations there, that
6 that involves, you know, not only just the whole health
7 of the individual, but the impact of navigating the
8 healthcare system. Because individuals, depending on
9 their ability to navigate the healthcare system, they
10 may have different risks and benefits and different
11 tradeoffs that they're willing to take just based on
12 things such as equitable accessibility to healthcare,
13 which can be, you know, a big barrier to their
14 determining what is the appropriate benefit and risk
15 for them.

16 Moving over to the conceptualizing the
17 clinical benefit. One of the things that I would
18 encourage us to take a look at is under the surviving
19 fields and functions, I think there's something really
20 important missing there. In our community we call it
21 thriving, and I've been cautioned that that is not the
22 appropriate word to use for this community. That it

1 means something very different.

2 So let me just share with you what we mean by
3 that in my community. We talk about we're not, we're
4 not looking to just survive, we want to thrive. And to
5 do that, I'll just give you an example walking through
6 the fields, which is symptoms and functions, and what I
7 mean by that.

8 I was talking to a woman from San Francisco
9 just last week, and this woman lives with a mental
10 health condition. She lives with a mood disorder. And
11 she has an MBA and has had a position as an executive
12 in a high level company in sales as a sales executive.
13 She is now working in the retail environment. She
14 works and is the top sales person at that store, and
15 she gets, you know, her commissions based on that.

16 But let's take a look at the charts here.
17 She's surviving, yes, she is. She's surviving. She
18 feels -- if you looked at a WHO-5 wellness index or if
19 she has a scale, you'd say she's doing great. She's
20 marking those all off. Is she thriving? She tells me
21 that there's nothing more than that she'd love to be go
22 back to the position where she can use her MBA. So I

1 would say she's not thriving.

2 And I think that that's something that we need
3 to be capturing from a patient perspective. And then
4 again, I'm not married on language. So if thrive is,
5 it means something different in the regulatory
6 community, I'm, you know, perfectly, you know, happy to
7 find a different word for that. But I think that's a
8 very important concept that's missing.

9 DR. CAMPBELL: Thank you, Phyllis, for those
10 concepts and those good thoughts for us to take back
11 and consider going forward. Stephen, do you have
12 anything you'd like to add?

13 MR. COONS: Sure, just a couple of points that
14 I'd like to just put out there as food for thought. In
15 terms of the conceptualizing clinical benefit, we, I
16 really feel that we need to think about the source of
17 the information there rather than in three.

18 You know, we talk about selecting the clinical
19 outcome assessment type, but I think when we're talking
20 about the concepts and who should be reporting those
21 concepts or how we should be assessing those concepts
22 that it's really an integral part of column two. And

1 we can certainly talk more about that.

2 The other thing, and there are a couple minor
3 things under C on column three, I don't understand why
4 construct, validity, and reliability are in the same
5 bullet. It's a minor point, and it's not anywhere near
6 as important as what Kevin brought up about, you know,
7 are we too psychometrically oriented here in terms of
8 this issue.

9 The other thing relates to engage FDA early
10 and throughout medical product development. And I know
11 the FDA says this a lot. And I think it needs to be
12 considered in terms of what that means and how it can
13 be done, particularly in the INDND, BLA sort of path.
14 Because I think there are a lot of folks that really do
15 want to get FDA feedback on a COA tool for their trial,
16 and they find it very hard to do. So just something to
17 consider.

18 And then there was another line that's not
19 here, but it was a note under this that said, "Note,
20 this roadmap can also be used to conceptualize
21 tolerability or risk." And I certainly understand the
22 issue of tolerability. We need to think about the

1 issue of symptomatic adverse events, and we should be
2 assessing that routinely, no doubt about it.

3 Risk, though, is a more objective phenomenon,
4 and that's not something that we would ask patients
5 about specifically. We can ask them about their
6 perceptions of risk or, as Patty was saying, the term
7 harm may be more appropriate. And if it's getting at
8 this issue of, you know, patients willingness to
9 tradeoff, you know, real or hypothetical risks for real
10 or hypothetical benefits, then that's a totally
11 different exercise. We might use discrete choice
12 exercises or something like that.

13 So I guess I'd like reconsideration of this
14 note, this roadmap can also be used to conceptualize
15 tolerability or risk. 'Cause it seems like it's sort
16 of a throwaway line. And then there's no further
17 discussion of, well, how would this roadmap be used for
18 that.

19 The other issue is that along with that,
20 safety is mentioned on page 14, that concepts related
21 to treatment safety tolerability or burden may also be
22 measured by COAs. And I think -- and that's a little

1 problematic. And I think we don't want to be
2 conflating safety assessment in a clinical trial with
3 what we're doing in terms of clinical outcome
4 assessment for efficacy on points essentially. But I
5 do understand how we can look at patient-reported
6 tolerability. But safety is a much broader issue. And
7 there is a path for collecting safety data that is
8 traditionally done in a way that the patient isn't as
9 involved as they should be.

10 And I'm very much a proponent of, along with
11 safety, safety reporting within a clinical trial, which
12 is usually done by the clinician, that there should be
13 patient-reported routine and systematic assessment of
14 patient-reported adverse events.

15 So those are just a few comments.

16 DR. CAMPBELL: Thank you. Alicyn, do you have
17 anything you'd like to add?

18 MS. ALICYN CAMPBELL: Yeah, thanks, Michelle.
19 I have four points on this topic. The first is similar
20 to Stephen's. I think at the bottom it talks about
21 engaging FDA early and throughout medical product
22 development. And I'm part of a number of

1 precompetitive collaborations where I have the pleasure
2 of partnering with a number of my sponsors. And
3 clarity and timing in expectations regarding agency
4 feedback and sponsor communication, I think it will be
5 really important to clarify.

6 In my discussions with other sponsors, this is
7 where things tend to fall down on the path for evidence
8 inclusion and labeling. Feedback is either not
9 received at the right time or often folks get feedback
10 in response to type B or C packages that acceptability
11 and inclusion will be a review issue. That's really
12 hard for teams to digest. Because it's really
13 challenging for them how can they derisk that along the
14 development program.

15 And so I think it'll be important to be quite
16 clear about the type of feedback and when it's received
17 if we want to be successful.

18 The second comment will be around digital
19 measures. It's similar to what was mentioned before,
20 but since my colleagues are passionate about this, I
21 want to make sure I'm super clear. So we really feel
22 that digital measures, including electronically

1 administered performance outcomes and passive
2 monitoring, since they're being increasingly used, we
3 need clarity on how exactly they will be classified and
4 evaluated in a regulatory context.

5 Our recommendation was similar to what I was
6 happy to see Elektra present earlier, which is to
7 really break the performance outcome category into
8 standardized tasks. So those are measures where a
9 patient is instructed to perform a specific task. And
10 then monitoring measures where the patient's instructed
11 to behave as normal, but in the knowledge that their
12 activity is being monitored.

13 We'd also recommend further discussion about
14 how you might determine which type of PerfO is
15 appropriate in column three of this figure. It would
16 be really helpful for clear articulation about how
17 either digital PerfOs or passive monitoring tools will
18 be evaluated by the COA framework and what their
19 empirical evidence requirements will be.

20 From a reading of Guidance 3, Appendix 1, it
21 would appear that all the information in that section
22 would be applicable. However, explicit clarification

1 would be extremely helpful, as their use is expanding
2 so that stakeholders can be prepared for agency
3 evaluation and interactions, and the agency's also
4 getting what they need for their evaluation.

5 Because I'm the oncology person, I have to
6 comment on blinding while I'm here. For those of you
7 who know me, you won't be surprised. While we
8 understand the desire to remove the potential risk of
9 assessor bias, this is neither operationally feasible,
10 nor frequently ethical in hematological malignancies
11 and rare diseases, for example, hemophilia A.

12 When treatments are being compared to active
13 entities with different schedules and routes of
14 administration, particularly intravenously, adding in a
15 placebo is quite a challenge and often not appropriate.
16 Additionally, treatment toxicities, if we were to
17 blind, can lead to inadvertent unblinding through a lot
18 of the social media and discussion forum that Patty and
19 others spoke about this morning.

20 So our perspective is in settings where
21 patients are receiving active treatment and the
22 concepts being reported are quite specific, such as

1 symptom severity or symptom interference with daily
2 activities, the bias should really be of minimal
3 magnitude as to not significantly impact the results in
4 their interpretation.

5 And then, finally, we really appreciated the
6 section on observer reported outcomes, and I was really
7 pleased to hear from Elektra's section that they'll be
8 kind of sub-guidances on these. And we really think
9 ObsRo is an important source of real-life experience on
10 how patients feel and function if we really want to get
11 at Section II, Part A. This is important empirical
12 evidence, and we really don't want to miss out on this.

13 And so I think to get to that next level of
14 success it would be helpful to have the agency clearly
15 define what they find a reliable observer to be.

16 'Cause in the past when we've collected this data we
17 haven't been as successful as we'd like to be in
18 including it in labeling. Thank you.

19 DR. CAMPBELL: Thank you, Alicyn. And, Robin,
20 do you have anything else to add?

21 MS. CARSON: Yes. And I think I agree with a
22 lot of what's been said today. And I just want to

1 reflect on the positive, certainly with respect to the
2 roadmap. I think the addition and emphasis on
3 modifying existing measures and leveraging those is a
4 wonderful addition, as well as the extension to broader
5 COAs.

6 The other thing that really resonated with me
7 coming from an ATOR [ph] background and training is
8 that it is reflective of the multi-stakeholder view.
9 In column one it certainly calls out the need and
10 emphasizes patient and caregiver, but it also allows
11 for a broader healthcare system perspective. And
12 thinking about clinical practice as well as how access
13 to medicines are achieved in a certain condition.

14 I think this is important because I think we
15 all recognize that regulatory approval is sufficient,
16 or is necessary, but insufficient. And, you know, what
17 we're all trying to do is get patients medicines that
18 will improve their lives. And so we really need to be
19 thinking to the extent we can what's relevant in a
20 regulatory context for patients, but beyond that as
21 well. Are there outcomes that, you know, core outcomes
22 -- and I know this was mentioned earlier in terms of

1 the RFI about looking towards core outcome sets that
2 might be the minimum set that are applicable across
3 both regulatory, clinical practice, and even market
4 access.

5 To that end, I think there might be a value in
6 building out what we mean by expert perspectives in
7 column number one. So giving some examples of those
8 other stakeholders for folks who have not used to be --
9 aren't used to thinking beyond the regulatory context.

10 In addition, as I eluded to earlier, I think a
11 big part of this roadmap for consideration to add could
12 be a fourth column or perhaps sprinkled within if
13 you're adverse to a fourth, but it stops short of
14 identification and development. And it doesn't talk
15 about the implementation or application of the measure.

16 And that's where things like the final
17 endpoint definition and what's prespecified in the SAP,
18 what analyses, what sensitivity analyses are we going
19 to be doing? How are we ensuring that quality is
20 preserved when we put it onto an ECOA or digital health
21 technology? Translation and linguistic validation, all
22 of these things tend to be thought of as extra. Oh,

1 they'll just happen. And there's groups that do those.

2 And I worry that we tend to regulate those to
3 a more operational aspect. And they're critical to
4 preserve the precision and quality of what we've spent
5 years, sometimes developing in a scientifically
6 rigorous way, especially as we go global.

7 So I think that's really important and could
8 also, again, come back to that cross-functional aspect,
9 make our stakeholders and other functions aware of how
10 the rubber really meets the road here in the context of
11 a clinical protocol and how they may help as well.

12 I would be remiss if I didn't also comment on
13 the, you know, double-edged arrow there at the bottom
14 in terms of engagement with FDA. I think that's a
15 wonderful addition, and I think everyone really does
16 recognize the value of that. But it's definitely one
17 of our biggest barriers today.

18 Particularly, again, getting cross-functional
19 buy-in and agreements that, that should be a priority.
20 So the more that we can educate others in regulatory
21 and, you know, statistics, and clinical, etcetera, that
22 the discussion around COA endpoints, the development,

1 the validation, the interpretation are just as critical
2 as the dosing and the trial design, I think we'll all
3 have much more efficient discussions.

4 So some clarity and timelines and even just
5 from FDA how to make our submissions more efficient for
6 you. Do you, you know, what do you like to see, and
7 how can we make that more efficient? Maybe there's an
8 opportunity to increase slightly meeting times instead
9 of additional meetings from the sponsor perspective.
10 Additional meetings are double the work. Adding a half
11 hour to an existing meeting would be incredibly more
12 efficient from our perspective. It might allow us to
13 address one or two more topics. I know that may not be
14 feasible, but I just wanted to throw that out there.

15 The other place that I see, and I'm looking
16 forward to the subsequent guidance for, I see a lot of
17 teams struggle when they get to the end of the roadmap
18 and they think, just, okay, well, we've got our line in
19 the sand in terms of interpretation. How do we
20 translate that to an endpoint? And, again, I think
21 where that fumble tends to happen is because that is a
22 very cross-functional exercise.

1 It requires statistical and PRO expertise, as
2 well as clinical expertise, inside and outside of the
3 company. And oftentimes it's not clear how to make
4 that leap from a responder threshold to a responder
5 definition, which might take into account time spent in
6 that health state. You know, what is the right number
7 of weeks? Is it responder or should we go continuous?
8 And so I really look forward to that endpoint guidance,
9 because I do believe a lot of folks are struggling with
10 how to make that leap.

11 I think we've spent a lot of time in years on
12 the aspects already illustrated here, but the endpoint
13 definition needs a bit more time.

14 And lastly, the one thing I just want to
15 mention, while it does seem that there's more interest
16 in leveraging existing measures, I think we have to be
17 careful that we're clear on what type of documentation
18 is needed when we want to modify and use an off-the-
19 shelf measure.

20 You know, we've mentioned here in 3C, Develop
21 and Evaluate a COA, I would say that probably needs to
22 be evaluate and document a COA. Because whether it's

1 new or modified, you need to evaluate it, and you need
2 to document that. But how far do you go? Does
3 precedence in labeling negate the need for additional
4 company to do their own content validity documentation?
5 I mean we're talking about improving drug development
6 and overall efficiency.

7 So I think some clear guidance on truly the
8 documentation needed in the modification space would
9 lead to a lot of efficiency.

10 DR. CAMPBELL: Well, thank you, Robin, and I
11 want to thank the panel for those thoughts. One
12 resonating theme I heard was that really this column
13 three is where there's good starting information, but
14 we need some more things. You seem to be missing or
15 there's maybe unclear information, or are we focusing
16 on the wrong things.

17 For example, Kevin mentioning, you know, 3C
18 seems to be a little measurement property heavy versus,
19 you know, such things. So does anyone have any
20 thoughts of what additional things they would like to
21 see or clarity or is there maybe a better way of
22 presenting this column? Stephen?

1 MR. COONS: Well, Michelle, I would like to
2 just second consideration of a fourth column. And I
3 think this idea of expanding this to not only selection
4 or development for clinical trials, but selection,
5 development, and implementation in clinical trials
6 because I think that's an incredibly important point.

7 And as you mentioned, Robin, Guidance 4 is
8 going to address more of the endpoint side. But
9 there's no reason why this couldn't go that next step
10 and talk about that and all of the other things that
11 you mentioned. The translatability issues, and
12 implementation on electronic data capture platforms,
13 etcetera.

14 So I think there are an awful lot of things
15 that ultimately mess up the implementation of a
16 clinical trial that would be in that fourth column. So
17 I second that suggestion.

18 DR. CAMPBELL: Kevin?

19 DR. WEINFURT: And I also second bringing in
20 considerations of thinking through how the measures
21 will be used as endpoints earlier in the process here.
22 And I think when we talk about endpoint definition,

1 endpoint positioning, I think this, in the context of
2 this here it's a, kind of an earlier rough version of
3 it. But when you're forced to think through exactly
4 how you'll use the numbers, one of the things that it
5 can do is to help avoid the error of trying to solve an
6 analytic problem with a measurement solution.

7 So, for example, taking presence and absence
8 of some symptom or function and agree to which that
9 symptom or function is happening, and trying to combine
10 those together into the same score somehow, when you're
11 just focusing on how should we measuring this thing
12 right now, that usually results in something not
13 helpful. But if it was built in, but right now the
14 analytic guys are sitting down and figuring out what
15 are the analytic options for this, or we've got this
16 high-dimensional diary data, all right.

17 If the analytic considerations are brought in
18 earlier, then we wouldn't have some of the clumsy
19 approaches that we use sometimes to try to reduce the
20 dimensionality of the data with a measurement strategy
21 rather than an analytic strategy.

22 DR. CAMPBELL: Thank you, Kevin. Phyllis?

1 MS. FOXWORTH: I agree with what my colleague
2 over here to my right has said about needing another
3 column for implementation. I think that would be
4 extremely helpful.

5 But when I'm going back again and looking at
6 the -- starting with section A, and what I see missing
7 is, you know, I see patient-reported outcomes and on
8 down the line, but I don't see anything that says are
9 we measuring the right, and collecting the right
10 outcome in the first place.

11 So I'd love to see something before that, that
12 you know, was an opportunity to understand what is it
13 that the patient wants measured? That's one of the
14 challenges that I think we have with just a patient-
15 reported outcome is that it's nice that a patient gets
16 to report their outcome, but are we reporting on what
17 is it we want measured.

18 So I would just love to see a bullet before
19 that list that somehow indicated that we actually got
20 the patient input into what it was that we wanted the
21 COA to be measuring in the first place.

22 DR. CAMPBELL: Thanks, Phyllis. I actually

1 think that perhaps what you're saying is maybe some of
2 the ordering in this column. Because you're kind of
3 referring to the content and validity that we're
4 measuring what's important to patients and we've
5 captured that.

6 Perhaps the ordering needs to be changed to
7 reflect that, which would help us guide was the best
8 way, as also was mentioned earlier about what is the
9 therapeutic aspect of the drug. So what are trying to
10 target? So are those symptoms matching? Have we
11 captured everything together? Maybe there's some
12 reorganization that needs to be done. Is that what I'm
13 hearing, perhaps?

14 MS. FOXWORTH: I think that would be helpful,
15 yes.

16 DR. CAMPBELL: Okay. Stephen?

17 MR. COONS: Well, I think the other thing that
18 Phyllis brings up is this issue of under D in column
19 one, Definition of Clinical Benefit. And I think
20 that's easily misinterpreted as what do clinicians
21 think about the benefit? And I think often we tend to
22 use the term treatment benefit. We think it's maybe a

1 little more patient friendly.

2 But I think that's one of the problems right
3 there because that, 1D is where we really are trying to
4 determine what is important to patients. What do they
5 want relieved. What do they -- what are they dealing
6 with that they would like to not have to deal with in
7 terms of this condition.

8 So I, I think we just need to make it clear
9 that that's exactly what that is getting at or is
10 attempting to get at in terms of what is important to
11 the patient's that we would want to treat the disease
12 and have an impact on.

13 DR. CAMPBELL: Okay. Do we feel good about --
14 I want to move on to the next figure. But I just want
15 to make sure are we comfortable with this discussion.
16 I think as we transition onto figure 6, which my
17 version is not going to be as pretty as Elektra's where
18 I did not separate them out. So it will be hard to see
19 on the screen. I apologize.

20 But it is that decision tree. And one thing
21 I'm hoping, if you can think about and reflect as well,
22 was a statement that a lecturer made when she said that

1 "We envision that people will use both this decision
2 tree together with the roadmap." And so if you could
3 also think about that, does it make sense together,
4 their use together? How do we make sure that's done?
5 Things like that. So if you could touch on that as
6 well.

7 As we think about this question is -- and I
8 think I'm hoping we get into this modification
9 discussion that everyone's hinting at. Does that
10 decision tree really capture the process of select,
11 develop, or modify sufficiently? And if not, what are
12 we missing?

13 And then, finally, I'd really like to hear
14 thoughts about should this diagram replace the wheel
15 and spokes that was in the original PRO Guidance of
16 2009. And what are your thoughts on that. So, again,
17 I do apologize for it being small. But what are some
18 thoughts? I don't know who wants to start. Kevin's
19 looking at me. So you win.

20 DR. WEINFURT: All right. I hate to introduce
21 math this late in the afternoon, but there are five
22 possible paths drawn through this, this thing. They

1 all start with step one in the steps of development.

2 Of the remaining four, they all involve two,
3 three, and four, all right. And I think -- so first of
4 all, I love this decision tree. And it helps to
5 highlight the need for even more guidance and tailoring
6 what two, three, and four mean in different parts of
7 this.

8 So the middle box, for example, is about using
9 steps two through four to confirm whether an existing
10 COA could be used as is. On the bottom left it's using
11 those steps to develop a brand new one. And on the
12 bottom right it's using those considerations to modify
13 an existing one.

14 So this is, this is great, but it also called
15 out to me the need for more guidance of what flavors of
16 two, three, and four would I need to accomplish the
17 developing, confirming, modifying. Are there examples
18 that we can give that would help people to understand
19 how if I've got a measure in front of me, how I might
20 review the considerations in two, three, and four to
21 figure out whether it's going to be appropriate for
22 this context of use, or which pieces would need to be

1 modified.

2 So it's great that it calls these things out.
3 And would be even better if there was one more layer of
4 detail than noting that these are three very different
5 functions for which two, three, and four are being put.

6 DR. CAMPBELL: Thank you, Kevin. So I think
7 I'm just going to start up with Robin and work our way
8 down, if that is okay. And, Robin, is that okay?

9 (No audible response.)

10 DR. CAMPBELL: Okay.

11 MS. CARSON: Sure, no problem. In terms of
12 whether or not this should replace the wheel and
13 spokes, I do like this presentation a lot. And I think
14 it will help folks really think through, sort of, the
15 new mindset, right. Does one exist? Do we need to
16 modify?

17 But there are three key things from the wheel
18 and spokes that I think if we could weave back in that
19 I really liked about that tool and that I emphasized
20 when speaking with my internal colleagues.

21 One was the importance of matching the COA to
22 the claim and thinking really early about that end goal

1 with the claim and making sure that we matched the
2 concept and the measure to that.

3 Two, there was an aspect in the wheel and
4 spokes that made it very clear that we were focused on
5 the hypothesized conceptual framework, but that we
6 would iterate that over time and continue to confirm it
7 with patient input, psychometric evaluation, and still
8 end up with a conceptual framework, which is the
9 foundation of any measure. And so I think there's a
10 way to bring that back. It's mentioned in step one
11 below, but we need to weave that back into the other
12 aspects.

13 And then, third, just an emphasis on the
14 iterative nature, which I think we were all debating a
15 little bit earlier about how to really emphasize that.
16 In addition, one thing that I find that may not be here
17 and often isn't top of my intro teams, and it started
18 to come up in the last panel was thinking beyond the
19 measure that you're focused on for the, you know,
20 endpoint in claim to the other measures you need to
21 evaluate it, right.

22 And often we think about those too late. So

1 we'll get to writing the trial protocol around this
2 primary measure and realize, we don't have an anchor
3 question. How are we going to evaluate that measure?
4 Or we didn't think about a measure to evaluate
5 construct validity, whether or not one exists, you
6 know, not always easy. But so I think there needs to
7 be an aspect in thinking about the broader measurement
8 strategy to make sure that you're set up to evaluate
9 your primary measure well.

10 And then in column two, in step two at the
11 bottom, it definitely calls out the need for patient,
12 caregiver, and expert input. But in my experience, the
13 best measurement strategies involve them throughout.
14 So it's not just about a defining the concepts and the
15 items, but re-engaging them with key results and the
16 interpretation thresholds and even conceptualizing the
17 endpoint and beyond.

18 So I would make sure that is pulled through.
19 And then, at risk of sounding like a broken record, I
20 think the implementation aspect is missing. So whether
21 or not we put it in the roadmap or hear, I do recognize
22 that there are some overlaps between the two documents.

1 And I'll have to think through that a bit more, knowing
2 that they're intended to be -- I should say the two
3 tools intended to be were used together. But I do
4 think the implementation here could be about how do you
5 actually think through that and what are the steps to
6 go through.

7 DR. CAMPBELL: Thank you. Alicyn?

8 MS. ALICYN CAMPBELL: Thanks, I unsurprisingly
9 agree with a lot of Robin's feedback. She's also from
10 the sponsor side. In particular, about the conceptual
11 framework and just the iterative process as we gain
12 more empirical evidence that we refine it over time.

13 I definitely prefer this to the wheel and
14 spokes diagram. I think the legacy wheel and spoke
15 figure implied that a new COA was almost always needed.
16 And so this new decision tree really addresses this
17 limitation by demonstrating that it is an iterative
18 process and that modification is not only feasible, but
19 desirable.

20 I was really placed to hear that feedback
21 today. Because there's many cases where we can modify
22 and reuse COAs and provide the requested empirical

1 evidence. For example, in oncology when measuring
2 symptomatic adverse events across tumor types, and due
3 to our development timelines and cost and the need to
4 get life-prolonging treatment to patients quickly, we
5 frequently lack the time for de novo instrument
6 development.

7 And so I really like the way this shows that
8 modification is not only desirable, it's feasible. And
9 I think for all researchers it clearly spells out the
10 steps.

11 Additionally, the only other feedback I would
12 have is I think it'd be helpful to clarify in section
13 two that not every step listed is required when using a
14 measure without modification in a new indication. I
15 think some clarity around what steps are for new COAs
16 versus existing will be helpful for researchers moving
17 forward.

18 DR. CAMPBELL: Stephen?

19 MR. COONS: Yes. I think that's an incredibly
20 important point, Alicyn. And I think that one of the
21 suggestions I have is that you have to give up on
22 getting this on one page. And ...

1 DR. CAMPBELL: We could make the document, you
2 know, legal size, right, paper, make it longer.

3 MR. COONS: Yeah. Right. Right. No, I think
4 because the other reason is, certainly the flowchart
5 deserves its own page, but I think the steps have to be
6 expanded, and it gets to what Alicyn was saying. I
7 don't think this is enough.

8 This essentially -- it says Steps of COA
9 Development. So it still emphasizes the de novo
10 instrument development. And I think you need to walk
11 the talk, you know. And you need. It needs to have at
12 least a couple more of these that actually talk about
13 the stages that you would go through for using it as
14 is. You know, what is the evidence?

15 Because up at the top here, you go across, and
16 yes, there is an existing measure. Yes, there -- it is
17 being used in that specific context of use. And then
18 it says, "Use the existing COA, no additional work
19 needed." Is it as simple as that? I mean aren't you
20 expecting to see an evidence dossier. But, indeed, it
21 does do what it's intended to do.

22 So I think that needs -- there needs to be

1 clarity there. But I also think that having
2 essentially an iterative or cumulative -- I think of it
3 more as cumulative, 'cause it is linear in terms of
4 these -- there are things that need to be done before
5 you can actually do the next step. So I think there is
6 something to be said.

7 I, I like, I prefer this to the wheel and
8 spokes for a number of reasons, but that's one of them.
9 But I do think you really need to consider, and I think
10 it needs to be for the levels of modification, have
11 these steps, but also it really would help. And I know
12 there are going to be appendices on PerfO assessments
13 and ClinRo assessments. There's already a draft for
14 the ObsRO assessments.

15 But I still think it would be helpful to have
16 a plan like this, of steps for performance outcome
17 measures and for the other measures that actually talk
18 more explicitly about the steps you need to take.
19 Because I don't think we can just say, oh, well, look
20 at this and apply what is appropriate for that type of
21 COA.

22 Because this still is very much PRO-centric,

1 PRO measure centric. And so I, I think it really would
2 be helpful. And I hear this from my colleagues within
3 the Critical Path Institute who are attempting to move
4 forward with performance outcome measures in terms of
5 the qualification program. And they really don't have
6 a good set of steps that they would actually follow to
7 get to the end goal.

8 And so I think if, indeed, the time can be
9 taken and you're willing to give up on a one-page
10 document that it would really be helpful to do these
11 other things. Thank you.

12 DR. CAMPBELL: Okay. You have followup
13 Alicyn? Okay.

14 MS. ALICYN CAMPBELL: Yeah, just to echo what
15 Stephen said, I know when discussing this internally we
16 were really hoping for a similar level of detail as
17 Stephen talked about for ClinROs and PerfOs. So in
18 some section the agency has identified differences in
19 the requirements for different types of COAs. For
20 example, inter-rater reliability is required for
21 ClinROs, but not PROs. But further guidance,
22 particularly around differences in determining content

1 validity would be helpful.

2 For example, it might not be appropriate in
3 some cases to ask patients and caregivers about the
4 conceptual relevance of performance-based tests,
5 particularly cognitive assessments. A clinician or
6 other expert might be better placed to comment how well
7 that PerfO captures the concept of interest. And so
8 more detail around that, I think, would empower
9 sponsors and other researchers to provide the level of
10 evidence the agency is looking for.

11 DR. CAMPBELL: Phyllis, do you have anything
12 to add?

13 MS. FOXWORTH: Sure. Thank you. I really
14 like decision trees. They're very easy to follow, and
15 they're very concise. I think this does a great job of
16 describing the what. And I also, you know, I must say
17 that I really respect the agency's commitment to
18 bringing in the patient advocacy organizations as a
19 major stakeholder and with some, with stakeholders that
20 are relevant and have something meaningful to say.

21 So my comment is more focused on that. It's
22 around the how. Because we don't have the legacy as

1 patient advocacy organizations that sponsors and the
2 agency has, we don't necessarily have the information
3 around the how. So how are -- how do we identify the
4 COA and whether there's one that's already of use.

5 How do we engage the patient input and make
6 sure that they're polled through the entire process.
7 And, again, that may be very obvious to many, to the
8 majority of the people in the audience. But as the
9 patient advocacy organizations who are newer
10 stakeholders, it's not as obvious to us.

11 And then just, you know, echoing what has, I
12 think, already been said with regards to the how is
13 that once we've gone through this process, how do we as
14 a patient advocacy organization collaborate with the
15 other stakeholders to move the process along into
16 implementation.

17 DR. CAMPBELL: Nancy, any additional thoughts?

18 DR. KLINE LEIDY: I support the replacement of
19 this, the replacement of the wheel and spokes diagram.
20 I often thought we were going in circles with that.
21 There was no exit.

22 DR. CAMPBELL: Literally going in circles,

1 right?

2 DR. KLINE LEIDY: A couple of just brief
3 comments. One is, many of these boxes are kind of
4 loaded, and I wonder whether they deserve a definition
5 or a description as a separate document. For example,
6 is the existing COA being used for its original context
7 of use. That is a loaded question in the sense that,
8 what do you mean by being used.

9 You mean in drug development and/or academic
10 settings, for example. And what do you mean by
11 original use? Is it completely within the original
12 COA, COU framework, or is it just slightly modified and
13 what evidence does that provide you to support its
14 continued use in that form. So it may be that you want
15 to describe it as a separate -- each of these boxes in
16 a separate annotation or document or appendix.

17 The other piece, the other component of that
18 loaded is used. Does that mean that it's been
19 validated and it's interpretable? Assuming that it's
20 already been used in a label, and the answer should be
21 theoretically yes.

22 The other piece here is -- which we all know,

1 I think, is that each of these yes's and no's are
2 actually not dichotomous. It's kind of a continuum.
3 And that gets at the, is this good enough for this
4 purpose, which was brought up earlier.

5 So but I think for the purpose of a decision
6 tree you kind of have to go with a yes or no and assume
7 that the continuum is part of the consideration.

8 And then last, but not least, is where in this
9 diagram can we actually put the FDA input? For
10 example, if you go from yes, no it has not been used
11 for its original context of use, can the existing COA
12 be used for the new context of use. Is that where the
13 FDA can actually provide input before you get too long
14 in the process, or too far in the process.

15 So I really like this in terms of another
16 component of that process of readying a measure for a
17 use in a trial in that it should be generic enough to
18 apply to all the types of outcomes, assessments we're
19 talking about here. So that we need to get the PRO
20 language out of there and make it much more generic.

21 DR. CAMPBELL: Okay. So are there any other
22 thoughts -- I want to make sure we have plenty of time

1 for question and answer from our audience. But I
2 wanted to highlight something that we're going to be
3 seeing a lot. You've already heard it this morning,
4 but the big picture of why are we here. So are we
5 missing anything out of this document? And then how do
6 we show flexibility while maintaining the regulatory
7 standards in terms with the COAs?

8 A couple things I did hear already that maybe
9 expansion is particularly in the modification area, and
10 this we need to kind of maybe decentralize our PRO
11 terminology to make it more COA-centric. If this is
12 the goal of being a COA guidance. But is there any --
13 does anyone want to expand on some of those things? I
14 know, Nancy, you brought up some of this modification
15 and what does it mean.

16 And I think we are, I feel like we are seeing
17 modification is okay. You can do it. We've been
18 saying that for some time now. But you brought up some
19 good concerns. And so I don't know if you want to
20 expand on that right now on what they are and what we
21 should be thinking about.

22 DR. KLINE LEIDY: Sure. I do think that we

1 could actually lay out a process for modification in
2 the decision making around modification. To use an
3 example, the EXACT is a nice 14-item daily diary that
4 we've used originally for COPD and exacerbations, but
5 over time we've been able to evaluate it for possible
6 other uses. Why recreate the wheel?

7 And if, in fact, these items are suitable for
8 a certain target population, could it be used or
9 modified in a new context of use. So rather than going
10 through and assuming we have to modify the instrument,
11 we've actually gone back to the new target populations,
12 IPF patients, for example, asthma patients, for
13 example, and to see whether or not what patients are
14 telling us, map and match to what the EXACT currently
15 looks like in terms of content and structure. And then
16 if it does, that's great, but will scoring need to be
17 changed because the structure of the instrument is
18 slightly different with this new population.

19 So we're not just going in and twisting and
20 turning items based upon what we know about the new
21 target population, but rather sort of going back,
22 seeing what patients will tell us, and almost do a

1 mini, if you will, sequence of steps, as though we were
2 developing a new instrument, but actually mapping it to
3 an existing measures so we're not starting from
4 scratch.

5 And theoretically we shouldn't, theoretically
6 we shouldn't require huge sample sizes for either
7 content validity or validation if, in fact, the measure
8 seems to be working in one form or another in these new
9 populations. So I actually think there are steps that
10 we could follow and/or recommend to people so that it's
11 an easy way of understanding what would constitute the
12 reason for modification and then what would constitute
13 a modification.

14 And get away from, you know, I really don't
15 like item four, so let's modify that because, you know,
16 I personally don't like item four. That, we don't want
17 to go there. I think that's not a good use of our time
18 or our efforts, so.

19 DR. CAMPBELL: Does anyone else have any
20 thoughts on that?

21 DR. KLINE LEIDY: And one other comment
22 related to that.

1 DR. CAMPBELL: Sure.

2 DR. KLINE LEIDY: Which is, the other thing
3 we're being very careful about is because the EXACT is
4 a standardized measure, and the evaluating respiratory
5 symptoms instrument, which is a derivative of that, by
6 the way we were able to use it for another purpose,
7 we're actually developing a naming convention so that
8 everybody knows the origin of the instrument, ERS is
9 for COPD. But the ERS for IPF will be named that way
10 so you can see the origin of the instrument.

11 So that's another reason why we really have to
12 think about this modification business very carefully.
13 And then last but not least, all of these items have
14 been translated in a reliable way using the
15 standardized process into, I don't know, 45 or 50
16 different languages now. We don't have to start from
17 scratch there. We can actually use those languages and
18 translations as a starting point for the new context of
19 use. So I'm a proponent of modifying instruments in a
20 very systematic evidence-based way, so.

21 DR. CAMPBELL: Thank you. Kevin, do you have
22 anything to add, or does anyone else have any thoughts

1 about this idea of modification, adaption before I turn
2 it over to audience question and answer? We're about
3 to go there. So if you have questions, start thinking
4 about them and heading to the microphones.

5 The word flexibility comes up a lot. We say
6 we're flexible. But how should we really show what
7 flexibility is when we still need to maintain our
8 regulatory standards and our COA development aspects?
9 So do you have any thoughts or things we should think
10 about as we're going forward with this? And you may --
11 Kevin?

12 DR. WEINFURT: This is kind of -- addresses
13 both three and four. I think the thing that is, that's
14 missing right now and that is an opportunity to
15 demonstrate what flexibility means is a focus on
16 starting with what inference you want to make. What's
17 the labeling claim? Starting with that and figuring
18 out what kind of a story that you need to tell that
19 will make sense.

20 What is the rationale for making the claim?
21 What are all of the things that need to be true in
22 order for that last step to be true? How do you tell a

1 persuasive story drawing on different supports for
2 different pieces of that story. 'Cause right now,
3 despite the state of commitments to flexibility and
4 reasonableness and everything, absent examples of how
5 you craft a story like that and what kinds of stories
6 would be regarded as acceptable, you will get what
7 Nicki Bush referred to earlier today as just a
8 checklist mentality.

9 Absent some picture of what that looks like,
10 people will just start checking off the stuff that's
11 listed again. And so I would actually suggest that
12 everything is here to make incredible progress, but if
13 we don't supply some narrative examples of compelling
14 arguments to justify the final inference, all of the
15 good work that's been done will just result in the
16 exact same type of behaviors again.

17 DR. CAMPBELL: Thank you, Kevin. So if our
18 panelists have no other comments or thoughts, I'm going
19 to turn it over to our audience to make sure we have,
20 we'll have a good question and answer session. I do
21 ask that you state your name and your affiliation. So
22 I'm going to start in the front, and then I'll go to

1 the back next.

2 DR. AMTMANN: Dagmar Amtmann, University of
3 Washington. Disclaimer, I haven't read Guidance 3, so
4 I apologize if it's like flushed out in the document.
5 Any chance you could go back to the framework, the box
6 three, box two?

7 So I think that in 2A we need to strengthen
8 that statement. We not only need to identify the
9 concept, we have to define it in a way that allows us
10 to check whether our measure actually measures that
11 construct. And we need to run that definition by
12 patients to make sure that we're not missing something.
13 And that kind of ties into modifying measures. 'Cause
14 I get really uneasy when we start cherry picking.

15 So I want to know when we drop items, I want
16 to know that we're still measuring the domain that we
17 set out to measure. And I want to know whether there
18 are pieces that should have been added that are not
19 there in this new context. And I don't see any
20 evidence of that in, anywhere in these steps. And,
21 again, you may flush it out a little later on, I don't
22 know.

1 And can you show the other part, the steps of
2 measure development? Yeah, perfect. So in box three
3 we talk about assessment of score reliability and give
4 the examples of test/retest or inter-rater reliability.
5 And I worry that that is a very limited view of
6 reliability. Reliability is amount of random error in
7 the score. And where that random error comes from may
8 be less relevant whether, you know, whether it's random
9 error that we observe in test/retest.

10 I would really like to bring in a little more
11 modern psychometrics here and maybe acknowledge that we
12 have better ways of assessing score reliability within
13 item-response theory framework. Where we can look at
14 the information where we get reliability at every level
15 of the trait that we're measuring.

16 But we're using language and concepts that are
17 firmly rooted in classical test theory, which makes it
18 suggest that IRT has no place here. And since we're
19 doing this for future, I would really like that kind of
20 pulled through the whole guidance.

21 DR. CAMPBELL: Thank you, Dagmar. Those are
22 really great comments that we'll take back. Just for

1 my people who are lined up for question and answer, the
2 person behind Steve will be our last one so we can stay
3 on track. So I can make sure we end at the right time.
4 So I'm going to go back to the person at the microphone
5 in the back. You're next.

6 MS. LEITMAN: Thank you. My name is Amy
7 Leitman. I'm the Director of Policy and Advocacy for
8 NTM Info and Research. So we're a rare lung disease.
9 And I wanted to just address something. And this is
10 more a comment than a question. But with the issue of
11 modifying COAs instead of, you know, creating new ones,
12 I think everybody would prefer to modify a COA instead
13 of reinventing the wheel, but I think especially in
14 certain rare disease spaces that's not necessarily as
15 feasible.

16 So my concern is that there's going to be an
17 overemphasis on that. And particularly since these
18 guidances are meant for all constituents, including the
19 agency, I wouldn't want to see there be too much
20 overemphasis. So for example, you know, if you don't
21 have as much natural history on a patient population,
22 or you don't have any drug development or you have very

1 little drug development.

2 So as you go into drug development, you're
3 learning about these patient populations and
4 subpopulations. Yeah, we've seen this happen in our
5 patients. We've seen this happen with bronchiectasis
6 patients. I've seen this happen with acromegaly. And
7 it can stem from anything, including, for example, the
8 physicians who treat them, making these assumptions
9 about these patients, like, oh, well, when they are
10 treated they feel better, and that's not necessarily
11 the case.

12 So I would just say that in the guidance it
13 needs to address the fact that there needs to be
14 allowance made for different rare disease populations
15 where you can't necessarily modify a COA or where
16 you're going to try to do that, and all of a sudden
17 you're going to find like this isn't really feasible,
18 and it has to be a completely different kind of COA.

19 DR. CAMPBELL: Thank you. Those are some good
20 comments that we'll take back. Sir?

21 MR. TEWELL: Matt Tewell [ph], University of
22 Rochester. And this will be a comment and not a

1 question. I completely agree with that statement.
2 Just looking at this flow diagram up here, can the
3 existing COA be modified for the new COU? I think that
4 really should be, should the existing be modified.

5 We can certainly modify any COA, but the
6 question is, is that really the right thing to do?
7 Whenever you modify an instrument, you're going to lose
8 the relevance potentially, you're going to lose the
9 responsiveness, the statistical qualities that make it
10 really a useful instrument for a clinical trial.

11 And I think we maybe shouldn't be encouraging
12 so much. I mean certainly it's convenient to do that,
13 but it might not be the right thing to do, especially
14 in rare diseases.

15 And so I think we have to acknowledge that and
16 realize that it's not always going to be the right
17 thing to do. It might be the easy thing to do. But in
18 some instances it's better to go ahead, and it's
19 probably not that much work, honestly, in some
20 instances to develop something from scratch. And then
21 you have a disease-specific very powerful instrument.
22 You do it once, and you're done for that point on.

1 So I think, you know, this diagram is
2 interesting, but I think we have to allow for sometimes
3 it is the right thing to do to make something from
4 scratch.

5 DR. CAMPBELL: Thank you for that comment.
6 The person in the back? Hold on. Megan is going to
7 look and see. I think she's bringing a different mic.

8 MS. MANSFIELD: My name is Carol Mansfield
9 from RTI Health Solutions. And I heard this morning
10 that patient preference methods are beyond the scope of
11 this, but I guess when you have a lot of comments about
12 what's most important to patients, how patients trade
13 off the benefits and risks, what is a clinically
14 meaningful difference to patients, how does that change
15 with their circumstances.

16 All of those things are things that patient
17 preference methods are one method you can use to
18 address. And I feel like there should at least be some
19 reference to their existence in the guidance document
20 and their usefulness, even if you're planning on a
21 second guidance document to address patient preference
22 methods.

1 And the other thing I'll say is that we often
2 try to design patient preference studies using a PRO
3 instrument where the PRO change in score doesn't
4 actually mean anything to the patients. You know, your
5 score went up by three. So I don't know how difficult
6 -- designing PRO instruments where the change in score
7 is something that you can translate into a benefit that
8 patients can relate to. Then that will make it easier
9 to use those instruments in preference studies or in
10 evaluating whether the benefits are worth the risks to
11 patients.

12 DR. CAMPBELL: Well, thank you, you're
13 highlighting tomorrow's session on, within meaningful
14 change. So that's critical. And that's some nice
15 comments on patient preference we'll take back. Steve?

16 MR. BLUM: Hi, Steve Blum, Bristol-Myers
17 Squibb. First, thanks for a great day. I mean a lot
18 of really great insights and comments and really
19 applaud the agency for going through a thoughtful
20 approach for revising these documents.

21 I do want to challenge the notion of context
22 of use. What concerns me is it doesn't reflect the

1 fluidity of clinical trial design. I have studies that
2 aspects of the design change on a daily basis. And I
3 think we have to recognize the fact that, you know,
4 there are certain aspects of this strategy that we can
5 get right up front before we select the COAs, but there
6 was a lot of aspects that are very fluid.

7 And I think we need to appreciate the fact
8 that some of those maybe fall further down on the
9 right-hand column. So when I think about context of
10 use, what I think we really want to talk about is, is
11 the concept of interest relevant to the population of
12 interest. Within the therapeutic context, other
13 aspects of the clinical trial design, that's not so
14 much the strategy, that's the implementation.

15 And we need to tailor the use of the COA
16 measure that we've selected to fit the clinical trial
17 design. So I'd like to see us consider, and I'll make
18 this in the comments to the docket.

19 DR. CAMPBELL: Thank you.

20 MR. BLUM: When we think about context of use,
21 let's really think about identifying what's relevant to
22 the population of interest. And acknowledge the fact

1 that there are implementation challenges that are at
2 the study level that we need to think about later on
3 down the road. Thank you.

4 DR. CAMPBELL: Thank you. And I will
5 encourage all people who have made comments make sure
6 you do add it to the docket. So I've got two left, and
7 then we're going to, promise, get to Megan for closing
8 statements. The person in the back? We're doing our
9 best.

10 MS. BRAVERMAN: This is Julia Braverman from
11 Celgene. So I would like to challenge a little bit of
12 a dichotomy we have here, but when using the existing
13 instrument and modifying instrument. That modification
14 requires concept elicitation and, you know, somewhat.
15 I think we do have a third option that I think in the
16 guidance and in the discussion we didn't pay attention
17 to this. And this is using individual models or
18 individual subscales from the existing instrument.

19 For example, in fact, we all know, you know,
20 FACT-G score or EOTC. In FACT-G we have physical
21 wellbeing, emotional wellbeing. Is it possible, and
22 what's the updated perspective from this of using an

1 individual subscale that has already been validated and
2 has already been scored individual and even have
3 calculated its own MID. So we have it for physical
4 wellbeing on FACT-G, EOTC we have it. So how about
5 this situation, and should we consider it separately in
6 the guidance.

7 DR. CAMPBELL: Okay. Thank you. We'll take
8 that back and think about how to approach that, about
9 using existing instruments and potentially point out
10 the main usage that's already existing. We'll focus on
11 that. And to our last comment.

12 MS. GODWIN: Hi, Miriam Godwin, Roche
13 Genentech. I've been sent up here by a colleague in
14 South San Francisco to ask this question. So what she
15 would like to know is --

16 DR. CAMPBELL: Was it Liz?

17 MS. GODWIN: It was.

18 DR. CAMPBELL: Liz should've come. Hi, Liz.
19 On the webcast, right?

20 MS. GODWIN: Given the opportunity to use
21 flexible item banks instead of static questionnaires,
22 how does the agency and the panel recommend including

1 this in the selection diagram?

2 DR. CAMPBELL: That's a great question. So if
3 you didn't hear it -- Liz's question, really, from
4 Genentech Roche was the idea of using the item banks
5 and the flexibility of pooling there instead of using a
6 static. For the essence of time, I will defer that.
7 Perhaps we can get to that tomorrow in another session
8 because I don't want to keep us any later. But that is
9 a really great question. And we'll take back that
10 concept in general and see if we can address that as we
11 continue writing this guidance.

12 I want to thank our panel and the people that
13 asked our questions today. I think we had a really
14 great discussion. It sounds like everyone likes this
15 concept of the decision tree as a replacement for the
16 wheel and spokes. But we do need to add onto it. And
17 we also potentially need to add onto the roadmap.

18 I do ask of our panelists, we'll just sit
19 there while Megan comes up to make her closing remarks
20 so we can move this flow and get us, everyone out of
21 here at 5:00. But I thank you, and I thank our
22 panelists for this. And let's give them a round of

1 applause.

2 (Applause.)

3 MS. MONCUR: Okay. And I promise I will make
4 this very quick. But most importantly, we really want
5 to thank everybody that has come together here today,
6 those listening on the webcast, those here in the room,
7 and also to our exceptional panelists throughout the
8 day. And you will hear more tomorrow.

9 You've really enabled us to come together and
10 have a really wonderful fruitful discussion. So we
11 thank you for that. So my job is to do a recap today
12 of the high-level themes, get you set up for tomorrow,
13 and cover some logistics.

14 In the interest of time, I have been reminded
15 about what an excellent job all of our moderators have
16 done throughout the day recapping. And we will also
17 have a recap tomorrow morning. So I am going to skip
18 right into the logistics.

19 So we will -- the meeting will go from 9:00 to
20 5:00 tomorrow, just like it did today. However,
21 registration desk will be open at 8:00. We also wanted
22 to mention that starting at 8:00 those who want to sign

1 up for our open public comments can start to do that
2 tomorrow at 8:00. And that list will be there out at
3 the registration desk.

4 We also, pop quiz, when does our docket close?
5 (Crowd responds, December 14.)

6 MS. MONCUR: Thank you. And we might -- I
7 think we have a slide just to reinforce that. So,
8 again, this is such an important resource for us. So
9 topics you've heard today, terminology clarification,
10 whatever it is that you want to communicate to us, and
11 something else that we've also heard is we really --
12 we've heard from you that you want more examples, more
13 case studies. So we would love to invite you to submit
14 those to the docket.

15 And that might be -- you might want to create
16 a whole case study for us, or you might just want to
17 say, hey, could you target this with a case study. It
18 could be as simple as that. But that would be
19 extremely helpful to us. And I just -- turn to my left
20 to get -- any, okay, any other parties -- with that we
21 will adjourn. And we look forward to seeing you
22 tomorrow. So thank you, very much.

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(Applause.) (Meeting adjourned.)

CERTIFICATE OF NOTARY PUBLIC

I, MICHAEL FARKAS, the officer before whom the foregoing proceeding was taken, do hereby certify that the proceedings were recorded by me and thereafter reduced to typewriting under my direction; that said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

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October 23, 2018

DATE

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