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PUBLIC WORKSHOP ON

PATIENT-FOCUSED DRUG DEVELOPMENT:

GUIDANCE 1

COLLECTING COMPREHENSIVE AND REPRESENTATIVE INPUT

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P R O C E E D I N G S

WELCOME

MS. VAIDYA: We'll go ahead and get started now. I know there are still some folks trying to get through security. Okay. Good morning, everyone. My name is Pujita Vaidya, from the Office of Strategic Programs in the Center for Drug Evaluation and Research, also called CDER.

I'd like to welcome everyone to our public meeting today, the first in a series of meetings that we'll be conducting as CDER and CBER work together to develop several patient-focused drug development guidances throughout the year.

We are happy to see so many patients, patient advocates, academic researchers, expert practitioners, drug developers and other very important stakeholders in the audience today. And I also understand that we have many more joining us remotely from the Web. So thank you all for being part of this meeting.

In our discussion today, we will be focusing on topics related to our Guidance 1 document,

approaches to collecting comprehensive and representative input and patient and caregiver input on burden of disease and current therapy.

Throughout the day, we want to hear from you and get your comments and feedback on the approaches and considerations that are proposed in our discussion document that we put out about a month ago. If you have not gotten a chance to read through the document, that is okay. We will be going over the key points in our presentations and discussions throughout the day today.

I do want to mention that in addition to this meeting, a docket will remain open until February 16, 2018 to which the public may submit general or detailed comments regarding the specific aspects of the discussion documents or other topics raised throughout the meeting.

We do have a full agenda for today and for us to keep our conversation flowing and our discussion moving, our moderators may need to jump in and ask you to provide a little bit -- provide detailed comments to our docket or discuss with --

or you may have the opportunity to discuss with your colleagues during the breaks.

Now, let me quickly go over the agenda for today and walk through that. So first, we'll start off with Theresa Mullin, director of CDER's Office of Strategic Programs, who will get us started with the morning -- in the morning with her opening remarks.

We will then have two presentations, first focused on FDA's approach to defining key terminology and developing the glossary, and then the second on FDA's approach to developing FDA's Guidance 1 discussion document.

We will then have panels focused on considerations on specific topics. The panel sessions will be as follows: session one, defining research objectives and methodological considerations for designing studies to collect patient experience data.

Session two will be on methodological considerations for data collection, analysis and operationalization. Session three, translating

best practices into real practice, developing guiding examples. And finally, session four on identifying key themes and next steps.

Throughout the day, the audience will have several opportunities to ask questions and provide their views. We have many people attending via the Web. However, we will not be able to take comments or questions from the Web during the meeting. So we encourage you to please submit your comments to the public docket.

Following the sessions, we will provide time for open public comment. If you wish to sign up to speak during the open public comment period, please do so at the registration table.

Participation is on a first-come, first-serve basis. We have 30 minutes allocated for this, for this time, and we can take up to 15 speakers, although we do hope that you get an opportunity to ask questions throughout the day since we have built in several Q&A sessions.

Before I get started with some brief housekeeping items, I would like to ask my FDA

colleagues sitting here on my left to introduce themselves. This panel will be in active listening mode throughout the day. And then, for each session that I just walked through, we will have a separate panel of speakers joining us up front here as well. With that, I'll turn it to Theresa.

DR. MULLIN: Good morning. It's Theresa Mullin. I direct the Office of Strategic Programs in the FDA Center for Drugs.

DR. JOHNSON: I'm Laura Lee Johnson. I'm the acting director, Division of Biometrics III in CDER and I'm also the patient-focused drug development liaison for the Office of Biostatistics.

DR. PAPADOPOULOS: Good morning. I'm Elektra Papadopoulos. I am the associate director for clinical outcome assessment staff here in CDER.

DR. IRONY: Good morning. I'm Telba Irony. I'm in the Center for Biologics and in the Office of Biostatistics and Epidemiology.

DR. LEE: Good morning. I'm Kerry Jo Lee.

I'm a medical officer on the guidance and policy team within the Office of New Drugs, CDER.

DR. KOMO: Good morning. My name is Scott Komo. I am a statistician in the Office of Biostatistics at CDER.

DR. DANIELS: Good morning. My name is Selena Daniels. I'm a team leader on the clinical outcome assessment staff in CDER.

MS. VAIDYA: Thank you. So just a few brief housekeeping items, this meeting is being transcribed and a live webcast is being recorded, both of which will be archived on our website.

We will have an hour lunch break at around 11:30 after session one and then a 15-minute break in the afternoon at 2:45 after session three. However, please feel free to step out to stand up and stretch as needed throughout the day.

There are food and beverages available to purchase at the kiosk outside of the room in the lobby. We strongly encourage you to preorder your lunches. So if you have not done so already, we definitely encourage you to do that.

Bathrooms are down the hallway in the lobby to the left, to the right. And then, Wi-Fi password is available at the registration desk and we did have it up earlier. So with that, I would like to now invite Theresa Mullin to the podium for opening remarks.

OPENING REMARKS

DR. MULLIN: Thank you, Pujita. Good morning, everyone. And I just want to begin by saying we are very happy to have you here today in the room and on the webcast. This is a very exciting meeting for us. It really marks a milestone in like the second phase of the patient-focused drug development effort that we have been undertaking here.

And, just to give you a little bit of background on this, about five years ago, a little over five years ago, we had our first meeting to talk about which diseases we should really be focusing on in what we consider to be a sort of pilot effort to see what could we do to better hear directly from patients about what it felt

like to live with their disease and what they were doing to treat their disease.

We received a lot of comments. We took sort of an experimental approach. We didn't really know how to approach this. But we had over 24 meetings that we conducted in this room and we've learned a huge amount, very powerful information that we learned from patients about each of their diseases.

But we also came away with some broader learnings than that. And this included that our coming to really understand and recognize that patients are experts, that they have -- that they are key informants to the development of drugs and to their care and that we needed to consider them as such and more systematically incorporate their perspective, their knowledge into drug development and our decision-making.

We often found that in our listening to them talk about their disease and their treatments, that their chief complaints were not necessarily factored into the development plans or captured

very well in the measures of benefit that would be collected during those trials.

So we concluded, we realized and we heard from our stakeholders, who were also trying to help us figure out where do we go next with this, the meetings -- those patient-focused meetings are a critical part of this effort. And we hope that the continue and we plan to continue to engage in those kinds of meetings as we identify the need to do so.

And there's an externally led approach that many of you are aware of that we also are working with stakeholders to take advantage of.

But we realized that we needed to engage you all in trying to figure out the best, best methods, the "fit for purpose" approaches to bridge from those early qualitative meetings to collect meaningful, measurable input that can be used in trials and be used as part of our decision-making when it comes to drugs and then issue guidance based on that.

And so, in the PDUFA reauthorization -- that's

the Prescription Drug User Fee Act, which funds most of our work on new drug review at the FDA -- we committed to develop four guidance documents, and there's a relationship between these four. And you'll hear, certainly if you've read the document, the guidance -- the discussion draft that Pujita mentioned, you know a bit about this already.

But there's definitely a dependence and a relationship and the first one is the one we're going to be talking about today. That's the collecting comprehensive patient community input on burden of disease and current therapy.

And then, following that, one on developing a holistic set of impacts, including disease burden and treatment burden that are most important to patients, identifying good measures that can be included that actually would help reflect the effectiveness of a therapy being studied in a trial and, finally, what measures to include that could be considered in regulatory decision-making.

And for each of these, we committed, as part

of this agreement under the Prescription Drug User Fee reauthorization, which was enacted in August of this year, to have a workshop first, to hear from stakeholders, make sure we were capturing everything that they thought of, the methods that they were using, the experiences that they've had. So we got the benefit of that as we moved toward developing a draft guidance.

And these guidances in the Prescription Drug User Fee Act are very well-aligned with the requirements for guidance that were put in place by Congress a little bit over a year ago, mid-December of last year, the 21st Century Cures Act was enacted.

And Title III, Subtitle A speaks to patient-focused drug development. And in particular, section 3002 outlines eight provisions, the first four of which are very well-aligned with the commitments that we have in the PDUFA again, which is great for us.

So you see again highlighted in orange lots more words, but we're going to talk about that

same intention that we have. And you'll be hearing about it all day.

But we'll be covering these four -- first four components of 3002 in our four guidances. And actually, we're going to cover some of these others as well, although I'll point out right now and say number five here, in the 21st Century Cures Act, of this provision is about FDA issuing guidance to stakeholders who want to submit guidance to us and how to do that in the most effective way and the most successful way.

And we'll be having a public meeting about that in March of next year. And some of these others, we'll be addressing all of these. We have a plan on our website that tells you exactly how we're going to go about it.

But this work is very exciting and it marks a new phase of our work. And along those lines, here is a picture that says -- just tries to convey that we really see that there are opportunities to collect patient experience data throughout the drug lifecycle.

And here, you see what you might consider to be stages in the drug lifecycle, from discovery, preclinical development into clinical trials development. FDA reviews a dossier based on that development program and then, following that, post-market safety. And so, we really see opportunities in every step.

And here are just some illustrative activities to convey that. In the discovery phase, or very early on, you might be engaging in identifying what the disease impact and treatment burdens are that patients and their families are most concerned about and really try to figure out how to address those in your development programs.

And in the next phase, further after doing that initial work, you may be completing identifying and developing and testing those data collection instruments to ensure that they're ready for use in trials.

But you could also be doing that earlier on in the development phase. So that's why that little orange box is there. I came up with this color

scheme, my very crude PowerPoint skills. But that's to convey you can be doing that even earlier.

But then, when you get to trials, you're conducting the trials and trying to assess whether the changes in those clinical outcome assessments during the studies are meaningful and are they clinically meaningful to the patient.

And finally, you're going to possibly be collecting information post-market to really understand the degree to which those benefits and risks that you reported on during the clinical development phase are consistent with what's happening in the larger population post-approval.

And what you see below here is our attempt to convey that we think the four guidances that we've committed to do and we'll be talking about over the next four years are really going to help inform and support all of those stages of patient experience data collection.

And finally here, the questions that we have for you today, and you'll know these questions

already. They're in the Federal Register notice that we put out for this meeting. But we'll be asking and listening for what is the level of detail that you think is appropriate for these guidance documents.

We want to try to hit that sweet spot of enough but not overwhelming people with too much information. And what is the document structure and content that would be most useful in these guidances? We want them to be very usable for you.

Does the document make clear that we understand that the research methods that we talk about in the guidance document are some of the ones which you may be using. But we're open to hear about other methods as well and that may occur in a proprietary drug development program or in the precompetitive space and be more publicly available.

What are the most important time points when we all have to say come talk to FDA? I mean, we have limited resources. But we want to pick those

times which, in your experience or with your work, you think would be most valuable to get FDA's input.

And then, finally, we're going to present to you -- Meghana is going to, in a moment, present to you that glossary of standardized terms that we've put together.

And are these proposed draft definitions that we've come up with clear and do they facilitate the dialogue and the discussion and do they really support the development work. And so, those are our questions for you and we very much look forward to hearing from you today.

And with that, I'll turn it over to Meghana Chalasani.

PATIENT-FOCUSED DRUG DEVELOPMENT: DEFINING KEY TERMINOLOGY

MS. CHALASANI: Thank you, Theresa, and thank you all. It's so great to see so many people here bright and early Monday morning in the Great Room. Okay. So, hello. My name is Meghana Chalasani and I'm in the FDA's Center for Drug's Office of

Strategic Programs.

As Theresa mentioned in her opening remarks, PDUFA-VI commitment for a glossary that's relevant to all four guidance documents. And so -- oops, if I can move these slides. There, great. Thank you, Theresa. Thank you.

Okay. So the goal of this glossary is to provide standardized nomenclature and terminologies related to patient-focused medical product development.

And a few key considerations regarding the scope of this glossary and to keep in mind as you read and use are that the terms are relevant to all four of the methodological PFDD guidances that Theresa mentioned.

There may be terms that are defined in the glossary that you may not see in a discussion document for this workshop or in the first guidance either. But it may be relevant to a topic in one of the following future guidances.

We did not want to reinvent the wheel when we were developing this glossary, nor did we intend

it to be completely exhaustive either. The terms in the glossary are defined specifically for the context of medical product development, evaluation and regulatory decision-making.

Sorry, I'm having a difficult time with these slides. They're just not cooperating. I think they just really liked my pretty background and they're just trying to keep it up there. All right. Let me try to click on it. I think this might be better to keep.

Okay. Great. So on this slide, you'll find a high level overview of how the glossary was developed. So identify terms, FDA conducted a literature review and outlined the topics that will be addressed in the PFDD guidance series.

As I mentioned, we really did not want to reinvent the wheel. And so, we curated any existing definition using federal resources, literature and other external resources as well.

And the development process was truly collaborative across our medical product centers. We had cross-center facilitated discussions with

experts from our Center for Drugs, Biologics and Devices to determine the relevant terms and their definitions. There were also multiple opportunities to seek feedback from other FDA colleagues.

And just to kind of provide a high level overview and bring it all together, in the glossary, we defined patient-focused drug development, also referred to as patient-focused medical product development.

We also defined the who. So, who do we collect information from? Patients, caregivers, patient representatives. The how, so the how do we collect? Patient engagement and the preference methods and so forth. And the how well, fit for purpose, methodologically sound. And we also did the what.

And this glossary is really intended to be a living document. FDA plans to post the glossary on its website so that it can be updated periodically. This version that FDA has posted for the workshop is really just a draft.

And so, we really are asking all of you to provide us feedback through the docket. You'll find the link here and these slides will be posted on our workshop website afterwards. And the link is also at the end of your agendas.

And so, the docket will be open until February 16th, as Pujita and Theresa mentioned. So please provide us with your feedback. Please keep the scope of the glossary in mind, remembering that it's supposed to cover all four of the methodological guidances.

And let us know if there are any terms that we may have missed or if there are any definitions that are not clear or not understandable. And that's really just a quick overview of the glossary. Thank you.

MS. VAIDYA: Thank you, Meghana. I'd like to now invite Laura Lee Johnson, from CDER's Office of Biostatistics to provide an overview of FDA's approach to developing the PFDD Guidance 1 document.

OVERVIEW OF FDA'S APPROACH TO PFDD GUIDANCE 1

DR. JOHNSON: Good morning, everybody, and welcome on behalf of CDER's Office of Biostatistics and Office of Translational Sciences and also on behalf of my colleague, Elektra Papadopoulos, who's head of the COA staff in the Office of New Drugs.

So we're going to catch up some of the time here today and talk about our ultimate purpose. So right now, our goal is to understand those patient perspectives on benefits and risks.

So starting off with the definition, we have a clinical benefit which is the positive clinically meaningful effect of an intervention, so the positive effect of how an individual feels, functions and survives.

Now, traditionally, people have thought about how long a patient lives. So they think about survival. But we also care quite a bit about how a patient feels or functions in daily life. And that may mean an improvement in how they feel or function, but it also may mean prevention or slowing of anticipated decline.

A clinical outcome is defined as the outcome that describes or reflects how that individual feels, functions or survives. And we tend to assess these using clinical outcome assessments, and you'll hear us say COA or C-O-A for short. But we'll try to use all of the words today.

But what we really want to focus on is that careful assessment of patients' views on benefits and risks and how they're important to part of our regulatory decision-making.

So what is patient experience data? As Theresa pointed out, we have a definition in the 21st Century Cures Act and we're looking at data that is collected about any persons and are intended to provide information about patients' experiences with a disease or condition.

That includes experiences, perspectives, needs and priorities of patients related to, but not limited to, symptoms of their condition and its natural history, so understanding what patients are experiencing there, the impact of the conditions on their functioning and quality of

life, experience with treatments, input on which outcomes are important to them, patient preferences for outcomes and treatments and the relative importance of any issue as defined by patients.

So why is it important to collect the patient experience data? As Theresa mentioned, patients are experts in their own experience of their disease. Many of us have described this. They're experts in their experience of the disease or condition and they're also the ultimate consumers of medical products.

Patient experience data can inform medical product development. It also enhances our regulatory decision-making to address a patient's needs.

So where does the data come from? It's the patient's journey and it should be defined by the patient's perspective, where possibly. It's also informed by input from patient partners and clinicians. We may need to have a multipronged approach in order to reach and cover our target

populations.

So we have several different types of patient partners. Many of us think about the patient. But we also have caregivers or care partners who help patients with daily activities, their healthcare, other activities a patient may not be able to perform due to illness or disability.

This person may or may not have decision-making authority for the patient and is not the healthcare provider. Patient advocacy groups are also part of our patient partners. And this may be a group of individuals.

They may or may not be part of that target population. But these are people who have a role in promoting an interest or cause to influence policy with respect to patients' health or healthcare.

Now again, as Meghana mentioned, we have a glossary. And so, if you want changes to some of these definitions, this is the type of information to submit to the docket.

Now, when do you collect patient experience

data? This is a key element. Input should start early and it might be before or throughout that medical product development process. Precompetitive collaboration is encouraged. You may have heard about our qualification program for clinical outcome assessments. But an important element is this information may come through an individual drug or medical product program.

It might come from outside in a precompetitive space and many times this precompetitive work can actually help move an entire disease area's research and development forward. So what we're talking about today can be used in a lot of different areas.

Who can collect and submit patient experience data? Anyone can collect and submit that data. That includes patients, family members or caregivers of patients, patient advocacy organizations, disease research foundations, researchers and drug manufacturers. And today, we in CDER and throughout FDA get information from all of these different groups.

How can external stakeholders submit that experience data to FDA? Stay tuned, but a lot of various pathways exist. We have under development FDA guidance on how to submit information in order to broaden and clarify how this information can come in.

But what's also important is to understand that, depending on the purpose and type of data, different content and formats may be appropriate. And so, we are refining this and making sure that we're going to be able to have the most efficient path for everybody in the office and for those of us at FDA.

How is patient experience data used for regulatory purposes? We use it to inform clinical trial design, as do many of the manufacturers and sponsors and companies that we work with. It might be that this type of information helps us consider what the appropriate control group should be.

It can help us consider a lot of different logistics for the trial. Also, may say, okay,

what is the natural history, what should we be considering.

But this leads also into that trial endpoint development and selection. In particular, if there's debate about what a primary endpoint should be, what is it that patients are really looking for.

But then also thinking about our reviews including benefit and risk assessment, how much change do patients want and how much risk and in what areas are they willing to take.

So how do we collect this information? We recommend qualitative, quantitative or mixed methods to collect robust and meaningful patient experience data. Selena Daniels will be talking more about these different types of methods in the afternoon. And they are described in the discussion document.

But the main element to consider is that really we need fit for purpose methods to get to the goal. So consider what your goal is. Again, this multipronged approach. Rarely will a single

study answer all questions. That's true for anything in clinical research.

But Guidance 2 is going to talk more about this because sometimes there are very specific elements to consider. What is the question? What is the approach? And what is the answer that we are seeking?

Now, we mentioned a little bit about those four guidances and I'm going to step us through these because our meeting today and the docket that's open is for Guidance 1, collecting the comprehensive patient community input on burden of disease and current therapy.

So you can think about this as what people am I gathering together to get information from. Who do you ask? How do you get that input from them and why are you choosing this group of people? How do you collect the information?

So things like you're going to have a lot of examples in the afternoon -- who do I gather. This is the underpinning for all of the other guidances in all types of work. It's an important

question from your very early questions, all the way to your final research qualitative work that may happen.

Our second guidance gets into development of that holistic set of impacts. So a little bit of how do you collect it and part of what Selena is talking about today in the afternoon will actually flow into the second guidance. So if you provide input on that, it may be something that we consider for the guidance that we're working on for next year.

What do you ask? Guidance 1 gets together the group. Guidance 2, what do I ask them? Why am I asking them these particular questions? How do I ask a non-leading question that's well-understood by a wide range of patients and others?

How do I avoid getting misleading results? A lot of times, if you slightly tweak the question, you may end up with a very different answer. So we need to think about how we are actually getting the information from that group that we've put together under Guidance 1.

And Guidance 3, we're deciding what to measure in a clinical trial. So in Guidance 2, I have a long list of impacts that are important to patients. Guidance 3, we're trying to hone down that list. How will I select what to measure in that clinical trial, refining that set of impacts to what's actually measurable? It might be an important concept.

Do I know yet how to actually measure it? What's going to be most likely to show clinical benefit in a specific treatment trial? Sometimes we have elements that might be extremely important to patients and their families. But we know that the treatment is not going to impact that particular issue. And so, that's not your best primary endpoint direction to go.

But four gets down to the final part of what should a primary endpoint, for example, be in a trial, identifying and developing good measures for those identified sets of impacts from Guidance 3 and incorporating clinical outcome assessments into endpoints. So for example, my clinical

outcome assessment, I might ask people questions every single day, something called a daily diary. How do I summarize that information into an actual endpoint in the trial?

But we also need measures and endpoints that are considered significantly robust for regulatory decision-making. So that's the information that will be in Guidance 4. What is the right endpoint and how do I select the tool to be in my trial?

But our purpose today is Guidance 1. We're going to start from the beginning, as they say. Who are the people that we're trying to put together to get information from? We're going to talk this morning about a set of methods for collecting information on patient experience that's representative of the intended population.

And our four lead authors, three of whom will be presenting today and one of whom is taking a lot of notes in the audience, we are going to hear from them today with a brief synopsis of their sections of the draft document, because I'm sure everybody's read it intently. But just in case,

we'll have that.

So Selena and Ebony and Kunthel will give you a brief overview of that discussion document today because we also want to present a synopsis of methods that will be further elaborated in our later guidances on how to operationalize and standardize data collection, analysis and dissemination of the patient experience data.

A focus for us to consider is we're going to try to not get too methodological in today's discussion. If you have a deep methodological area that you want to go into, please submit it to the docket because our guidance is set up in a way that's different than many FDA guidances.

We have a very broad audience to serve and we also want to make sure that the people today both in the room and online can participate and everybody, regardless of your training, can have a deep understanding of where we are going and what we want to do.

So this is a focus for discussion among FDA and multiple stakeholder groups, with our patient

partners really being first. This is intending to encourage patient involvement as partners before and throughout the medical product development process and to promote a collaborative process in the collection of robust patient experience data.

Guidance 1 emphasizes the concept of fit for purpose, as will our other guidances. So the tools match the specific research questions and our regulatory needs. And we also want to make sure that it's recognized that the science of patient input is evolving field.

So this is something that you'll notice was one of the specific questions asked up front and in our closing remarks I'll be asking again.

We've heard many times from our sponsors that the regulatory groups inside the companies will point to FDA guidances and say what you want to do is not specifically spelled out here. So you can't do it. That's not what we want to have happen.

It says in almost every FDA guidance, if you want to do something else, come talk to us. We

mean it. So one of our large points here is this is an evolving field. What's missing that we should be putting into an ultimate guidance for Guidance 1?

But then also, is it understood that, as methods come up, we want you to come and talk to FDA about what you want to do? And even for methods that may not be listed, again, we want you to come to FDA to talk to us about what you want to do.

Our approach also recommends, we hope, a pragmatic stepwise way to provide usable patient experience information to FDA. So does Guidance 1 address clinical outcome assessments or patient preference information? We've been asked this question before we came up. So we decided, Elektra and I, to address it directly.

Guidance 1 provides a framework for collecting representative patient input that can be used to inform clinical outcome assessments, patient preference information and a whole host of other types of research. It does not cover collecting

or analyzing clinical outcome assessment or PPI data directly, that patient preference information directly. Some of those issues are in other guidances to industry out of FDA. So a couple of those are listed. But again, this is a basic framework for collecting representative patient input.

So today, we're going to start off in the next session where Ebony and Kunthel will talk about general considerations for collecting patient experience data, going through defining the research questions and objectives, from whom to collect information, looking at determining the study design and research setting, constructing a sampling frame and additional considerations to achieve sufficient representation.

Then, in the afternoon, Ebony will talk about the methods for collecting and analyzing data. Again, this is the beginning. We're going to do more in Guidance 2 and later guidances, and then operationalizing and standardizing data collection and data management. And with that, I'll turn

this back over.

MS. VAIDYA: Thank you, Laura Lee. Now, we'll move into Session 1. This session will be moderated by Michelle Campbell, from the clinical outcome assessments staff in the Office of New Drugs in CDER. And I'd also like our panelists to please join us up here. With that, I'll turn it over to Michelle.

SESSION I: DEFINING RESEARCH OBJECTIVES AND METHODOLOGICAL CONSIDERATIONS FOR DESIGNING STUDIES TO COLLECT PATIENT EXPERIENCE DATA

DR. CAMPBELL: Good morning. My name is Michelle Campbell and I'm with the clinical outcome assessments staff in the Office of New Drugs in CDER. It's my pleasure to begin our sessions today taking a closer look at the discussion document we have drafted.

The first session we will discuss will look at considerations when determining the study defines and research setting, including selecting a sampling frame when collecting patient experience data.

With us for this session today, I have my colleagues Ebony Dashiell-Aje, from the COA staff, and Kunthel By, from the OB, along with Steve Cohen, from RTI International, Richard Gershon, from Northwestern University, Mia Karr, from the National Center for Health Statistics and Liz Piault-Louis, from Genentech.

Unfortunately, our patient advocacy representative, Suzanne Vernon, from the Bateman Horne Center, which is a patient advocacy group for MECFS was unable to join us today. However, Suzanne did send us some comments and thoughts and I'll be sharing them later as we continue this session.

How we're going to do the session today is we'll be seeing a brief presentation from Ebony and Kunthel. And they're going to be discussing a little bit more looking at how we define our research objectives and sampling frame.

We will then turn it over to our panelists to give their initial thoughts and go into some deeper discussion with the panelists and a couple

of questions. We will end with questions and comments from our audience, if you have any. Please know that if we do not get to your questions or comments, please consider putting them on the docket, which is a recurring theme you'll be hearing all day today.

But we do encourage you to make sure that if you don’t feel that your voice was captured today or you have additional thoughts, to please make sure you go to the docket.

So I'm going to turn it over to Ebony, who will start our presentation.

FDA PRESENTATION

DR. DASHIELL-AJE: Good morning, everyone. So today, in this first session, Kunthel and I will discuss potential methodological considerations and practical implications for defining research objectives and designing studies to collect patient experience data.

So when determining the best approach for conducting research to collect patient experience data, there are a number of factors that should be

considered during the study and design phase. These include research goals and questions to be addressed, the target population under study, which includes recruitment feasibility, as well as factors related to the amount of time to collect the data and study budget.

Now, if there are constraints related to time and budget, you should consider scaling back objectives and questions. Along with these, you should also consider the type of information that you generate from the study, including the value of that information, short-term and long-term impacts of the information that you intend to generate as well.

And all of these factors, as outlined in this diagram and in the discussion document, are equally important to consider when selecting the most appropriate research approach and to ensure the success of a study.

So the following are some general steps that we've outlined in the discussion document and subsequent appendices to help provide guidance

during the study and design phase. As these steps are outlined, decisions can be made to determine what the most appropriate research approach will be for a study.

Within the guidance and discussion document, we intend to discuss these elements in detail and my colleague, Kunthel, and I will give a brief overview of steps one through five, while my colleague, Selena Daniels, will pick up on steps six through eight in session two today.

So how do you define research objectives and questions? Research objectives should be specific and defined by research questions. Subsequently, these will inform the methodological decisions that you make for your study. For instance, whether you're going to use qualitative, quantitative or a mixed methodology to generate data and analysis plans.

When defining research questions and objectives, you should consult the literature, as well as content experts to determine what information each question or objective will yield

and whether this information will best meet your study goals.

So here's an example that we've presented in the discussion document to help illustrate the relationship between research objectives, questions and study design considerations and characteristics. So within this example, we've provided a case study of HIV. We've given a sample research objective, along with proposed questions that can help define that research objective, and the potential next steps for designing a study and specifically a qualitative study that can help address the potential research questions of interest.

So once you determine the objectives and questions that you would like to investigate, you should then determine the most appropriate target population to obtain this information from. And we've provided this example, just like with the research objectives and questions example, to help researchers understand what constitutes a target population in a given study.

For this example, we're taking from Parkinson's disease and we're trying to define the target population for you all. Now, when you are defining the target population, it's important to communicate with the agency to make sure that the proposed target population is aligned with regulatory needs.

So when determining from whom to collect this information, it's important to consider who would be the best reporter of the patient experience information that you want to collect. So the following are a number of factors, including, but not limited to, age, level of cognitive development, communication skills, health literacy, the level of insight that a patient might have on their condition, health state and comorbidities.

Taking it a step further, here's a case example that we've provided in the discussion document regarding age to help illustrate factors that should be considered when determining who would be the most appropriate source of

information in a study designed to collect patient experience data.

In this example, we outlined considerations for determining the youngest age of self-report and the most appropriate informant based on developmental limitations.

Some other important points to consider are related to subgroups. When possible, subgroups should be pre-specified during the study design phase.

Likewise, we should consider the number of subgroups being processed -- proposed, excuse me -- for analysis and inference; the reporter type, including patients versus primary caregivers; reporter characteristics, socioeconomic, demographic, cultural, linguistic, et cetera; and, prevalent symptoms for disease or conditions with notable symptom heterogeneity.

So I will now turn the rest of this presentation over to my colleague, Kunthel By, and he's going to further discuss study design characteristics, including importance of sampling

and other study design considerations.

DR. BY: Thank you, Ebony. Good morning, everyone. Again, my name is Kunthel By. I'm a reviewer in the Office of Biostatistics in CDER. So I'll briefly go over some of the design considerations that we've outlined in the discussion document.

You heard earlier that the purpose of Guidance 1, or at least we were tasked with writing a document that provides or at least intends to provide a framework for collecting patient experience data that are not only comprehensive but also representative of the underlying target population.

And as representative is an important concept, I'd like to briefly go over it, at least in terms of how we've thought about it in the discussion document.

So what is representativeness? Another way of asking the question is what is a representative sample and why do we care about it? Well, we care about it because, in general, we cannot study the

entire target population. Usually there are financial and physical constraints to do so. And so, oftentimes we can only afford to study a sample from the target population and we use what we learn from that sample to make statements about individuals in the target population.

And we would feel more assured about our statements if we have a sense that the sample is somehow representative of the target population.

So what is representativeness? In our document, we interpret representativeness in two ways. One, in the sense of generalizability and, two, in the sense of representation. And I'll go over each one of these in a few minutes.

The document does not insist on a particular interpretation. The relevant interpretation depends on your research objectives. So genrealizabilityh, I think most of us are familiar with this terminology.

But in our document, representativeness in the sense of generalizability is when statements made about patient experience based on your study

sample is generalizable to the target population. That seems a little bit circular. But another way of saying it is statements made about patients in your sample is also valid for your target population.

To illustrate, consider the following diagram. I have a sample of 30 diabetic patients I interviewed. And I characterized the distribution of views and preferences with regard to treatment burden among these 30 individuals.

Now, if these views -- if the distribution of views and preferences are also true of the target population of all diabetic patients, then we say that the sample of individuals in our study is representative in the sense of generalizability.

In terms of representation or representativeness in the sense of representation, patients in the study sample reflect the diversity of patient characteristics in the target population.

So in this interpretation, we do not insist that the distribution of characteristics in the

sample approximate those in the target population. In fact the distribution of these characteristics in the sample could be very different from those in the target population.

For example, in the sample diagram I gave earlier, the sample of 3 0diabetic patients might consist of similar numbers of blacks, whites and Asians and similar numbers or proportions of young and old.

But in the target population of diabetic patients, there might be a substantial number of whites relative to blacks relative to Asians and there might be a substantial number of older patients relative to younger patients.

So in terms of generalizability, we encourage, or at least in the document we encourage the use of probability sampling.

In our document, we enumerate examples of probability sampling. I listed a few of them here, which include simple random sampling, stratified simple random sampling and so on.

However, we do not describe each of these

sampling schemes in detail. Instead, details of a lot of these methods are provided through references and we ask the readers to consult the references.

One important feature of probability sampling is that selection probabilities are known and, in principle, reweighting of information in the sample using these selection probabilities provides a mechanism for generalizing to the target population.

We acknowledge that not all studies will have the goal of trying to generalize to the target population and, for these studies, non-probability sampling is often used. And representativeness in the sense of representation is, or may be sufficient.

In our document, we also list examples of non-probability sampling schemes which includes convenience sample, purposive sampling, quota sampling and so on. And as with the non-probability sampling, as with the probability sampling, we don’t go into detail in the document

on each of these methods. Instead, we refer the readers or the literature.

What distinguishes non-probability sampling from probability sampling is that the selection probability or the selection mechanism is unknown. So your sample may or may not generalize to the target population. You just don't have a formal way of making that determination.

As representativeness is an important design consideration, so is sample size. Now, the document does not instruct or provide formula on how to calculate sample size, as that depends on a multitude of factors, such as your research objectives, the types of endpoints that you will be using.

It depends on the study design, how you will analyze your data, operating characteristics and whether you will be paying attention to particular subgroups.

In general, sample size calculation is based on some sort of criteria. So establishing that criteria is helpful, even if sample size formula

is not available.

Sampling frame goes hand-in-hand with probability sampling. Essentially, it is a list of members of the target population. For example, to the extent that it is current, a disease registry could serve as a natural sampling frame. And ideally, you would want your sampling frame to cover your target population, meaning to be complete or near complete.

And having a sampling frame facilitates the implementation of probability sampling in the sense that you could apply some sort of random device on the frame to pick out members from the target population.

And we acknowledge that it's not always readily available for us and to the extent that it is possible to do so, sampling frame may need to be created on the fly as you conduct your study.

And finally, whether your study is intended to achieve representativeness in the sense of generalizability or in the sense of representation, we encourage enrollment of

patients that reflect the heterogeneity of the target population, including diversity with respect to demographic characteristics such as age, sex, race and education, diversity in cultural background, diversity in reading, writing and speaking abilities, diversity in disease severity and disease subtypes as well as diversity in physical and cognitive abilities.

And before I hand it over to Michelle, I'd just like to summarize some of the key takeaway messages in terms of general considerations for study design.

It would be useful to have clear research goals and questions established, to have clearly defined target population and to have -- to decide in advance the type of information that you need to collect to answer your questions, to decide who will provide the information that you will need to answer your questions and to decide how you will achieve representativeness or which interpretation of representativeness you will use and to decide in advance how many people to include in your

study.

I think I missed one bullet point and that is to include -- decide on whether you will be looking at particular subgroups. And with that, I'll hand it over to Michelle to begin the panel discussion.

MODERATED PANEL DISCUSSION

DR. CAMPBELL: Thank you, Kunthel and Ebony, for that overview of the beginning part of the discussion document. So we're going to start with some initial thoughts and feedback from our panelists. And I'm going to start with Steve Cohen, from RTI. So Steve, what are your initial thoughts?

DR. COHEN: Michelle, let me make sure I've got this on right. So I thought that the guidance was a very good initial step in terms of framing the broader context of data collection in terms of the analytical questions at hand.

And I really like, particularly in figure two, the strategic objective coming up first. Clearly clarifying what the analytical goals of the study

are. What are the criteria of variables? Sometimes there are competing objective and that has to be factored in, in terms of ultimately what are the priorities of the design.

Then, in terms of the guiding questions that potentially could answer the research questions, there was a framing of when they existed, when there were very clear-cut, evidence-based measures that might be taken from other surveys, nationally represented, or they really have to be developed.

And that was the path in terms of considering focus groups, non-probabilistic designs to really engage small groups of patients with particular chronic diseases or whatever the criteria would be.

But for well-developed measures, being right upfront in terms of what type of reliability is necessary for this underlying study. If it's just the overall estimate, it's what kind of a confidence internal. If within subgroups that you're trying to detect differences, what kind of a difference can you detect?

What is the type one error, the type two error, the power of the study? That's covered in here and, as more references are provided, I think that would be even more helpful.

The one thing that I think is really critical here, when one goes through a well-designed study with very clear-cut analytical objectives, criterion variables well-specified, is understanding when you're in the field, whether it's in person or by mail or by phone, high level of nonresponse in these studies.

And that has to be factored in the design. Otherwise, even with the best frontend design, if you have significant nonresponse and adjustments, whether it's -- I'm going a little bit further in terms of the guidance, but there are techniques known as adaptive design, responsive design, to get the representation up so that you won't be hit with nonresponse bias.

And you have to factor that into the underlying sample size specifications. If you're only expecting like a 50 percent response rate,

you're going to have to double the underlying sample that you need.

Then, another issue is the target population. And that's really key. And many times, for select populations, very difficult to get in a very cost-efficient manner.

Now, there are national surveys that are very large. There's the National Health Interview Survey by CDC, which has over 100,000 individuals. There's the medical expenditure provider -- Medical Expenditure Panel Survey.

On occasion, they add supplements for individuals with particular chronic diseases. It could be cancer survivors. It could be a supplement for individuals with diabetes. To the extent one can benefit by those existing surveys, that's something that might be worth giving consideration to.

And then, in terms of going forward, pretesting is critical. Really taking out the study first and seeing, you know, what the pitfalls are in terms of it might be a beautiful

instrument, but it just doesn't resonate with the patients.

And just the final point I'd like to make, again, I'm maybe giving a little too much attention to the fact that not everybody's going to participate. Even when they participate, there's item nonresponse and having mechanisms to actually correct for that or see you're not going to have sufficient representation. The question doesn't work. So I'll stop there. But I was sort of going over the field.

DR. CAMPBELL: Thank you, Steve. Richard, would you like to start off with some comments?

DR. GERSHON: Sure. First of all, thanks to the FDA and helping to bring patient input into the 21st century drug development. And I'd like to push that envelope even a little bit further in my observations. Just a few quick examples. If we have time later, we can dive in.

First of all, things like the HIV example giving earlier suggesting, you know, group discussions or administering surveys, we have a

new generation who actually would prefer to text their responses or participate in social media-based survey methods.

And indeed, that's a little bit in conflict with discussion 3.1.1.2 regarding social media. I believe the only way to talk to some of these people will be that way.

And to preclude that is similar to our view of phone-based surveys which we used to think was the only way to get a random sample. And now, people don’t have phones. You can't get there.

So very often, I mean, social media can be used, one, to get overall opinions in a non-probabilistic way. But it can also be used as a method to talk to known patients and experts.

Also relative to guidance on things like age, you know, there's a growing body of literature demonstrating that children are indeed accurate self-reporters of health-related quality of life.

Things like the patient-reported outcomes measurement information system has measures and encourages self-report down to age eight. And

also, very interesting for drug outcomes or any research, is to contrast that with the caregiver. But that doesn't preclude the importance of the child's input.

And also with regard to health literacy, I was a little struck here that I think that, to me, weak health literacy should be a requirement for inclusion and not as a potential grounds for exclusion.

Just because the patient can't understand, read their medication instructions or understand the prescription label, they can still be able to accurately state their level of pain or emotional status.

Finally, when we talk about probabilistic and non-probabilistic sampling, I think the world is changing and I think we need to recognize that Web-based sampling may very well be non-probabilistic -- or I'm sorry, probabilistic sampling.

We're at this point where actually finding a pure probabilistic population and being able to

obtain them, as was mentioned a few minutes ago, there's response bias. Fifty percent of the people don't respond and you don't get to them. That is not a pure probabilistic.

I have yet to see -- you can get probabilistic in a classroom of 30 children who all show up that day and force them to respond. Short of that, we certainly can't get that in a drug category.

So, and it turns out that things, Web-based samples are being found by traditional groups who always relied on probabilistic sampling to be more representative, such as prediction of election results. They're much more accurate when done in a Web-based panel, when they're done with traditional random digit dialing or other manners.

And further, things like we talk about registries are limited by preregistered panelists. Well, Web-based samples don't have to be limited by preregistered panelists. There are different types of web-based samples.

And in that regard, registries are also not probabilistic samples. There is bias. I'm

unaware of a registry that contains a hundred percent of the population. I think registries are a great way to go. But they have a place, as does Web-based sampling.

DR. CAMPBELL: Thank you, Richard. Meena?

DR. KHARE: Yeah. I'm Meena Khare, from National Center for Health Statistics. I'm also a survey methodologist. So I will give my opinion, and thank you for inviting us for the panel discussion.

I think Steve has covered a lot of ground and comments that we also as a survey methodologist look at it. Yes, and this document has covered a very comprehensive list of all the required things, concentration you should do.

So for the objective, yes, you have to have a very clearly defined objective for what the stud you are doing and how you are collecting because that also could impact your target population. As for the data collection questionnaire, as Steve said, we have to do the pretest.

A question -- at NCHS, we have a questionnaire

design lab. Any surveys that we do, we always test the questions and then sometimes there is a measurement error that some questions may not mean or they may not collect the information that you want to collect.

So it's very important to do either a focus group or some kind of testing or use the preexisting questions that already have been evaluated for data collection.

So that's on the objective part. And for the representativeness of the target population, you have to really look at what population subgroups you're trying to target and where your data is available because we do, as a household-based, provider-based, establishment-based and all different ways of method that we use for data collection to get the representative sample.

So it's very important to start with the frame and see where your subgroups are. If it's a specific disease, where you're going to get the collected data or find the patients, whether it's a patient level or at the proxy or caregiver. So

you need to also think about the difference.

The caregiver may or may not be representing your proxy information that patient might have experienced sometime, especially when they talked about the cognitive disability or something. So you have to make a balance or do some kind of quality assessment for that.

So, and data can be like collected from -- it depends on how you're going to do sample survey, clinical studies or from registries or nowadays there's the medical records. Then you have to think about it's the patient level, how you're going to get the patient level data, experience, directly from the patients or from the visit level or providers or clinics.

Sampling methods and sampling size, as Steve also said, that okay, you have to think about it. Just having a random sample of 30 is not sufficient all the time because you have to build in the adjustment for the nonresponse, non-coverage, missing data, item nonresponse, power of the analysis, what kind of precision you want and

what kind of prevalencies in the population that you're trying to target.

If it's rare, then you probably need to increase the sample size quite a bit and we deal with it all the time at NCHS. And I already talked about the mode of data collection with respect to objective and sample size.

Quality assessment I think as a pretest I think it's good to do with some small study pilot or some kind of partial data before you go into the field for full data collection and like pilot to do the assessment and make some changes, quality improvement in your data collection methods.

For the probability and nonprobability, yes, we have an issue with the response rate. Response rate, they all have a response bias issue when you have -- but nonprobability nowadays, we are trying to collect in multimode data set with the multistage surveys.

There is a mode of fact there when you have a -- and we are trying to get data from all

different methods. In one of the surveys that I recently worked with, it was a mail from the providers.

Also we gave them the option for Web and telephone. And guess what? It was a very low response rate for that particular study. But most of them returned the mail survey. Web surveys is still not there. And then telephone, for some reason, telephone follow-up, very few data we got.

When I looked at the Web surveys, it's very important to look at what is the demographic that you're trying to focus. When I looked at it, the younger group and the elderly, they are not that Web savvy person with social media, savvy people.

But when you do some survey for young adults, yes, that is one way to do it. So there are a lot of issues going on with Web panel surveys. Yes, is there -- a lot of the panels are increasing in size and you can do stratification by demographic.

But it still is not there. There are a lot of self-selection bias issues. So that's where I'm going to stop.

DR. CAMPBELL: Thank you, Meena. Liz, would you like to add on to this conversation.

DR. PIAULT-LOUIS: Sure. So, Liz Piault-Louis, from Genentech. So first, thank you for having me here. I would like to also commend the chair of this panel because I think this is going to foster better patient-focused drug development. And those guidance I think are really key for collecting good patient input to inform the assessment of clinical benefit for novel treatments.

So I have two general comments. I think within drug development program, we are not interacting with the patient only at one point. We are aiming at interacting with the patient community and their caregiver or patient advocacy group throughout the drug development program.

And that means that at the beginning we are going to seek insight regarding the disease burden. Then, we are going to try to better understand how do we document this concept that makes sense to inform clinical benefit so that we

can use this information alongside documentation of treatment activities. And very importantly, we need to also have feedback our protocol and on the feasibility of this administration and so on. And eventually, we are looking also for exit interviews so that we can learn about the patient experience throughout the clinical trial.

And for that, we are often relying on convenience sampling or purposive sampling. We need to have -- we have obviously like some targeted questions. But we need to have a relatively small sample and basically random sampling won't be feasible at this time.

And then, we have also other type of research when we are trying to develop a questionnaire. And for that, we have also like other opportunities then.

Only random sampling, we are usually using purposing sampling and we are matching that to specific target or equipment where we are targeting certain proportion in terms of race, education, physical functioning, communicative

ability and so on.

So it's really like a tradeoff about like being able to get these patients inside to be able to ensure the nice flow of information between the patient advocacy group and the research team and at the same time making sure that we can use the information to inform all drug development program.

And for that, I understand that we have to have like -- I mean, we have to have -- we need to be able to generalize the data.

But we have also other mechanisms when we are doing, for instance, concept elicitation or communicative debriefing. We have this concept of concept saturation where we do make sure that having more interviews is not going to give us more information.

So that's help in terms of the comprehensiveness of the feedback being collected. So that's my comments regarding of course this gathering of information from the patient perspective, having clear questions make sense.

However, again, in early drug development process, we don't have so much information available. Most likely, if we are looking at a rare disease, we don't have a clear profile of the final target population for the Phase III trial.

So we have to be -- we are doing like a hypothesis at this time. So we need to make sure that the guidance -- I would encourage the FDA, the draft guidance that is not too prescriptive because we need to make sure that we have a nice flow of information.

My second comment will be about this guidance. I think we are currently at the industry collecting this type of information early. But we don't submit that to the FDA yet because we have no clear understanding on how this is being used by the FDA.

So I know that there is some discussion coming in March on how to submit this type of information to the FDA. But I would really recommend for this guidance FDA to tell us how they intend to use this information to inform the risk-benefit

assessment because we collect this information in early phase of protocol development.

We do also have lots of patient-relevant endpoints in our clinical trial. And what we see so far is that we submit that to the FDA. We are told that it is part of the treatment benefit assessment. But unfortunately, we don't see that in the label.

So we are I think trying to better understand how we can use this new section in the patient experience label and really trying to understand the evidentiary standards that are applied to the type of research we are discussing today. Thank you.

DR. CAMPBELL: Thank you. So, Liz -- and I just want to recap some of the themes I heard our panelists discuss is their initial reactions. I heard the need for considerations and using of pretesting before we administer the survey out.

The use of social media, and I know that will be touched on a little bit in our next session. The considerations for nonresponse. How can we

potentially use large survey data that may exist? The use of the reporter, who is the reporter, what type of information will they be giving and how they may complement each other.

And remembering our demographics and how that relates -- of our population, how it relates back to our research question and that we are working continuously in our -- in our -- for our industry members, they are continually working on the patient experience concept throughout the entire medical product development cycle and that one method that some people are exploring to continue to learn on the patient experience is exit interviewing and wanting to know, as we move forward with this guidance and other documents, is how is the FDA using this patient experience data towards making the benefit-risk framework in decision-making.

So those were some of the themes I heard from our panelists. I am now going to put up a couple of questions to start with, with our panelists. And we're going to start with the first one: are

there any other factors to consider when defining research objectives and designing studies to collect patient experience data that should be included in the guidance.

I'm actually going to start with Suzanne Vernon, our patient advocate's response. She wrote a really great response and I want to make sure her voice is still represented today.

And so, while our panelists continue to think, we need to remember one of the things that Laura Lee put in her slide that I know we talked about on our prep calls with our session, is that we need to make sure we're finding the correct balance and the voice in what we're describing in the guidance. You know, and so this is the opportunity to let us know is there things we need to add, where we may need to put more information and take some stuff out.

So keep that in the back of your mind as you're thinking, to our audience, to our panelists today. We need to make sure we are making this document broad enough to be useful and providing

the right level of information. So while our panelists are thinking about that first question on this screen, this is from Suzanne Vernon, who again is from the Bateman Horne Center for MECFS.

I will note that Suzanne refers to a specific figure in her talk, her thoughts. It's figure three, and that is the nice arrowed figure that Ebony showed that kind of talked about the flow of the discussion document and how Ebony talked about I think the first one through five steps in session three.

She referenced that diagram. So if you hear me say that, that is the diagram she was referencing. So these were the words of Suzanne Vernon.

First, you need to go in with your eyes wide open. Let me start with a personal story. When I was a young scientist at the Centers for Disease Control and Prevention, I jumped at the opportunity to lead a pathogen discovery study for chronic fatigue syndrome because this disorder was a blank slate and there was ample opportunity for

discovery.

However, despite the high prevalence, debilitating nature and profound unmet needs of CFS, few scientists or physicians believed this disease -- that this was a disease and worthy of research. This makes obtaining substantive funding and publishing an uphill battle.

Fast-forward 20 years. Defining research objectives and designing studies for CFS, now called myalgic encephalomyelitis, or chronic disease syndrome, MECFS is still stifled by the multiple case definitions that have not been operationalized, lack of funding, absence of validated objective markers and lack of interest from the pharmaceutical industry.

In order to make progress, it is essential to start research about the patient experience with establishing partnerships.

So for step one -- and this again refers to figure three -- should be, one, establishing partnerships that include patients, caregivers, advocates, clinicians who manage the disease,

multidisciplinary team of scientists, regulatory experts and peers. Note that this will be a lot of upfront cost. But in the long run, it will pay off.

The second step in figure three should be working with your partnership team, understand the condition. For example, is there a case definition. Is there an ICD-10 code? Is that natural history of the condition known? Are there objective markers? So understanding better.

Once these essential steps are in place, the research objectives and questions can be more easily defined.

When working with patient organizations to leverage their constituent populations and decrease cost, patient organizations have very vast reach for social media and can help researchers reduce recruitment cost.

Understand the degree of disability caused by the disease and understand that many with various medical unexplained diseases and work with clinicians that accept SSDI. Engage community and

indigent clinics and hospitals to help obtain representative input from target populations.

Wherever possible, use open-ended questions and passive data collection to ensure representative input. Patient and symptom heterogeneity and ceiling effects impact validity and generalizability of survey questions in standardized questionnaires.

As a patient's experience with their disease is personal, I would like to see a greater use of artificial intelligence and natural language processing sampling methods to obtain more precise and representative information about the patient experience.

And again, those were from Suzanne Vernon, who was our patient representative, who was unable to join us today. So turning to our panelists who may have had some time to mull over this first question, I will start with Steve. Do you have any initial thoughts on what other factors we should consider?

DR. COHEN: I do, Michelle. One is, is this

data collection, this enterprise primarily for monitoring, for establishing a baseline or is it going to be impactful to actually facilitate change.

So the question is who is the end-user. Is it information back to the patients? Is it to the medical community? Is it to legislators?

So being right up front in terms of who the users are, the timing of it and that will clarify whether or not it actually would be useful to go forward if you can't get the information in the hands of those who could make a change fast enough. So those are things that would be key to consider.

DR. CAMPBELL: Richard?

DR. GERSHON: Yeah, two things. One is I think it was Suzanne's comment on passive mechanisms of data collection. Recent research has shown that analyzing movement data is a better predictor of depression status a year later than given a depression questionnaire or a clinical depression examination. There are -- and that's

simply -- that unfortunately can be analyzed just by looking at information gathered by your cellphone provider or by an app that's put on a phone, without getting an active survey being answered.

Also I believe it's going to be next year or the year after that there's going to be more discussion of the measures themselves. But I'd like to put forward the thought that quickly developing an instrument, getting a little survey data on it or some clinical interviews with people does not guarantee you a reliable measure.

I kind of liken it to the person who uses their relative who thinks that they have a good sense of homecare to be their interior designer versus a survey expert. People spend three to four to five to 10 years developing survey measures that are highly reliable.

And yet, you can go anywhere and find somebody that says I can have that survey ready by tomorrow. There's significant differences in reliability. The other part of surveys in general

is that there's been a historical preference for very specific disease-based survey measures.

And I'm struck by CMS's observation that only 30 percent of their patients have zero or one condition. Therefore, when you ask a patient who has a specific condition about their level of fatigue, they're not giving you the level of fatigue relative to this particular trial. They're giving it also relative to the fact that they have diabetes or something else.

And so, spending a lot of time narrowing down that measure to do this one thing is just not well-informed.

DR. CAMPBELL: Meena?

DR. KHARE: Hi. I think I covered pretty much all the answers to those questions. A couple of things I think I had missed is, again, when you're doing it, look for also some of the availability of data to benchmark or compare your estimates. And if it's a disease as specific as Richard said, yeah, you have to look at the whole profile.

In National Health and Nutrition Examination

Survey, we have an interview where we ask for self-reported data and then also follow up with the examination. And then, we can correlate any specific disease that we follow in the enhanced data.

Another thing, I think we already have covered the mode of data collection. It's very different. And then also look at the nonresponse bias and non-coverage, all those representativeness.

One thing I missed saying is very, very important for us as a survey agency is the disclosure review. We have a disclosure review board.

So when you release the data, I think we have to be very careful that we do not identify -- as an NCHS survey methodologist, we look at it and not identify not just the patient or caregiver or who is the respondent, also the manufacturers or any other establishments because sometimes in the rare disease situation, you might have a very small group of people who are using it. So those are other considerations we look at.

DR. CAMPBELL: Thank you. Liz, do you have anything else to add?

DR. PIAULT-LOUIS: Yes. So for question one, I think in terms of a research objective, we should be -- we should not be afraid to be -- we need to define those research objectives. But we don't have to be too specific. And I really encourage the FDA to think about the spectrum of research we can do throughout the drug development process.

So at the beginning, we don't have so much information. And we need the breadth of information. So we need like very general objective, which is understanding the disease burden, understanding the treatment burden, what is the clinical benefit for the patient.

So those very broad objectives versus when we are further along when we better understand the disease and when we are like having interaction with the FDA, then we can be much more specific. We want to understand this specific function or we want to understand this specific symptom evolution

over time.

So to me, it's like trying to find the balance throughout the drug development process, not relying on one study, but designing multiple studies so that we could ensure that there is a nice flow of information between the decision-maker, between the patient experiencing the disease and between a researcher designing the studies to provide patient with new treatment.

DR. CAMPBELL: Thank you. So let's talk about the third one, the third bullet. I'm going to jump around a bit to keep us on our toes. And we've talked a little bit about using the probability-based methods.

But what situations do you think it's more important to use that, the probabilistic-based methods, and maybe in what situations it may not be as important and what are some pros and cons from that and what information could we gain. So I'm going to start with Meena. Do you have any thoughts on that?

DR. KHARE: As we do in the survey, I think

the first question is what situation is important for sample patient using probability-based method.

We use most of the time probability-based method because you have some frame information and you can do -- you know the probability of selection and you can adjust the data after collecting and then how to weight it and how to get the weighted estimate.

When it's less important, nowadays we are talking about a lot of nonprobability sampling because sometimes data collection, probability-based method, multistage registry or face-to-face, whichever way or multimode you do is very cost-prohibitive and also the nonresponse is going up.

So then, look at the alternate options. And there is a lot of literature also, how to combine two different sources of data. So those other research can be looked at, even though you have a nonprobability and probability. There's a lot of recent research that is going on. So that will be a gain.

Loss is -- I think it's again going back to

nonprobability surveys, is what is your target demographic because it's very different from demographic and there is a lot of literature right now coming up on Web-based panel.

I mean, so I looked at the data, the National Health Interview Survey is address-based. So it's total population. But when you start comparing the people who said, yes, I use the Internet and people who said I use the cellphone, only -- there are differences.

So you need to make sure you evaluate your estimates or findings. And then, timeliness is another thing, how timely your specific disease that you need the data to be disseminated or estimate.

DR. CAMPBELL: Richard, do you have any thought?

DR. GERSHON: Sure. Do we have an hour? I think two things. One is that we use probability-based sampling so we can project on what a population or to get normative information. And very often, we use it to keep expenses low and do

power analyses.

I think that what's known as non-probabilistic methods very often are a lot less expensive and I probably would rather have 20,000 people collected from a non-probabilistic model than 30 people collected from a probabilistic model. And I don't use that number flippantly. I was able to collect 12,000 people on the Internet in a 48-hour period. It took me another six weeks to get completely balanced by demographic information.

Now, is it -- are there biases in that sample? Yes, there are. Were those biases probably less than any traditional model of gathering probabilistic data? Probably were less, because as Meena pointed out, there is no model of reaching anybody.

And while I agree that getting young people on Web-based is now a problem, that's because they're already passed the Web. They're already ahead of us. Okay? You can get them on Facebook, although Facebook is not so much. They're on Instagram. They are responsive. Indeed, they're much more

responsive than others. But trying to figure out what method they're using tomorrow is really going to be our challenge into the future.

DR. CAMPBELL: Steve, do you have any additional thoughts?

DR. COHEN: Yeah. I see some opportunities clearly in what's known as hybrid designs. But I'd like to -- in the air -- I'm not Pablo Picasso. But think of a bull's eye.

And while Richard gave an example of something like 20,000 observations, think of an arrow that really misses the target completely but's incredibly precise versus the 30 sample size I think was really unfortunate because if you had something like maybe 2,000, 3,000, it might be more scattered. But it would be more likely to be in the center if you took the average.

So I have to say there is a whole theory that's been developed in terms of probability sampling. So one can make inferences. If one could get the sweet spot of where this representativeness is from the Web-based survey

and have like a dual frame design and a lot of research is going into that area.

I think this is maybe behind the guidance. But I really like that FDA is very receptive to innovative methods and it isn't one size that fits all.

But right now, it's to completely depend on a non-probabilistic sample, unless it's really at the beginning of like coming up with like a focus group and measures development, I would still be more supportive of probabilistic methods.

DR. CAMPBELL: Richard, do you want to --

DR. GERSHON: I would. I'm suggesting that you can use Web-based data collection as a probabilistic model, that it is -- it has all the same pros and cons as a frame, as a registry so that -- so yes, no, I'm a big believer. I don’t want to leave here thinking Richard Gershon doesn't believe in probabilistic models. I do.

I'm just thinking -- I believe firmly that you can -- there is no single way of getting the people on that registry and the Web may just be

very well a way to get that or consider it a registry in many cases.

DR. CAMPBELL: Liz, do you have any thoughts on this and the considerations that you may have to think about from your side?

DR. PIAULT-LOUIS: So I'm going to take the opposite view. So I think probability-based method is quite attractive because it decrease the novel authenticity. That I could not agree more.

However, I think when we are looking to inform the patient experience, we might not need those large samples or to collect to such an extent to make sure that we have a random sample.

I think throughout drug development, again, we are focusing largely on purposive sampling, so that it could be representative of our clinical trial population. We have some limitation, of course. We have some bias, like any research.

And I think if we are clear of we're getting those limitations, those biases when we do interpret the results, I think we should again rely on what is practical, what is feasible to

give us the information we need to make decisions for our drug development and for feasibility assessment.

And again, I want to sort of emphasize that there are some framework we can use for purposive sampling. Again, recruitment targets. Again, making sure that we do document situation of the concept.

I also want to emphasize that most often, we don't know so much about the population. So we don't have all those AP data available. So we need to keep an open mind so that we define our objective and with that the limitation of the findings.

DR. CAMPBELL: Okay. I'm going to turn over to my panel on my left side, your right, and see if there was any clarifying questions from what they've heard today they might want to ask our panelists, deeper thoughts. Laura Lee?

DR. JOHNSON: So I guess I have a couple of thoughts and comments. And I'm going to start with something that Richard said in his opening

which is interesting because we were actually hoping to go where you went. And so, I'm worried that it was misunderstood.

And so, part of what we're interested in is actually seeing people with low literacy be included so that they are not excluded so that -- this was misinterpreted by you as important information for us as we start writing that Guidance 1.

Another couple of comments pertaining to some items that Liz brought up, I'm also thinking not everything that is being collected needs to be submitted to FDA. And so, thinking about kind of what to submit, I would say that when a decision needs support, that is -- so a lot of work happens in all of research.

But not everything comes into the agency. And when trying to parse out what to submit or not is that, you know, if you're making -- if you're asking for a decision that probably needs that extra boost from us seeing that information, that would be where I would focus on what should

actually get submitted.

Another element is that not everything is going to go into the label. A lot of information comes in and is considered, but doesn't actually go into labeling.

So if you want to know what that label is, that's that sheet of paper that you pull out, like you know, it's this big. You can barely read it because it's such small font. But if you're lucky, find it online where it's a much bigger font.

That is what we in FDA call label or labeling. And it's not everything is going to go in there. But that doesn't mean the information wasn't used to make a decision about what is going in there. So those are a couple of comments and thoughts I had while listening.

DR. CAMPBELL: Okay. Great. I'm going to let my audience know that in a little bit, we are going to turn it over to ask you if you have any questions or comments you'd like to add to this conversation. So you may start thinking about

them. We will transition over to you shortly.

But I wanted to touch with something that Steve brought up about figure two. And to refresh your memory on what that is, that is a box of factors to consider when selecting a research approach.

And it has -- it's eight boxes and it talks about your research goals or questions, your target population, what type of information you want to generate, short- and long-term impacts, the type of information that's most valuable to achieve these goals, what is the expected impact, the amount of time and then budget cost things.

And Steve brought up a comment that these are often competing objectives, which is true. I would agree, as a former researcher myself.

But how -- of those things to consider, what is one that you would think that we need to make sure that we don’t miss, that because they are competing -- and I'm not sure if I -- I don’t know if I want to hear budget because I feel like that's always the answer I get.

But some of those, what are things we want to make sure that, in the end, when we are putting that final research question together and then to move forward, that ones you take into consideration is to make sure that you really remember to check into that consideration.

So does -- I want to start with our panelists. Do you have any thoughts of what that might be, that you may have seen where it was forgotten? Steve, do you want to start, since you were talking about the competing objectives?

DR. COHEN: Yeah. I just want to say it's very hard to just say one. I think, and that's why you said, it all in figure two.

But I just have to raise one thing, because Richard, you know, mentioned something that really resonated with me in terms of the fact that an individual who has a chronic disease has multiple chronic diseases or multiple conditions.

And recognizing that in the study design is perhaps one of the most challenging things in terms of what you're trying to eke out. So

factoring that in.

But I would have to say the research goals and whether it's going to be impactful and whether you have the dollars to do it would be the three things I'd look at first. And then, if all those three resonate, then go forward with designing what you could design.

DR. CAMPBELL: Does anyone else have any considerations? Liz, do you have any thoughts on --

DR. PIAULT-LOUIS: So to me, it's how do we avoid duplication of information, right? Because you eliminated the budget issue. I think we don't want to have like five different groups doing the same study, right?

So again, how do we make sure that we collaborate, regulators, payers, patients, industry, so that we could address those questions within unmet medical need.

DR. CAMPBELL: Okay. Richard, do you have some thoughts?

DR. GERSHON: I didn't, but I love where Liz

started with this. So I'm going to take it from there. And that is that the opportunities for team science and the opportunities to conduct joint research studies is simply a missed opportunity time and time again.

When I got into patient-reported outcome measurement, I went to my first International Society of Quality of Life Research, which is where people hang out who want to develop survey measures.

And I was struck that the NIH had funded 40 different studies of fatigue that were being demonstrated. Forty. And when all is said and done, from the patient's perspective, I'm completely convinced that all of them measured the same thing.

From the patient's perspective of course, they weren't related to each other. There were not correlating statistics between those measures. And yet, we took 40 times, 40 x an amount of money that could have been done in joint studies. And I would -- it's an interesting thing to consider is

how much of the drug development process could be more in terms of shared research, saving just a ton of money and make this more efficient.

And I would hesitate to say that anything could be prioritized or taken off this list. I think they all have to be considered, maybe some a little less than others. But couldn't really make a decision without considering all of these items.

DR. CAMPBELL: Great. So I'm going to talk about the second bullet because we've kind of talked about this a little bit in other responses.

What are those other factors and approaches we need to consider when we're looking now at a representative input from our target population? And I might add a little flare to that because it's been brought up a couple of times now the idea of the multiple chronic conditions, that when we're going in, we're looking at one specific disease, but the patient may have multiple.

And so, you know -- so what are some considerations we need to think about now when we are looking at developing that research question

and, down the line, that sampling frame to get to that? So, thoughts? I know Richard, I see --

DR. GERSHON: Well, one thing on the multiple conditions is that is the real patient set. And every once in a while, I'll see something that was only done in patients that had the one condition. That's not representative, right? That simply isn't. I mean, that just shows you found a small group of people who only had one item and therefore that's not generalizable at all.

I think the other thing is we are struck with increasing ways of finding patients and of determining populations and target populations.

And for instance, something I think that probably should be added to the discussion document is the advent of electronic data warehouses that almost any hospital has, any consortium of hospitals has and now super-consortia of hospitals which that you can literally find any patient with a given ICD-10 code or a given disease and find those people.

And depending on how those hospitals have

consented those patients, you can get a list of those patients and contact them, and may be much less biased than any opt-in panel, although I like opt-in panels too.

DR. CAMPBELL: Steve?

DR. COHEN: That really resonates with me, going to either physician offices and then drawing a sample. You then need like multiplicity adjustments, which you actually talked about.

But then, there are those patients, think of those that have hypertension that are not diagnosed. And you know, maybe they're not going to get treatment. But they're a group that you really have to worry about too because eventually they're going to enter into the system.

So having some sort of a coverage and more of a general, overarching sample that would allow for false negatives to be included in. So that would be, you know, recognizing whatever screening device you have is not really capturing the entire population. Hopefully that's going to be small, but recognizing that.

DR. CAMPBELL: Meena, do you have any additional thoughts?

DR. KHARE: I can just add, because at NCHS, we do a lot of provider-based, which is hospitals, providers, physicians and we have started looking into the electronic medical records to do the sampling instead of going into the office. So that gives you more power to search and do.

So that's right now we are in the middle of looking at it, the quality of it and at some point it's not there yet because not all the hospitals and providers are right now again collecting electronic data.

But at some point in the next couple of years or five years probably we'll be there and that will be very helpful. The same thing with the registries. It depends on what you're looking at. Sometimes registries are not complete.

With my experience with national immunization survey, we always tried to go back to the registries. But it's not as complete as going to the provider's office and contacting them. So

yeah, it's coming up. But probably we have to consider that.

DR. CAMPBELL: Okay. So I'm going to take the flip side of that. What about with our rare disease or smaller population?

Is there anything that may be more unique or some additional considerations when we're looking at representativeness that we may need to touch on or people think about?

DR. COHEN: I just think of somebody who's lost their keys and then goes where the light is. So given that it's so challenging and so rare, some information might be better than no information.

So if there was some ways of conveniently getting at those patients, that would be another time to be -- you know, the costs are so prohibitive and any information you could get would be valuable for the next stage, it's worth considering.

DR. KHARE: Yeah. I will agree with Steve that sometimes it's better to have some

information and we have done an analysis of our data, some of the rare diseases.

So even if it doesn't qualify as releasing the estimate, we do have to have a lot of documentation that limitations there. Btu it's good to have that, such as like when HIV infections started among the general population, not the high risk population.

And then, all of those sampling methods are there, networking, snowball. But then you have to document, well, that okay, what is the focus and objective of that. So that is good to have that. Thank you.

DR. CAMPBELL: Liz?

DR. PIAULT-LOUIS: I'm mixing my thoughts. I think often we are talking to the patient at one time and we have now digital health. We have the Fitbit. We have the iPhone. I think we do have opportunities now to follow the patient a little bit longer.

So instead of having a large sample, why not having a smaller sample, but follow this sample a

little bit longer so that you have data for like 10 days, let's say. And you're able to document some of the variability in the symptoms. But again, that requires not to have one method fitting everything.

It's more like, again, it's a field of research. So what is the objective? If it's to get like the breadth of information, trying to mix the method, qualitative and quantitative.

DR. CAMPBELL: Okay. So I am going to turn it over to our audience in the room, if there's any questions that you may have or comments.

I will open the floor at this time. We have four microphones. I would ask that you at least state your name so we know who you. And I will start on this -- on this side and go this way, you know, swear if I can. So gentleman, sir?

AUDIENCE QUESTION AND ANSWER

DR. DEGBOE: Hello. My name is Arnold Degboe and I'm one of the patient science directors working with AstraZeneca support in oncology. Thank you very much, Michelle and the panel and

the FDA for organizing this. And this has been a very beautiful discussion.

I think your last question will be a segue to my comment and thoughts about what has been discussed, that what you do in terms of when you have a rare disease and in situations where you have patients who have diseases that are diagnosed very late and they have a very short survival.

For instance, pancreatic cancer, that patient may come very late. He's diagnosed. Within six months or sometimes three months, they are no longer alive.

So I think we need to -- the discussion appear a little bit to probably assume a lot of idealistic situations where you have all the time and the resources in the world. You can do a standalone interview and all that, use that to inform your trial and do everything.

I think we should also look at it from the perspective that sponsors will respond to incentives. People -- and not just companies -- would just not generate data but they don’t really

know what it will be used for. Anybody who works in PRO knows that.

Even slotted in questionnaires sometimes into your trial can turn into a whole discussion and with a lot of pushback about people asking what are you going to use their data for. You are already analyzing survival and all that. Why do you want to use PROs or you are using too many PROs.

So I think it's important that when patient experience data is going to be generated in a nontraditional way, you tie in some incentives.

And in that way, I think we should break the data collection between data that you are collecting to inform your trial design and data that you are collecting when the trial probably is already going on and you want to use that data to provide an additional layer of interpretation of the data.

When you break it that way, I think the second one, in-trial interviews can come in. When you have a very rare disease where the population is

few, you may not have the time to interview those and inform your trial. You have to do both concurrently.

So in such context, whilst the trial is still going on, there can be a simultaneous or concurrent qualitative survey where you also collect additional data about the patient experience during the trial.

What made more sense to you? Are there aspects of the assessment that should have been done? What bothered you most? What were some of the side effects that you never got the time to discuss with your clinician?

And that kind of information can also be considered by the FDA for the label. I mean, if there were different modalities of treatment, some were injection and some were tablets.

I think if the patient went through that kind of experience and the drug is approved, new patients may want to know about that, that probably the oral form is preferable. And even for the drug sponsor themselves, they might decide

let's go with an oral formulation rather than an injectable.

So I think we should break this up into what should be done to inform design and what should be used and can be done concurrently during the trial.

That way, we will be able to come up with some kind of incentive for sponsors to know that this is just not an exercise you are doing again to produce data that you don't really know what it will be used for. But in that way, it can be used.

So my question to the FDA and to the panel is do you have plans to develop this in such a way that sponsors will see the need to do that. Thank you.

DR. CAMPBELL: Thank you, Arnold. I think that was highlighted earlier about how we will be using this data is something that we will be discussing and trying to determine. And obviously, we'll make that known once that determination is. That's -- we know that's

everyone's important question everyone has, is how will this information be used. Theresa, did you want to add on?

DR. MULLIN: Well, I guess I think that we're hoping sponsors also see the importance of collecting this kind of information, even on their own.

And that in the example that you offered, I think you'd probably be planning quite early in the target profile if it's an oral version versus injectable or whatever other mode of delivery.

And so, I guess we are thinking that it's information that will be very important to FDA and very important to the sponsor.

We think that if you involve the patient early enough and you involve endpoints that are meaningful, if you involve them in thinking about trial logistics, you may do better with avoiding dropouts. You may do a better job of trying to reflect what matters most.

You may do a better job of responding to questions that health technology assessors may

have later when it comes to reimbursement, all things that would imagine to, I would imagine, a sponsor. So hopefully there is a win-win, if you will.

We're certainly trying to make these guidances accessible and easy and we're also trying to help avoid reinventing the wheel as much as we can. Liz asked earlier about that information. It might be collected very early on that might just really help gain insight about the disease, people living with the disease and what it is like to live with the disease and current treatment.

And although that may not support regulatory decision-making per se, FDA is planning to build a repository of things sent into us that maybe those early qualitative studies by disease, that may not only be valuable to the person, the company or whoever conducted it, but would be very helpful to others pursuing therapies to treat that disease.

So we're hoping to help you avoid redoing work someone else has done that's available to make use of.

DR. PIAULT-LOUIS: Yeah, and in my experience, we would like to figure out like a path for people to submit this information not only to support drug decision-making process but to facilitate the discussion between the agency and the sponsor at the early stage when, you know, you are encouraging us to come to discuss the study design.

We would like to understand what -- you know, how do we submit this information because we have the -- we gathered the patient insight and we want to be able to provide that to you so that our discussion regarding the target population, the treatment, the endpoint can be basically evidence-based rather than only hypothesis.

But I do agree with my colleague. It's early stage versus evidence generated to support development.

DR. CAMPBELL: Great. Well, thank you. Next comment?

AUDIENCE QUESTION: Hi. I'm Xia Ha (ph). I'm a software engineer. So I had a question about

how the real-world data, real-world evidence initiative compares or contrasts with the patient experience conversation that we're having here. How does it align or how does it differ?

DR. MULLIN: So there's a lot in the real-world evidence, real-world data sphere there. So if you look at what's focused on in 21st Century Cures, most of that is observational.

But at the same time, I think as was mentioned, a lot of information is in fact available in electronic health records and available in other areas that are considered, quote, unquote, "real world".

So a lot of this does interface with each other, either trying to find ways to interface with people that our sponsors and other groups might want to use and finding them period.

But then also, I think, you know, where this data is collected, we talk to each other pretty regularly. So our lead for that in the Office of Biostatistics in CDER is Mark Levinson, who's the division director for our safety division. And he

was chosen because they've already started in this realm.

That's a really important part of what they do in safety work and it goes well beyond Sentinel, for those of you who know what that is. But an important thing to consider is we do work together and we all talk to each other.

So I don’t think there's a lack of interface. But it's more when we need to talk to each other, we do have a lot of conversations.

DR. CAMPBELL: Thank you. So to the person in the back wearing the red?

MS. MURRAY: Hi. My name is Mary Murray. I work in industry. But I'm actually here today as a caregiver for a young man with sarcoidosis and while sarcoidosis is --

DR. CAMPBELL: Mary, can you speak up a little closer to the microphone, please?

MS. MURRAY: Sorry. Okay. Is that good enough?

DR. CAMPBELL: That's -- yes.

MS. MURRAY: Okay. So I'm here today as a

caregiver for a young man with sarcoidosis, which is actually not a rare condition, but a certainly subpopulation of it that's symptomatic is rare. And so, he's a part of that subset.

And what I wanted to say was my big observation here this morning is that there's a very heavy concentration on kind of the statistical strategies that we're employing and the conversation seems to be around a study level approach. You know, the target population, et cetera.

But what's missing for me is how we're going to be able to incorporate some of the patient narrative data that hopefully we're collecting in electronic medical records through shared decision-making processes and motivational interviewing and that type of narrative data.

And how are we going to have the capacity at FDA to incorporate that in some of the decision-making? And the other piece I wanted to bring up was if this is study level, that seems to feed into the issue that you were addressing before

about sort of the cumulative burden on patients.

If there is a lot of redundant -- essentially redundant studies going on out there, those redundancies have a big patient burden. It's tissue. It's blood you're collecting. And to answer the same question, you know, it's very burdensome on, you know, us as patients who might not have a lot of lung tissue to spare.

So those are the two questions I'd have. Number one, how can we incorporate some of the narrative data that hopefully we're starting to see showing up in the electronic medical records into this process? And number two, how can we reduce the cumulative burden on patients?

DR. CAMPBELL: Thank you, Mary. So Richard, you want to --

DR. GERSHON: Yeah. It's interesting you raise that because I didn't comment on the qualitative type methods outlined because I think they're actually here in a lot of places in the guidance.

They're discussed about, you know, statistical

methods for qualitative data, how we get the voice of the patient, how -- so actually, to the contrary, I'd actually argue that the qualitative methods are nicely outlined. Very often, they're forgotten.

So I'd actually like to compliment they're there. But I will admit none of the panelists chose to discuss them.

DR. CAMPBELL: Theresa?

DR. MULLIN: I'll just add to that that we do see those as extremely important methods. But what we've been trying to do -- and qualitative and narrative anecdotal accounts are very important and very powerful.

But they won't be a substitute for data collected for a whole population in terms of how we can use it in decision-making.

And so, we're able to use narrative data, including extracted from, you know, interviews, in a way to ogive us general insight about how patients feel, the clinical context for regulatory decision-making, a general sense of the burden of

disease and burden of treatment that are available today.

But in these guidances, we've been trying to see if we can provide a clear way for patient advocates and sponsors and others to go from that, which is still quite valuable and informative in a general way, to trying to collect this as data that can be used to actually measure the performance of a particular product that's under development or investigation.

So that's still very important to us. But we are trying to take it further in a certain way with these guidances, this being the first.

DR. JOHNSON: I also want to comment I am a big fan personally of data reuse, I will say. But I'll also say it is very hard.

Many times, documents that we think might be in electronic health records aren't or they are not in there in a way that it is easily usable and accessible. And I say this both as someone who's spent a lot of years in research hand from what we hear sitting here.

So I would encourage patient, patient groups, other folks who really have discussions about how to maximize the ability for data reuse and to think about the multiple different groups who might need that.

That may be your payers of the insurance types of companies. It might be regulators around the world. It might be sponsors. It might be researchers that are funded by a whole host of different organizations.

So that's something to also consider because, while being aware of that burden, it is also something that many times it comes up because there hasn't been appropriate consent or literally the data can go in and it cannot easily come back out. And that's a fundamental concern. But I'll leave it there.

DR. CAMPBELL: Okay. Thank you. Sir?

DR. LEVITAN: Hi. Bennett Levitan, from Janssen Research and Development. So many people here may know there was a recent drug label that had a novel section on patient experience data.

And many of us were excited to see this and I have no doubt that part of the guidances in the future will start outlining how to do this in a more general sense.

But in the interim, do you see it appropriate for sponsors to start drafting labels that include their perspective on patient experience data and benefit-risk assessment?

DR. PAPADOPOULOS: I think that's a great question. I think that, you know, there's only so much real estate in our labeling. And the purpose of labeling really is to, you know, assist the prescriber and, you know, in the safe and effective use of a medication.

And so, it's not clear whether all patient experience data actually belong in the labeling and, you know, are there other mechanisms of communicating and incorporating important patient experience data.

So I think that that's something that's still under construction. But we do want our labeling to be patient-centric and to provide information

on the, you know, benefits and risks on topics that are important for patients and their decisions.

DR. LEVITAN: So this is an issue that came up in a recent experience where we attempted to put in some benefit-risk information that we thought would be very relevant to a provider. But there really wasn't a place for it.

What I'm trying to get to is I'm sure you'll be addressing these points over the next couple of years.

But in the interim, if a sponsor starts putting together patient engagement sections and benefit-risk sections of labels, would they get rejected out of hand or would they start being considered as potentially applicable?

DR. MULLIN: So Bennett, I think at this point we're just going to take it as a comment that you've made about the need to do that. And we'll just note that it's something that's, you know, identified as a desirable thing to address.

DR. LEVITAN: All right. That's fine. Thank

you.

DR. MULLIN: Thank you.

DR. CAMPBELL: Thank you. The gentleman in back?

MR. WHITE: Good morning. My name is David White. I'm a patient advocate and a kidney transplant recipient. I'm relatively new to research. I think this patient's been answered a few times. But I'm not sure.

To what extent do the people who are participating in the survey need to understand the terminology that is used in drug development?

DR. CAMPBELL: Well, that is a great question. Andi don’t think it has been answered today. So that was a great question.

So I'm actually to turn it over to some of our methodologists on our panel to talk about those experiences and what do patients need to know when you're particularly testing surveys and the correct terminology. So Richard, do you have some initial thoughts?

DR. GERSHON: I think that it's -- I think

whenever we do survey models or methods, we try to find -- create a survey that's understandable by the lowest, lowest possible literacy level because that's the only way to cut it.

Somebody who has a high reading level will be able to figure out something that's more readable at a lower level. And when we design surveys, we actually put them through computer-based engines that assess the readability and what grade level it goes.

We're very often able to get adult surveys down to a sixth grade reading level which, by the way, is not that low relative to the U.S. general population. And so, even going lower is helpful. I think relative to vocabularies in general, a word that would hit a vocabulary list is probably too high a level to be on a survey.

So it would have to -- if you need a word for a particular disease, you really have to define it within the survey itself. But there's major danger -- those types of items in a survey typically get kicked out later on. A person

simply doesn't understand it.

So I think it is important to consider what you're talking about. And this gets back to me comment about anybody can write a survey. What we found out later on, when that anybody wrote a survey, the data's pretty poor later on.

So really getting some expert methodologists in there and frankly following -- there's survey guidance that is thicker than what this discussion document is and how to create those surveys, how to make certain that they're reliable, how to get sufficient input just on the survey document that will later be used in a trial.

DR. CAMPBELL: Liz, do you have any thoughts?

DR. PIAULT-LOUIS: Well again, providing that we want to capture the patient perspective, we need to ensure that this is an appropriately and that we use patient advocate, patient as partner.

So at the end of the day, we generate evidence that are meaningful and discernible and explain the clinical benefit of a drug. So I think it's a basic criteria to ensure that a patient or

responder are going to understand the survey, but also the objective of the survey.

DR. CAMPBELL: So, and as Richard mentioned earlier, there was talk about the qualitative methods section that was in the discussion document.

This is when you start talking to your patients to say do you know what this word means, what does it mean to you, to really try to determine what is the correct terminology to use because there is some understanding that people with health conditions may understand their health condition-related words.

But you do need a test to make sure that it can be applicable across the boards. I didn't know if anyone from my other side wanted to chime in. I don’t think so.

I've got two people left at the microphones. You will be my last two speakers for today. And then, while they're asking their questions, if our panelists want to think of a final comment. So we'll be wrapping up shortly. So, ma'am?

MS KWON: Hi. My name is Jeemin Kwan. I'm with the diaTribe Foundation. We're a nonprofit that focuses on diabetes based in San Francisco. And my comment is surrounding the idea of representativeness.

And I wanted to bring up the idea of making sure that the actual patient experience data that is being collected is representative of that individual's experience. So I guess this is coming from my own musings.

So for people with chronic conditions, I think that often the burden of disease, it isn't a three-month average. It isn't a month-long average. It is really like a daily, day-to-day sort of experience.

And so, with these sort of patient experience collecting methods, I think it's really important to make sure that the timing of the questions being asked really gets to the timing of events that you want to understand.

So I'm wondering what sort of consideration has been given to this and, yeah, what your

thoughts are. Thank you.

DR. CAMPBELL: So I think the question had to do with how do we capture in chronic conditions the timing of events to the timing of how we're asking someone to reflect back in their question. So I don’t know if anyone has any thoughts on a way to handle that or -- sure.

DR. GERSHON: It's hard because -- and that doesn't make it something that shouldn't be done.

But it does bring in electronic data capture and having an app on a phone that allows a person to respond to an event when it happens rather than a week retrospective or a monthly retrospective or frankly an annual retrospective of what occurred. You know, a person's pain on average may be very, very low. That doesn't make it almost unbearable at 10 p.m. for a certain condition.

So I think this is where we're likely to be able to use new methodologies and new data collection methods to go there. But they're really new. You know, I'm saying if you pick up a textbook or a methodology book, there's nothing in

there about this area.

And the flipside is it's completely legitimate and our current -- you know, the well-known methods simply ignored that because we could get a retrospective piece.

And by the way, that's very patient-based. Many patients, when you ask them about their experience over the last week, will truly average it. And therefore, a daily event that took place for half an hour actually doesn't get included.

And the other patient will skip the fact you asked them about the week. They will zoom in directly to their most high impact event and tell you about it.

So I think that could be taken into consideration and finding out from a patient and also hopefully new methodologies allow a person to report in real time, contact your research desk in real time. Those are methods that are now available. But we're really at the dawn of that, but so --

DR. JOHNSON: And I want to comment a little

bit on that too. And I think part of what you alluded to also goes into Guidance 4.

So some of it starts very early, trying to figure out and talk to patients like what is it that we really need to focus on and then, moving on, eventually not just that timing but also what is that ultimate endpoint.

So if you talk about averaging over a month or something like that, realistically that becomes the endpoint of the studies that we're interested in and how we're going to actually analyze the data that's come in on the trials. So your question actually nicely touches across all of our guidances actually.

But I want to second what Richard said. It is also an evolving area. When can we be asking and how -- what information can we get when we do those asks. And that's going to possibly change per patient population.

But there may be a lot to be learned within a given population and also maybe across multiple chronic diseases or in other areas that can then

be gathered and used.

And we've seen that in the past as something that could move forward. But it is, I think, thinking about what is it that patients care about is -- and finding that out from them is a very important element.

DR. CAMPBELL: And to add on to what Laura Lee said, as that is a great question that we'll be expanding over our course of guidances over the next five years, we do have the patient -- the roadmap to patient-focused drug development where the first column of that roadmap really does highlight that understanding of the condition and when are events occurring and what does it look like in that patient population.

So while we are still beginning our journey on these guidances today with Guidance 1, that might be a start in looking at that resources that is already available on our website to helping us, you know, really tie in what are the events that are important to patients, when are they happening so we can accurately make sure we're collecting

them. Elektra?

DR. PAPADOPOULOS: I agree. That was a really great question, very thoughtful. And I think as we're talking more broadly about gathering patient input, we really do need to consider the entire journey of the patient, you know, from the time when they're diagnosed all the way through, you know, to their treatment experience, et cetera.

And so, having patients -- you know, sometimes we can't help but to have them recalled back to provide that journey.

And so, it really -- and then, if you want to -- if you're talking about development of an endpoint on the other hand, you know, you might want to minimize that burden of recall to maximize the accuracy of the data that you're achieving.

And so, you know, this will really depend on your purpose of your research.

DR. CAMPBELL: Okay. Our last question?

AUDIENCE QUESTION: Great. Two-part question. One is maybe Meena, if you've seen any health literacy being done in audiovisual manner so that

if you're looking for that sixth grade or lower literacy level, does audiovisual make a difference in the explanation.

I have family members who are in clinical trials and some of them get the very long explanations. But nobody -- I've never seen one where they've actually had a video or something explain that to them each time that they do the entry.

And maybe Richard, you can talk a little bit about -- we'll geek out for a second and talk a little bit about conversational user interfaces and how the chat bots and other interactive conversations that you could have, instead of asking a 40-question survey all in an hour, could you ask those same 40 questions over a week and get a better answer, more through, in an interactive capability through SMS or chat bots.

So, and I mean, any one of you can answer both questions. But I thought just anecdotally letting us know what you're seeing in the marketplace might be good.

DR. CAMPBELL: So before we have our extensive conversation on chat bots, which sounds very interesting, if we can get maybe a high level response on that from Richard and then you guys can connect during lunch on that.

But then, and let's not forget the first part of the question is the uses of audiovisual aids to help us in the health literacy when we may be dealing someone with a low health literacy level. So Richard, do you want to start?

DR. GERSHON: It's a very popular topic in research right now, is burst designs and EMA designs, which allow -- exactly focus on that. Let's get people many, many times over the course of a day versus a summary event or over the course of a week and aggregate that data together.

So that's -- there's actually a lot of research funding available right now to prove that. I think it will be useful. I don’t think it will solve everything. It's literally the wave of the moment if you look at funding that's available for researchers in this area.

And I'm going to sneak into Meena's area and respond for one second because I work with several people who do health literacy research. And they very often are providing surveys with a button to have an auditory response along with it. And I haven't seen anyone actually add video.

But that's a very neat thing where technology is today, that to add that type of thing is much, much less expensive than it used to be. So, and we can talk about chatrooms and things like that at the break.

DR. KHARE: For our surveys, in National Health Interview Survey, I don’t have the current recent information. But in the National Health and Nutritional Examination Survey where there is an interview and then they come to the mobile examination center, there is some audiovisual. I'm not sure how much detail.

But then, there is the interviewers go through extensive training to explain the terminology, the definition and also they have hotkeys to explain. And some of the time, we do use some audiovisual.

I don't know how specifically for certain disease. But then, there is some because now they have iPads and others things that you can bring it in, which is not those days when you had a paper and pencil or just a big heavy laptop.

But yeah, they do try to do it. But how extensively, where it's feasible, because you have to reduce the respondent burden and then interviewers are trained and retrained to explain everything that comes in the questionnaire. And they are pretested. That's all I can add.

DR. CAMPBELL: All right. Well, great. So I want to thank everyone from the audience for their questions.

As we wrap up, if our panelists have one final thought they would like to add that's not been said or they've thought about, this is the opportune time now to add anything. And if Ebony or Kunthel have anything they want to add from what they've heard today, this is the opportunity. No? No?

So if there's no additional final thoughts, I

want to thank firstly our panelists for participating today. I think we did a great job and I think we had a great discussion. And we've heard many things. My note pages are completely covered. So I know I cannot do a good job in summarizing.

But I think some key messages were the possibility of collaboration and trying to reduce patient burden through us doing multiple studies of the same thing and working together.

What is the information in patient experience data being used for? Is this being used to inform trial design or is it being ongoing during what's occurring during a clinical trial? And how do we handle when a person doesn't have a single disease, they have multiple diseases and what are those considerations?

So I thank you again for listening. I thank panel one. We will adjourn at this time for lunch. Please be back at 12:30 for the remainder of our afternoon session. Thank you.

(Applause.)

(Whereupon, the foregoing went off the record at 11:33 a.m., and went back on the record at 12:31 p.m.)

MS. VAIDYA: Hello, everyone. We'll get started in about two minutes, so if folks can start settling in, thank you. Welcome back, everyone. I hope you all had a nice lunchbreak and enjoyed the bagged lunch that we had here.

We are now ready to begin our next session and kick off the afternoon with session -- we'll have three sessions in the afternoon actually. So we'll start off with methodological considerations for data collection, analysis and operationalization.

I'll turn it over to Scott Komo, who will be moderating session two, from the Office of Biostatistics in CDER. Thank you.

SESSION II: METHODOLOGICAL CONSIDERATIONS FOR DATA COLLECTION, ANALYSIS AND OPERATIONALIZATION

DR. KOMO: Thanks, Pujita. Hello. My name is Scott Komo, from the Office of Biostatistics. I was going to tell you I hope you had a nice lunch.

But apparently Pujita already handled that one.

So first, this is for our session on methodological considerations for data collection, analysis and operationalization. I'd like to first introduce our panel. First is Dr. Kai Ruggeri, who's the director of global research analysis for population health at Columbia University.

And next would be Dr. Steve Cohen, who's the vice president at the Division of Statistical and Data Sciences at RTI. And next to him is Dr. Sheri Fehnel, who is the vice president of patient-centered outcomes assessment at RTI. Next would be Dr. Gary Globe, who's the director of global health economics at Amgen. And last is Ms. Isabelle Lousada, who's the president and CEO of the Amyloidosis Research Consortium.

So I'd like to first give you a brief overview of sort of what's going to happen in our session. First, Selena Daniels, from the clinical outcome assessment staff at CDER will present the key concepts from the sections three and four of the

discussion document. Then, I'll quickly recap sort of what was presented. And then, each panelist will then give a short overview of their initial response and reactions to the presentation and discussion document.

Then, the panelists will then be asked to address the questions that were in the -- that are listed on the agenda. We'll then follow that up with questions from the floor and finally we'll wrap up the session. Okay. Selena, would you like to come and please give your presentation?

FDA PRESENTATION

DR. DANIELS: Thank you, Scott. As Scott mentioned, my name is Selena Daniels. Good afternoon, everyone.

So in the previous session before lunch, we heard some considerations on how to define research objectives and design studies to collect patient experience data. In this session, I'll present some considerations on what types of methods that can potentially be used to collect patient experience data, including analysis as

well as some considerations on how to standardize the data collection process.

So this slide should be familiar. These are some general steps for conducting studies. The last session focused on the first five steps and the content I'll present in this session will target the last three steps, first beginning with considerations for methods of data collection and analysis.

So this is an overview of the different methods that can potentially be used to collect patient experience data, which includes qualitative, quantitative and mixed methods. Qualitative methods can include the act of just talking to people by using direct communication to explore or confirm the meaning of interpretation of a topic from the participant's perspective.

An example of a qualitative study may be just talking to a group of patients to describe their experience with their disease or condition. And a potential scientific objective for this method could be related to exploring the most important

aspects of that disease for your target population.

Quantitative methods are characterized by the collection of quantifiable data or the use of numbers and apply statistical methods to summarize the collected data. With regard to collecting patient experience data, this information could be collected by the use of a tool, for example, a survey or a questionnaire.

And an example of a quantitative study may be surveying a group of patients with a questionnaire, allowing them to rate the severity of their disease symptoms using questions with response options to choose from to create a score. A potential scientific objective related to this method could be the development of a questionnaire based on that patient input.

Lastly, mixed methods are where both qualitative and quantitative methods are used. An example of a mixed method study may be surveying a group of patients with a questionnaire but then also including an interview component which allows

patients to further describe their response with more detail that may not have been provided with those response options in a questionnaire.

And a potential scientific objective related to this method could be determining whether symptom severity or symptoms frequency is most important to patients by looking at severity and frequency scores but also looking at patient quotes or patient narratives.

So overall, each of these methods can allow one to understand patient experiences, perspectives and feelings. And in later slides, I'll break down these methods a little further.

So we have these methods, but how do we determine which methods to use? Some potential factors to consider in selecting a method including the following, but not limited to, research questions and goals.

So does your method address your question or goal? Individual characteristics of the method. Your target population, is your population accessible for the particular method that you want

to use. And then, expected data, what type of data do you want to produce from your study?

So I'm going to take a little deeper dive into these methods. The key outcomes for qualitative methods is to discover or explore rather than test a concept.

Another outcome is determining the meaning of and refining specific research concepts. And some potential sources to obtain this data or these outcomes includes talking to individuals.

You can talk to participants in different modes or settings. For example, the use of interviews. This could be one-on-one interviews or these could be focus groups where you're talking to a group of participants at one time.

It can be social media, as we discussed in the last session. A consensus panel could also be another approach. For example, a Delphi panel in which you're talking to a group of experts to gain consensus on a certain topic.

In regard to analysis of qualitative data, there are some general steps that should be

considered which involves, one, compiling and organizing data either through your notes, a glossary to sort of see what kind of terms are coming up and/or software; second, classifying data by coding data, by creating themes or topics that are coming about in the discussion; interpreting data by connecting the data to your research questions; identifying the main theme of the data and/or patterns, if any; and lastly, representing and visualizing data. And this is considering how you would you present the data, whether it's tables, pictures or graphics, et cetera.

The key outcomes for quantitative methods are to test, rather than discover, concepts. And to obtain data to test, a source could be a survey or a questionnaire. With regard to the analysis of quantitative data, the analytic approach to use should be appropriate for the research objectives, the study design and types of data generated in the study.

The key outcomes for mixed methods are to

discovery and/or test concepts. And the sources used for both qualitative and quantitative methods can also be used with this method. Likewise, a combination of analyses for qualitative and quantitative methods can be used as well.

So we know that there are different methods to collect data. The next question becomes how can we standardize this data collection process with a method that is used.

This slide provides a brief overview of the data collection activities that should be considered to help operationalize and standardize the data collection process. And these activities are sort of interrelated, sort of like a chain, as illustrated on this slide.

So first, beginning with locating patients and sites, a critical step in the process of data collection is to identify the appropriate sample and/or sites to study.

For any study that involves gaining access to sites and patients, one should seek permission from a human subjects review board prior to

studying and comply with the institutional review board, or IRB. And just like any clinical study, a patient experience study should comply with good clinical practice.

Next, the activity of sampling. You should consider determining the strategy for sampling of patients or sites. And we have been told about the different types of sampling methods in the previous session.

The act of data collection itself, you should consider the most appropriate data collection approach for the research objective. And once you have collected that data, then how do you record it. Recording that information, you should develop written forms or protocols to collect data.

And in an attempt to avoid or maybe resolve site/field issues, you should consider providing standardized training to research team members. And lastly, data management and storage. You should consider formulating a data management and storage plan prior to the conduct of your study.

So in addition to standardizing data collection activities, the reporting of results should also be standardized to the extent possible.

Materials that would help benefit FDA would include, but not limited to, would be the study protocol and this can include the interview or discussion guide or the tools, if applicable, to the method that you've selected, as well as the study reports. And this may or may not include transcripts, if it's applicable to the method that is being used.

So there are some levels of detail that was included in the discussion document that may or may not have been presented extensively today, which are located in the appendices.

And these appendices contain information regarding the timelines for the development of guidances, standards and requirements pertaining to submission of data, best practices on qualitative interviews, Delphi panel techniques and characteristics, considerations for data

management and, lastly, some more information on methods for collecting patient experience data.

And so, before opening up to the discussion, I'll leave you with some key takeaways. Research objectives/questions should inform the methods that are used to conduct research.

The other factors to consider are the individual characteristics of the method, target population and expected data and, second, data collection process, including data quality issues, and reporting of findings should be standardized to the extent possible. And I'll turn it over back to Scott.

DR. KOMO: Thank you, Selena. Great. So that gave us a nice overview of the methods that could be used to collect data. These would include qualitative, quantitative and mixed methods and also how to determine which methods to use.

We also had a discussion on how best to collect data and how the collection should be standardized. Also we had a discussion on reporting and how submitting the data to the FDA.

At this point, I'd like to call on our -- ask our panel to provide a brief initial reaction to the presentation and the discussion document. First, I'll ask Kai Ruggeri, please, to --

MODERATED PANEL DISCUSSION

DR. RUGGERI: So, good afternoon. Thank you very much. So first, I should say I'm a behavioral researcher interested in the policy impacts on population wellbeing.

So from that perspective, I find the guidance document to be very useful, largely because I think it does an excellent job on three principles of public engagement, which is that it's salient, it's simple and, most importantly, it's actionable. So anyone who can read it can take away what to do with that information.

I was going to make some comments about generalizability, as mentioned earlier. But a lot's been said this morning and I believe more is coming. So I'll skip that part for now.

I wanted to focus on just one of the questions that was asked to us which was about more or less

detail in the future, which is a big part of any guidance document. I think more detail is always fine.

I think the issue is to make sure that any guidelines or frameworks remain salient, but where further information is easily accessible and clear.

So you don't want to miss out on the key principles by just overwhelming with loads of information because in many cases, when providing these frameworks, we're talking about how to give clear guidance and then how to make use of information when we deviate from that guidance or what to do when that happens.

And I speak about this largely because I was asked to speak discuss -- or largely focus on the qualitative side of things. One of the big guidance that we hear a lot when qualitative data is being generated alongside other studies or quantitative data is that you don't want to just repeat what's being captured in quantitative data by interviewing people.

While I agree with that sentiment, there's also a risk that you end up doing something completely new that has no common denominator with the quantitative data, and in which case you wouldn't have complementary data. You would have two separate data, pieces of data talking about two different things.

So I think one of the main things in that framework is to make sure that there's still common denominators regardless of which type of data or method are used. That way, what you have continues to complement. And in this way, what's ultimately important about any of these guidances is that it should be very clear on what is the purpose.

So before any data is selected or methods or analytical approaches, the purpose has to be clear. In my lab, we use four P's when we talk about purpose: precision, prediction, pattern and perspective.

The first three are really about deciding are we trying to be incredibly specific with the

information and the analyses we're generating or are we okay with a more broad, general understanding. So we pick different analytical approaches to the data that we have.

But when we start getting to prediction, we start having to be much more specific and the biggest distinction really between qualitative methods and quantitative methods is prediction because using qualitative data for prediction would be a big problem. If that weren't true, my family would never get into an argument about where to have dinner.

But when we start shifting over to actually wanting and desiring that individual perspective, we start having to think of more structured approaches to the qualitative. But the challenge within that then enters into our area of research which is heavily focused on bias.

So I'll just say a few words about bias, which I think would be a very interesting topic to consider within this, largely because when we open up the qualitative methods, we acknowledge how

important the individual experience is and we're saying this is critical in our decision-making. But we're also opening ourselves up to the most explicit form of bias, which is individual narrative. And I don't say that in a bad way.

But I think it's something that has to be understood. Some examples are when we ask questions in open settings, we often ask them in a way that's more likely to confirm what we already think than it is to likely find new information or to contradict what we may think of refute a narrative.

In addition, because this is meant for an open comment, do the people who are providing it understand the decision-making structures of the organization, because another form of bias is we have the bias to think the insights we generate and the narratives we provide are the ones that should be actionable.

So taking into account these biases in guidelines is always something important. We've converted this into an ethics guideline for when

we generate data and run analyses. I won't go through all of that now. But those are some of my thoughts.

And I just would wrap up by saying really it comes down to if it's ultimately clear to always refer back to the ultimate purpose, then I think it's a very useful thing, regardless of the extent of detail or the specific frameworks provided because being very clear about that purpose, you're more likely to use the methods that are aware of the biases you might have, but also speak specifically to your objectives that were mentioned earlier. Thanks.

DR. KOMO: Great. Thank you. Steve Cohen, could you please give your thoughts?

DR. COHEN: Yeah. Sure, Scott. Thank you again. I also thought this component of the guidance was well-articulated. A lot of attention was given to the qualitative methods.

So I'd like to focus more on the continuum, moving from this morning from design aspects. Again, we refocused on some of the issues in the

chain that Sylvia presented. It's also presented in figure 12, is more of a linear continuum from data collection to sample to then actually getting the data in hand.

And from this perspective, having a very clear set of what the analytical questions were, making certain that the design actually had all the ancillary information for controls in terms of testing underlying hypotheses.

Many of the designs that would be required to target some select population subgroups would probably require quite a bit of oversampling to meet some of the objectives.

And so, bringing in the adjustments to the probabilities with selection, in many of the analyses this is known as weighted, making adjustments, and then further adjustments for a complete nonresponse.

And there is going to be some Swiss cheese in some of the responses and making a determination of what is the lowest threshold for acceptability and coming up with the correct imputation

strategies.

So then, you go forward with the analysis. And having some -- a bit more reference in terms of the analytical techniques that would help you get the best precision in your estimates and using the appropriate variance estimation strategies for designs that don’t necessarily follow a simple random sample.

There are a lot of design complexities that might be coming to the table. There's a term known as a design effect which is the price you pay in a way in terms of the loss in precision relative to a simple random sample and to have that in the underlying analysis platform.

So all along the way, recognizing that you really want to inform what's going on. And to the extent in the analytical strategy you could think of ways to fast-track some preliminary estimates, to get back to those individuals who have designed the study and who were the sponsor of the study, to point out some interesting unexpected results or counterintuitive results.

Having early result, you know, and resonating with that is very, very important. Having transparency in terms of the analyses that were done. So there's reproducibility. That's critical.

So it's not like a black box solution that comes out from the investigation, that you actually -- it's well-documented. It's reproducible. And then, thinking about the questions in terms of how analysts would gain access to the data.

There is a bit of -- quite a bit of attention to protecting confidentiality. That's first and foremost critical in terms of making sure you have future participation for surveys, particularly for longitudinal surveys.

But if there is a decision to make some of the data available in the public domain, being very aware of what's known as the mosaic effect, that even by itself, this data might not be identifiable. But with all of the information that's in the public venue, there still might be

some methodology that would violate a confidentiality protection.

So those are some of the things the guidance addresses. Perhaps a bit more reference to some examples there. And then, my final consideration is that there is a wealth of ancillary data for individuals with one or multiple chronic conditions from national surveys.

And at a higher level of aggregation, they could be used for additional analytical power. And there's actually an effort. Actually, it was presented at an FDA PDS symposium I guess about two months ago. PDS is Project Data Sphere.

It's actually an enclave that has Phase III clinical trial data that's available. It was primarily the comparator arm of that, for a particular clinical trial. Now, the actual treatment arms are being made available.

For approved projects, researchers can get into that enclave. So you have some of the data from clinical trials. There's also some work now supported by Robert Wood Johnson Foundation to

actually synthesized existing survey data for cancer survivors for particular cancers, to do statistical linkages to demonstrate some other factors that perhaps might be insightful in terms of from a nationally representative sample of cancer survivors, who makes it into the trials.

The trials are randomized. But the representation and the overall population sometimes doesn't meet the representation that you would see.

So making use of available data for synthesis will give one additional power in terms of prediction, but also facilitate additional analyses that might not have even been considered at the get-go. Thank you.

DR. KOMO: Thank you. So Sheri, could you --

DR. FEHNEL: There we go. All right. Good job. So again, like other people have said, I think this is a really comprehensive, extremely well written document. Obviously a lot of work went into that. So thank you very much.

I think there's a theme, you know, in kind of

thinking about where we want to go and how we need to get there.

And it seems like there's one thing about the guidance that maybe is not completely clear, and honestly, I didn't really understand until we had a conversation kind of in preparation for this panel, in that this document is really intended for patients and patient advocacy groups, to encourage research within these organizations.

It's hard for -- a lot of us have the hat on of being used to either working in pharmaceutical companies or working primarily for pharmaceutical companies. There's so much in here about all different sorts of research that might be done.

I think if we're thinking about the audience and we're really thinking about organizations like patient advocacy organizations, I think there's a wealth of information there about that can be gathered about the patient experience and maybe not worrying too much about some of -- a lot of the quantitative information that we've been talking about and sort of trying to say that

everything needs to be generalizable and all of that.

I don’t think where we're going with this guidance is going to end up being the final word on almost anything related to drug development. I think it's a beginning.

And so, I think this is a wonderful place to start and I think maybe the focus really will be more on qualitative research and really understanding from these patient advocacy organizations, you know, who have this wonderful membership, a source of information, if we can encourage some of these organizations to collect some data on their own.

I've had the opportunity to work with a couple of groups like that and I think by having those folks collect some of these data themselves, it may take out some of the bias that maybe comes in, in the process of different pharmaceutical companies or depending on how a drug works.

It's really focused on what is important to this patient group. And I love that the FDA is

encouraging that kind of work. I think from the perspective of the guidance, there's lots and lots of information. And one thing that's really clear is that there's lots of flexibility. And I appreciate that as well. There's lots of different ideas about how qualitative data can be gathered.

One place that I didn't feel like there was quite that flexibility is in the analysis of qualitative data. In the appendix, it talks about grounded theory specifically as FDA's recommendation. And I think that was the only place that I found a specific recommendation for one method versus another.

And I think there, we have to think about, well, what are we trying to do and make sure that we have a qualitative analysis method that's also fit for purpose, if you will.

There are also a couple of places in the document that are talking about focus groups as a place for cognitive debriefing. And personally, I don’t believe that that's really the right venue

for cognitive debriefing.

I feel like if you're really trying to understand people's thought processes and how they understand an item, how they're responding to it, you really need to have that individual interaction and really hear what that thought process is rather than trying to have a group of -- trying to have a group of patients do that or feel like somebody's going to be willing to say, hey, I don't understand what this question means.

You may not find that in a focus group. But you're going to get that in an individual, in a reaction. So I would think about maybe thinking about that differently. But I think generally, you know, there's so much information here. There's a lot of good ideas.

You know, and I think that even the things that, you know, maybe could be framed a different way are really minor issues in the grand context of things that I think could be easily addressed. So, thank you.

DR. KOMO: Great. Thank you, Sheri. Gary?

DR. GLOBE: Thank you. I had the same reaction as Sheri did. So I'm not sure what patients could read and understand this guidance. It's not for patients that I would -- I don’t know how they would really understand all these methods.

I think it would be -- I'm not even sure the advocacy groups would have people on staff that could really understand most of this. It's good information. But I'm just not sure how they could use this and operationalize it per se.

What it would -- what I would think it would tell them is you need to go hire people that can then follow this for you.

And so, the other thing is that it doesn't seem to really direct people down the most common paths, the most common swim lanes that those of us in industry need to follow to really have robust data at the end of the day, whether it's for regulatory decision or for label.

And I think that you can talk about Delphi methods and other things. Those probably are not

the things that most people use. And so, I think there's a lack of clarity about what's the most common path that you're going to need to go down to have something at the end of the day that could actually go in a trial and be analyzed and be presented.

And I think right now, you have an ocean of opportunities, but nothing that's really saying here's how it usually goes and here's what you usually need to do. So those are my comments.

DR. KOMO: Great. Thank you. Isabelle?

MS. LOUSADA: So I think this is timely. I'm a patient advocate. My organization is led by me, a patient. And patient preferences, it's so critical. Everything we do comes back to that and should be the starting point. The model has to be bedside to bench and back again. So this is absolutely key.

And I think one of the things that we have to think about, that how patients engage is -- we're just sort of at the foothills of discovering the pathway to doing this. I think we've seen with

the patient-focused drug development meetings, which have been fascinating and insightful and we have taken part in one, that they really -- there are so many unexpected outcomes from them.

The other thing that we see is that for organizations, for rare diseases and other diseases, it's a huge amount of work to do one of these meetings. And we're just capturing one moment. And what we know is that we're capturing a moment in a changing and evolving landscape.

So something that I think we need to consider -- and I think it's wonderful to have engagement with organizations.

But there are a number of things we need to look at. One of them is that if an organization like mine is investing a significant amount of resources to do a study like this, what are we asking. What is the outcome? And how do we evolve as the disease evolves?

And the other bit that I think happens that is it's easy to catch a patient preference at a moment in time. But those change throughout their

journey. So how do we catch those? And it's very different than getting a group of patients who have advanced disease, different stages of disease.

But actually tracking those changes because those, in the end, are what really influences -- influence their decisions. It's where they are and what's preceded their journey.

And likewise, as we capture this data from a broad population, which we then choose the pristine population for the clinical trial, we see that in one of the diseases that I work with, they have 1.5 comorbidities. They're on five medications a day.

That's the population who will be taking the medication. But they're not the ones that will be in the clinical trial. So that's been challenging. How do we take this data, that we're going to collect the data.

Prospectively, we have ideas about the questions we're asking. We need to make sure that we have the rigor to interrogate the data to a

level that's satisfactory for the FDA. And there's also pathways to then retrospectively be able to go in and ask questions. So can we make sure that we establish that in the beginning?

We need to then understand how that works in with the trial and those endpoints, but also how that data becomes used in the real world. So I think there are a number of levels that it needs to be looked at.

I think one of the things we need to understand as patient organizations is what partnership and guidance we can expect because, by the very nature, you know, I sort of think I'm an architect. And it took me 10 years to train and five years in practice. And if somebody was given a manual of how to design a building, it would never have the nuances of the architecture.

And it won't have -- as organizations, as hard as we might try, we will miss that, the nuances of the science that you rely on. So we have to understand what the flexibility is in this as we collect and generate the data. And I think also

having some pathway to understand what the ability of an organization is, so how do you rate what you're able to do.

Our patient resources, our finances are scarce. So we don’t want these to be repeated in many studies because we can't do that. So how do we work through and identify when is the right time to do one. What is the right thing to do?

At what point do we need to have external support from experts, from the FDA, from other organizations to really maximize the potential of these hugely critical and important meetings?

So I could talk on and on about this. But I want to just say I really think this is a phenomenal effort. I think we just need to think about this as we're looking at these guidance, you know, coming through and for, it's such a circular process.

And that fourth guidance will inform the first steps that we do and, likewise, we need to think of this very comprehensively, that it's not a four-year plan, that how we can make sure that

this really is a continuing and evolving conversation for each of these stages.

And I think just also talking through and thinking about the flexibility that needs to be considered and how more specifically we can engage with FDA to make sure that the work that's being done is a benefit. Thank you.

DR. KOMO: Great. I'd like to thank all our panelists for all their thoughtful comments. At this point, I think we'd like to address the -- let's see, where's the -- the questions to address. So maybe if we could address the first question.

So it's for future guidances, we'll discuss in more detail qualitative, quantitative and mixed methods in more detail or less. Is more detail or less needed in the first guidance about which source -- example, interviews, focus groups, consensus panels, et cetera -- to use to collect data?

Is anything missing? Include in your comments feedback on the information in the appendices as

well. Would anyone like to start? Please, Steve?

DR. COHEN: Well, this is more related. I think we've given a lot of attention to the guidance in terms of those three areas.

But I was really intrigued by Isabelle's comments in terms of how this really is also going to be directed, a document for the patients.

And I was thinking in terms of what the findings are, making sure the design has some sort of a feedback loop to get it back to the patients, and there is some sort of a portal where some of the impacts from the study is made available to them.

And having some sort of mechanism where in many of the analyses, you're going to see results gravitate towards the mean. But there are some very vulnerable subsets of the population that even if they're not really the core experience that most of the individuals are having, they're equally important.

And actually drilling down to those cases, having the capacity to actually inform some

research or some interventions that could help their lives I think would resonate well and sort of -- so I was just thinking more about the continuum of to get the information from the patients, if you could make them front and center, like in the driver's seat or like riding shotgun in terms of it's a partnership. So I would just put that perspective there.

DR. KOMO: Great. Thank you. Would anyone else like to address this question? Isabelle, please?

MS. LOUSADA: I was just going to say that I think, you know, it's quite hard to separate between the first and second guidance of what you ask from whom.

But I also think the -- will help people to -- if there was more context and relation -- partly in relation to drug development, to really understand what the advantages are and disadvantages are of different techniques to use.

So I think that would really help clarify and at what times they might be appropriate to

consider each one.

DR. KOMO: Great.

DR. GLOBE: Yeah, in answer to that, so people like me in organizations that develop products, we see products coming up through the pipeline. There isn't even always a lot of money in our organizations for early products because nobody knows whether they'll work or not.

And so, everyone's competing for funds. And you tend to focus on the things that you think will bring the most value, the concepts most important.

So we tend to follow the PRO guidance. So that's cardinal symptoms, proximate impacts. And then, we don’t even go further anymore now. We don’t even really think about quality of life too much, which is sort of akin to what we're talking about here today.

So it could take us two years and a million dollars just to come up with those with a proximate or a cardinal symptom measure. And then, we might be barely ready by the time we get

to the Phase II.

And so, the question is what else could we add, right? We already have a number of PROs. We have a lot of items. What other concepts would we bolt on? And how quickly could we get those?

And would we have really orchestrated that at the right timing so that it could actually go into a study, make it into the study? It's not -- it's not going to be easy.

MS. LOUSADA: Yeah, and I'll just add when we come to look at labels, as a patient, the list of symptoms that you may have, the list of side effects that may come out, having those all listed, what patients really want to understand is the nuances of those.

And so, while we understand that on the label there isn't the real estate to do that, that's really what we're getting at. And so, trying to understand and tease that out becomes I think part of what we have to look at and is truly challenging and we have a long way to go on it.

DR. GLOBE: Sometimes the concepts that are

important to patients are not even going to change within the period of time of a trial. So say a person has certain coping mechanisms for their disease, like in ulcerative colitis or Crohn's.

Some of those coping behaviors won't change until way after the trial. So you could try to measure that very important concept to the patient. But it's not going to change in the trial.

So you also have to make sure that you're measuring things that are going to happen during that 24-week period or 48-week period. And they may not always be the things that are most important to patients.

DR. FEHNEL: I think for me this kind of goes back to sort of what's the overall goal of the guidance. I don’t think it's is meant to be complementary or supplementary to the PRO guidance where we're talking about, you know, developing COAs.

I think if we get too focused on that, we may miss some things that are really important and

some opportunities to gather data from these patient advocacy organizations. We keep going to these -- you know, even in a lot of what we're doing right now is in rare diseases.

And there was a comment made earlier, kind of that Laura Lee made, about data reuse. And maybe, you know, there's some discussion in the guidance document about limiting patient burden. And I immediately went, oh yeah, we're not going to ask everything every day.

But we're also burdening patients and KOLs and these advocacy organizations because we're -- people like me are coming to them, you know, on behalf of multiple different pharmaceutical companies working in the same area. And we're often asking about the same sorts of things of the same people and demanding, you know, their time and resources.

And if there was some way to really encourage more of these advocacy organizations to do some of their own research, and I recognize that funding needs to happen to be able to do that. But we're

working with one organization now that's developing a registry. And their idea is that eventually that will actually produce funding by helping pharmaceutical companies recruit patients for their clinical trials. So there's sort of a business model kind of in there.

But what they're going to have is this incredibly rich source of data about what the patient experience is and who these patients are.

And I think having it encouraging some of these organizations who basically nobody cares more about these patients than these organizations, to be able to fund some of that work or to work collaboratively with these organizations, I think we could have a wealth of information about the patient experience.

And then, maybe the PRO instrument development, that kind of comes later. Like this -- I think this is just a beginning to that process. I don’t think it's the end. And maybe I'm misunderstanding. But it just seems like we're going too far.

DR. GLOBE: You know, it was my -- maybe I misread, but it was my understanding that Isabelle's going to have to generate items that are going to go into our trial.

DR. FEHNEL: I hope not.

DR. GLOBE: That -- yeah, because otherwise, we can't measure it longitudinally and see if anything changed.

DR. JOHNSON: So I'm going to jump in here, Scott. Sorry to take that prerogative away from you. But I do think that we see this work as being complementary to the PRO guidance.

So just to be clear, much of this came from -- you know, the PRO guidance, for those of you all who don't know, was finalized December of 2009. So it's been about eight years, almost to the day now. And Elektra can talk more about that because she was here when that was all happening.

But one part of how these guidances came into being was our looking back and saying, okay, this guidance has been out there. And what are some of the issues we're still having? And also, what are

we hearing from patient advocacy groups, that we're hearing from sponsors, that we're hearing from some of these expert groups that are hired and what pushback are they getting internally as to what needs to be done?

So Gary, I think you talked about this a little bit. But I do want to say that our hope is that the patient groups do hire experts.

So it's not that necessarily individuals are going to go out and do all this work on their own, but that they are informed consumers about the wares that are coming out because we realize, you know, there is limited time which may be the most precious commodity that everybody has and limited money, which is also very precious and true. That's an issue for everybody involved.

But when we give exact swim lanes, that tends to be all we see. And so, we want to make sure there's flexibility because we will then hear back sometimes, now okay, if you give not even the parameters of the pool, then there's a problem too.

But one time, you know, we hear -- not just one time, many times -- an expert will say, okay, this is what's needed or a patient group wants to do something. But there's an underestimate on behalf of the people with that money as to what actually needs to be done.

So part of what we're hoping to put forward is kind of scoping this is what may need to be done. If this is your goal, here are the things that you need to consider.

And if you're not going to be able to consider each of these, you might need a different goal or other partnerships or other ways to work together.

So this is -- again, it's complementary, trying to fill in some of the issues that we've been seeing as regulators with what has come to us but also being forward-thinking, because the world may have been at a very different place in all of those early 2000 discussions that led to that 2009 guidance.

I don’t know if Selena, Elektra or others have something they want to add to that?

DR. PAPADOPOULOS: I'm going to be very brief because I really want to hear from you all. But I think that, you know, this is much broader than just the COA.

I think, you know, if a patient group is going to put together a meeting and they're going to try to map out the patient journey, being forward-thinking and trying to think ahead, okay, what can this information be used for.

Can it be used not only for the COA development and the endpoint development, but understanding who to enroll in studies, what the eligibility should be, understanding, you know, what are the unmet needs of patients, understanding things like what do they value, what are their preferences, what risk and uncertainty they want to take.

So this is very far upstream from the actual endpoint. Yes, it will be used to inform the actual endpoint. But to me, it's much broader than that and I don’t think we should focus prematurely on just the COA.

DR. DANIELS: Yeah, so I'll echo the comments that Laura Lee and Elektra just said. But I want to try to redirect us back to this question in terms of methods.

Are there any methods that you think that we may be missing in this discussion document, anything that you guys can think of?

DR. FEHNEL: Really for me, just the issue of the qualitative data analysis and, you know, just making that as flexible as everything else in the document, which is great.

DR. KOMO: Okay.

DR. PAPADOPOULOS: Maybe -- maybe one other question is, you know, rather than are there any methods missing, are there any methods that maybe should be emphasized a little bit more so that we're not losing, you know, the forest for the trees?

DR. RUGGERI: Could I give a slightly annoying response to that, by sidestepping it but trying to answer it at the same time? With the work that we do, we're often provided data long after the

original collection and asked to try to make sense of it with a very broad question.

And one of the things we find is that it would have actually benefited those who are collecting it originally to understand what useful data looks like, more so than understanding how we analyze it.

And for those who are generating it and may not later be responsible for analyzing it in a way that gets used in policy or in regulation, to spend more time emphasizing what does good, clean, reliable data look like, how does it get generated and how do we get a nice sample of people, whether it's representative or not, engaged in that material so we can rely on what they're providing.

Non-representative samples are something that can be worked with if the data is easy to work with. You can have a great representation and really well-done sampling of really bad data that's incomplete.

And I think the emphasis really could focus on what does it mean to generate something that

others can use or that the people generating it can use. That's really where the investment I think can be made all the time because you can always get support. There's plenty of reference material. You know, the supercomputer -- or sorry, statistical computing has gone, you know, exponentially in the last 10 years in terms of who can make use of it.

So I think the best methods really focus on how to generate good data, not trying to comprehensively cover every possible analytical approach because in some cases I'm actually getting more and more concerned how much analytical methods have been overly simplified and people are throwing them into statistical algorithms.

I know a lot of people that do machine learning that never understood fundamental statistical principles. And I think in that case, it's more important to emphasize and invest in really that methodological understanding of how data get generated. So I hope that's a reasonably

useful.

DR. KOMO: Steve, I had a question for you. So you had mentioned in your initial that a variety of analytical approaches and is your thought that that should be included in the document?

DR. COHEN: -- the analytical question, the most appropriate analytical technique. But I guess I was gravitating towards more -- as you were mentioning the data going into this effort, again, it's primarily on patient experience data. But any design that also facilitates linkage, I think electronic health records was brought up, physician medical records, claims data.

That's the gift that not only gives pre-dispositional information but gives ongoing continuous longitudinal connectivity and outcomes over time to the extent the patients allow for that and, on the other side, whether it's the provider or it's the insurance carrier would make that data available.

But that's something to the extent, right at

the get-go, you could built in this data integration mechanism that would give more power to the underlying research questions, how -- what the patient experience is, many times there's an asymmetry in terms of they might really enjoy, you know, the connectivity of the protocol they're getting.

But it's not really doing any good for them or something like that. So you know, understanding those nuances when you're planning your study. But again, I'd push on designs that would try to bring some coverage to integrated designs.

DR. KOMO: Thank you. Anyone else?

DR. GLOBE: Can I make a -- I think this is an increasingly important topic because very soon, especially with the way social media has driven this, qualitative data is soon to be, if not already, analyzed in the same way we analyze quantitative data because the statistical computing power is there now.

And I think those linkages are going to be incredibly important to understand alongside

because if we understand how to link different sources together, then that really massively increases the value of every data set, even if it wasn't initially intended to be used in the same set of analyses or body of work.

DR. KOMO: Anyone else want to address this or talk about this question before going to the next one? Okay. Great. All right.

So the next question would be -- that we'll address is a similar question about operationalizing and incentivizing data collection and also data management. So please go, Steve.

DR. COHEN: Just being tied to a lot of data collection efforts where it's not just the front end, but it's all the outputs and the analysis, tremendous amount of attention is given to the backend quality control of the data coming in.

And to the extent in data management, right at the front, understanding the design, building in the quality control checks, fixes to the data, to the extent there is a computer-assisted interview mechanism, if some response is either

inconsistent, having those corrections or bringing it to the attention of the patient will really minimize all the efforts post-data collection to cleaning the data.

And you know, the capacity to do that is available for those that are using computer-assisted techniques. So to the extent one can capitalize on that, there'll be a lot of efficiencies down at the end when the data comes back.

MS. LOUSADA: So I would just add I think that it was very well-covered in the guidance. And the only part I thought was missing is that it would be helpful to understand the limitations of the different approaches.

DR. KOMO: Okay. Great. Thank you.

DR. RUGGERI: I would only go back briefly to a point I made earlier about biases. Operationalizing your standards are excellent and very helpful in research, as long as we haven't biased those standards that we set that drives the narrative we're already trying to drive, and an

example being if you're doing research in mental health, what's the threshold for someone having depression or not.

That could be looked at very differently depending on the narrative that's trying to be used and the state of the research.

So I think as long as those biases are checked as things are operationalized and standard and people who are setting those for themselves are aware of that, I think then this has done a very good job. I just think that could maybe be raised to the forefront a little bit.

DR. KOMO: Great. Thank you. How about maybe we can move on to the next question now, whether there are any other factors to consider regarding the selection methods to collect, analyze patient experience data that should be included in the guidance? I think we sort of addressed that, but --

DR. FEHNEL: So in collecting qualitative data, there were a number of different modes that were sort of offered as potential. And they sort

of focus on being able to have good quality data and representativeness of the data.

The only thing I would also encourage is that thinking about kind of patient comfort and being able to build a rapport. I think a lot of times, there's really no substitute for in-person data collection with qualitative research.

I think particularly some of these patient populations, you know, we do so much in rare disease and folks want people to understand, you know, what they've been through. And I think you can collect a lot of data through the Web and through phone and that sort of thing.

But I just find that the richness of the data that we capture when we're sitting in a room with somebody and we can really observe their body language and really listen to their stories and be present with them, that to me there just isn't a substitute for that. I feel like I understand it better when I've spent time with somebody.

DR. KOMO: Thank you.

MS. LOUSADA: And I would just add to that we

have, one of our populations, very sick. The treatment is very difficult. And the choice about survival versus treatment is a really challenging one and it's something that should be addressed.

Who is able to elicit that information and who should has to be very carefully thought about and how that's -- how those patients are handled and curated because otherwise you will not get accurate representation of their feeling.

And the other part I would just add is I think it would be very helpful to contextualize and give some examples where possibly it goes through and embeds in the -- from early development through to early stage drug development and sort of early understanding about which tools, giving some examples of which tools might be good ones to consider or examples of that would be helpful.

DR. KOMO: Great. Thank you. Yes?

DR. COHEN: Just one more thing in capitalizing on the qualitative. Either right at the beginning of the survey or clearly at the end, informing the respondent, the patient that if

there was anything missing from this survey that really impacted on what was being studied, there should be a mechanism to capture that. And perhaps right at the -- that would be at the end.

But at the front, bring that to their attention, that if there were any questions that they were struggling with, there should be a mechanism to bring either an uncertainty of response to the data that was coming in and in the analysis profile.

DR. KOMO: Great. Thank you.

DR. GLOBE: I would just add one more thing.

DR. KOMO: Sure.

DR. GLOBE: Just it's hard, even when you're trying to develop a cardinal symptom or a proximate impact measure, to get very severe patients. That's usually the most challenging group to recruit and, you know, it's very important to hear them.

So, you know, it would be great if we could come up with some other strategies for how to actually get their voices into this development

work. Usually if you have 40 patients, you know, just a couple of them are very severe because they can't come in and be interviewed or they don’t want to participate.

So I think that might be a place where you could work with, you know, other groups and maybe we could use some hybrid strategies to get their voice included in that work.

DR. KOMO: Have you found that does that work better than others that you might be able to suggest?

DR. GLOBE: I'm sorry?

DR. KOMO: Have you found that there's a -- did it work best to get the very severe patients in?

DR. GLOBE: Well, it goes back to representativeness. Usually that's a -- we do want to get some sampling of it. But it's usually always barely enough or it's a small amount because it's just very hard to get those sickest of sick patients to want to participate.

So if there were other ways of us doing that

and getting that input in some way, that would -- that could be helpful.

DR. KOMO: Theresa?

DR. MULLIN: Oh no, I think that I would just say to Gary, I think we've got examples of how that could be possibly handled in the discussion document. But I guess we'd invite your views to see if you feel that that's enough.

I think we talk about a basic approach, maybe a focus group or some approach like that. And maybe using another method to augment the group that you've got included that way to get at some of those other subpopulations.

But please look at what's there to see if you think it addresses this issue. Thank you.

DR. KOMO: Thank you. At this point, I'll open the -- does this panel have any more comments before I open to the floor? Okay. Great. Does anyone in the audience have questions?

AUDIENCE QUESTION AND ANSWER

MR. BARTEK: Hello. I'm Ron Bartek. I'm a patient advocate, president and cofounder of the

Friedreich's Ataxia Research Alliance.

I'd like to first thank the FDA for convening this meeting and thank them moreover for creating and driving patient-focused drug development from well before it was congressionally mandated and doing such a great job with that.

I'd like to then voice what I think is sort of an underlying frustration that a lot of us are feeling because of the confusion between possible measures or tools that would report on the -- how we can better understand and characterize our diseases, you know, conducting surveys and things that will help instruct that understanding and characterization and even populate our natural history studies and so forth, confusion between that kind of measure and tool and the kind of measure and tool that was raised in the very first comment this morning about measures and tools we can use to report in clinical trials.

And that's so important to a lot of us in the room now because we're getting strong encouragement from our review divisions saying,

okay, you've got your primarily endpoints that you've developed over the years, you know, from your natural history studies and so forth. That's wonderful.

But as long as we keep hearing, you know, signals of improvement or signals or benefit, that can or may or may not really report on the way the patient is feeling and functioning and surviving, we need additional evidence.

We need additional evidence demonstrating that the patient is feeling and functioning better, to at least the same extent that you're reporting in these signals from your primary endpoints.

What they're really saying is give us another reason to say yes. And you know, so what we're all struggling to figure out is how to collect that additional evidence in the midst of a clinical trial where we're getting an incremental -- a signal of incremental improvement from our primary and even secondary endpoints.

And our reviewers are saying give us evidence that the patient is feeling and functioning better

to at least that same extent.

So maybe as you're drafting the guidances, you might want to differentiate between measures that are helping with surveys, tools that are helping you collect information from your patients as to how to characterize which symptoms are important to them and so forth and how to populate your natural history and measures and tools that you can use in clinical trials to report and to measure and report compellingly and reproducibly the way the patient is feeling and functioning in the midst of that clinical trial to add to your primary endpoints. So just a --

DR. KOMO: Thank you.

MS. KENNEDY: Hi. Good afternoon. I'm Annie Kennedy, with Parent Project Muscular Dystrophy. And I just want to start with a thank you to all of you for being here and for helping us get here.

Today is really I think a landmark day for many of us in the community. Many of us in this room worked very hard on the 21st Century Cures legislation, along with many of you and spent many

years working on the provisions in that legislation.

And so, we're very excited to see the discussion draft come out that really reflected the spirit of those discussions that took place over the years that led up to the passage of that bill and then to the guidances that are now coming out.

To that end, I just wanted to maybe go back to the clarification that Laura Lee did, which I think was incredibly important, and thank you.

And that one of the things that went into that provision that we're here to discuss today was that we were really looking to ensure that there were signals back to all of us who were innovating in these spaces, that this wasn't a trend, that the science of patient input is really here to stay and is incredibly important to FDA.

And those of us who've been here engaging with you know that and feel it and believe it. But especially the patient groups who are investing in it, the industry groups that are investing in it,

needed -- we talk about signals. And I've heard Theresa say many times what signals do you need. And this discussion draft, this guidance is one of those signals that are needed.

But it wasn't -- the intention wasn't to shift the responsibility to patient groups to be doing all of the work. It was to make sure that industry also continues to invest.

And many of the people in this room are those in industry who do the job and do the functions, but needed to understand how it's being used in regulatory decision-making, how to continue to use our data that we're producing, that they're producing from patient communities within their protocols, et cetera.

So if you could just clarify that this guidance isn't being written just for patient groups, but it is being written for all of those stakeholders who are listed in Title II, Subsection A, that all of the groups who are working in this space are the intended recipients of the guidance, that would be incredibly

important.

DR. JOHNSON: Yes.

MS. KENNEDY: Thank you. And then, the second part of that is that, to the comments that were made today around that this might be a little too in the weeds for patient groups, I would argue that it's not too in the weeds for a lot of patient groups.

So a lot of patient groups, we are hiring capacities, we are hiring people who do these jobs. We're contracting with people who do these jobs. Or in the comment that was submitted by the patient advocate who wasn't here earlier today I think really framed it nicely.

We're working on precompetitive partnerships very early on with our industry partners, with social scientists so that we're ensuring that the right people are at the table with us when we get started.

And so, the guidance that you're developing around the methodologies, around the taxonomy is incredibly important to us to make sure that we're

creating data that you need, that you can use and that's informing the decisions that you need to make. So, thank you.

DR. KOMO: Thanks. Please?

MR MOEHRING: Good afternoon. My name is Henry Moehring. I'm with the Alpha-1 Foundation. And I'm Alpha-1 patient myself. I could not have said it better than my two colleagues earlier and my initial reaction was to go sit down. But I want to emphasize those points.

The document is appreciated. We thank you for the work that has gone into it. We are committed to the project as well. In our community, we have a very strong patient voice and that voice wants to be heard. And I think we're looking for ways to effectively support that process.

I've walked away with some things today. But the message is strong that we can't do this as a patient community alone. And we are dependent on the bigger partnership. The voice or the expertise that I have is the expertise that I have as a patient. I'm not a statistician. I

appreciate your analogy to an architect. I'm the MBA guy. When you get to the point about writing the budget, call me because I'm really good at that.

But the statistics part is not where we're at. But we bring that information to the table that I think can make a difference and finding a solid voice to carry that forward is something we're committed to.

The last point I would make is we also are looking at longitudinal studies and longitudinal information gathering sources. And I hate to use the term registry because it seems to pigeonhole it. This document would seem to support those efforts as well.

And as a patient, I understand the process going out to 2020. But as a patient, that's a very long time. So the sooner that information can flow so that we can formulate our questions today to have better answers for you when we sit with sponsors. So thank you very much.

DR. KOMO: Thank you. At this point, I'd like

to give our panelists, they have one thought before we wrap up? Anybody? Does anyone have anything else they'd like to say?

Okay. Well, I'd like to thank everyone for a very informative and your thoughtful comments. We've heard quite a bit in this session. Let's see.

So I think some things we heard were -- some takeaways were -- you know, that some of it is -- while generally we want to have more details that are refined, sometimes we want to highlight the principles that are critical so we don’t get sort of overwhelmed with the details.

There was a large we always do want to worry about bias from both the quantitative as well as the qualitative sides of it. And I think we want to make sure that analytical strategy should also be looked to and used, the early results to help inform the later studies.

And the reproducibility is critical. And also, sort of with the -- what we need to always think about and be mindful of is now with the link

-- possibility to link the linkages that potentially that ensure that the data is not identifiable. There were some suggestions to add more references.

I think it's very clear that we need to be -- we want to encourage the patient advocacy organizations that collect the data and recommend more flexibility in the qualitative analyses.

I think also we want to -- so there was some discussion -- we had some discussions on how best to do this with some of the rare diseases, which was very helpful.

And I think what's critical, I think what's important is this is that we want so not just patient advocacy groups but also the -- all the stakeholders will be working in this space. So we want to encourage that. So thank you very much.

(Applause.)

MS. VAIDYA: Thank you, Scott. And thank you to our panelists for a great discussion. Now, I'd like to invite our session three panelists and Sara Eggers from the Office of Strategic Programs

in CDER will be moderating this session with Megan Moncur. Yeah, Megan Moncur. So --

SESSION III: TRANSLATING BEST PRACTICE INTO REAL PRACTICE - DEVELOPING GUIDING EXAMPLES

DR. EGGERS: Good afternoon, everyone. I'm Sara Eggers. I'm from the Office of Strategic Programs. And while we get set up here, I'm going to invite you to stretch your toes. I know those are the most comfortable chairs that we have on FDA's campus. That's why I chose to sit up front in this more comfortable chair up here.

So get up, stretch your toes, shake your legs out and we'll just get everyone setup up here. It can have a laugh too. I know it always makes for a laugh when you have to get up.

All right. I think we have everyone up here and ready to go. We have learned a lot today and our heads are spinning. But this is the fun part of the day where we try to make it real. We've heard a lot this morning and this afternoon about the methodological issues and the practical implications. And we also recognize that any

guidance, eventual guidance that comes out needs to help translate the best practice into real practice. And we hope to do that through guiding examples.

And so, the focus of our session today, in a nutshell, is to discuss what would make examples be really good examples of the stakeholders that are the target of this eventual guidance document. Some examples are embedded in the document. Some examples are embedded in the document.

For example, defining the research objective for HIV or discussion about mixed methods research in diabetes. These are peppered through the discussion document. And we want to get some feedback on those today.

But we also think there may be a bigger opportunity to expound on some of the things that we've talked about today that can get into a little bit more detail through vignettes or scenarios that could be appended to or somehow otherwise linked to the eventual guidance.

And that's what we want to discuss today.

What a good one would look like, what features it would have and what things should we highlight through examples and through a big longer treatment scenarios.

So we have a great set of panelists today. I find that it's best for panelists to introduce themselves. So I'm going to ask you all just to go down the line and just say who you are and where you're from. And we'll start with April.

DR. NAEGELI: Good afternoon. April Naegeli, senior research scientist at Eli Lilly and Company.

DR. MCCUNE: Good afternoon. Susie McCune. I'm the director for the Office of Pediatric Therapeutics in the Office of the Commissioner here at the FDA.

DR. GERSHON: Richard Gershon, vice chair for research at Department of Medical Social Sciences at Northwestern University.

DR. IRONY: Hi. I'm Telba Irony. I'm from the Center for Biologics. I'm deputy director of the Office of Biostatistics and Epidemiology.

MS. OKUN: Hi. Good afternoon. I'm Sally Okun. I'm the vice president for policy and ethics at PatientsLikeMe and I'm also the human protections administrator.

DR. STUART: Hi. I'm Liz Stuart. I'm associate dean for education and professor -- I'm a statistician by training -- at Johns Hopkins Bloomberg School of Public Health.

DR. EGGERS: Great. Thank you, Liz. All right. So we have, in the same style we've done our other panel sessions today, we're going to invite our panelists up here to give a few minutes of remarks.

They've reflected on the overall objectives that we've put forth about really maximizing this translation into real practice through examples and the questions that we have put forth here to them.

And then, we will discuss today a couple of things. We have some FDA colleagues up here who are not -- have not been as part of the -- are as intimately involved in this discussion document

draft. So you are also being asked to think of examples where things might not have gone as planned or where there are challenges or where there are novel opportunities to illustrate through examples.

Also, we're not intending to rehash methodological considerations up here. It's really just how we're going to take what we've discussed already throughout the day, a lot of which I think is very relevant and will come up again through our discussion of examples.

So I'm going to start with April. If you could just give a few minutes of responses?

MODERATED PANEL DISCUSSION

DR. NAEGELI: Sure. Great. First, thank you for the opportunity to be a part of this panel today. I commend, as everyone else in the room today, FDA on this discussion document.

It's apparent that it was well thought out and a lot of input has gone into that. So given the breath of the audience and the stakeholders that are targeted for the guidance documents, it is

important to acknowledge that a lot of tremendous amount of preparation goes into planning and conducting a study to collect patient experience data and also too that, you know, each study that is done is valuable in itself.

And it will take more than just one study in order to meet, in the end, the evidentiary standards that are required in drug development to meet FDA expectations.

So the examples in the discussion document seem appropriate in my mind and reflective of the research that may be initiated by any of the stakeholders to collect patient experience data.

The examples are high level. And I think as was mentioned in the previous panel discussion, perhaps consider putting the examples more in the context for the intended use in the medical development program process as well as how is it going to be used in regulatory decision-making. So thinking about how it could be used and for these purposes.

Full case study examples would be great.

Having an example that could then -- components of it could be pulled to each of the various sections to put things into context would be -- would be nice and also having examples on common diseases, common diseases with comorbidities, as we heard this morning from the diabetes examples and also, as we've been hearing, rare diseases it's important to help us understand.

So how does this research fit into the benefit-risk framework and, in the end, clinical trial design and endpoints?

A few concepts that I think are important to further expand on examples are identifying the target patient population and dealing with the heterogeneity that you see in target populations. Ultimately, clinical trials focus on specific populations that may be subgroups where the highest unmet needs are.

So making sure that the data is available and able to go back and analyze to look specifically at these important groups that where the unmet need may be focused.

Additionally, recall bias, it should be acknowledged that it occurs. We heard in the last panel that patients -- you know, the most severe patients aren't always participating in our patient experience research because they're very sick.

So patients will be on medication. And so, we will have to ask them how did you feel, how did that impact you. So just acknowledging that recall bias is a factor and note it as a limitation. So I'll stop there.

DR. EGGERS: Thank you so much, April. We'll go to Susan.

DR. MCCUNE: Thank you very much. I want to thank the organizers for inviting me today. I think I'm the voice of pediatrics maybe here today, which is really exciting.

But I am not clearly the only one because other folks have brought up the pediatric arena. And I'm thankful for the example, the pediatric example that is already in the document.

I would say that I think it's really important

to remember both the patient and the parent or caregiver viewpoint, especially in terms of the impact on their lives. We think about pediatric patients as potentially not being able to give as much information about their disease.

But I think you have to recognize that children who have been in the medical health system from a very young age are really able, even at a very young age, to talk about the impact of their disease on their lives.

And so, it's critically important to be open to collecting data from all of these patients, even the youngest patients. And also, recognize that the patients and their parents may actually have a different outlook on their disease and trying to capture those differences.

I think it's important to understand that one method to be able to capture information from a parent or a caregiver may be very different from the type of tool that you would use to collect that data from a young child and then from even an older child.

I also wanted to talk about the fact that we were talking a little bit about consortia and collaboration in this last session.

But I think it's critically important to leverage the work of consortia efforts in this collaborative space in order to decrease the burden that we were talking about and also have increased access to patients, caregivers and clinicians.

And two examples of this, one is the International Neonatal Consortia, where they're bringing together stakeholders from academia, industry, patient/parent advocacy groups and regulators all to discuss neonatal-specific diseases in the precompetitive space and how to approach those.

That might be a nice opportunity, these kind of consortia efforts, to be able to bring these groups together.

I'd also mention in the pediatric space there's the International Children's Advisory Network, or ICAN, which is actually a group of

children of various ages that have been asked to provide input on clinical trials. And so, these are all mechanisms by which we can actually expand access to patients with particular diseases.

I will also -- I just wanted to say that we have a couple of other groups that are facilitating access to pediatrics through pediatric trial networks.

One of them is Duke for the Duke Clinical Research Institute and the other is the Institute for Advanced Clinical Trials for Children. Both are working to develop clinical trial networks in pediatrics and would be an opportunity to be able to access patients, parents and clinicians.

And I also wanted to just point out that there may be some gaps in groups that are willing to provide information in terms of their disease.

But then -- and that includes patients, parents and physicians. But then, they're not willing to then participate in clinical trials or have their patients participate in clinical trials.

So I think that there's a gap there that as we are able to obtain more information about where the needs are from a patient/parent/physician perspective, that we also have to look at what some of those reasons are for why they either may not want to participate in the data collection about their disease or the risk-benefit associated with that. And then, why they might not want to participate in clinical trials.

And then, just finally, I wanted to talk one second about recognizing international trials because in the pediatric arena we're doing a lot in terms of international trials and making sure that the tools are understandable for folks globally but also understanding that, depending on where you are in the world, the risk-benefit associated with your disease, both for pediatric patients and for their parents, might be different and recognizing that.

And then, finally, we talk a lot about multiple technologies that we're able to access in order to be able to generate this information.

And I will tell you that for someone my age, I'm talking about doing things with these things is a little daunting.

I will tell you that for the adolescent population and even for the younger pediatric population, they are all over these kinds of technologies.

So having the parent or the caregiver or the physician using certain tools may be very different from what would be the best tools to use in the pediatric population. So, thank you.

DR. EGGERS: Thank you so much, Susan. And Richard?

DR. GERSHON: Really, I had a hard time with the examples because first I thought these are great. And then, I thought, oh, there are little problems here. And then I thought I'm not sure I can improve on them. So, but I'd first like to echo, I think, Theresa, your earlier statement. These are merely examples.

And actually, I'd like to see the document changed even to highlight that more firmly. I

think there's a historical, maybe it's just human nature to say an example or the way we did things yesterday are more likely to lead to a drug approval or to FDA approval. And I think that would be a mistake.

And because of that, you know, enabling a process to preapprove novel methods, perhaps in advance of a clinical trial to help facilitate continued growth, while minimizing the risk to study sponsors, who I think otherwise are going to stick with the old things because we know you are going to improve them and perhaps outdated research methods.

And as we just talked about, phones and things like that, these are -- we're going to be -- we're going to be living in a bleeding edge technologically speaking for the rest of all of our lives. And it's going to be extremely difficult to ever have enough examples that keep current with that.

And I just want to be picky about a couple of the examples to show ways where they could be

misinterpreted or misused. And again, I always say, well, if you've got a problem with it, make it better. I'm not sure I can. So, but it's just maybe perhaps an issue of pointing out to people they're exemplars and they could have issues too. You have to think them through.

So for instance, the example that talks about 100,000 Parkinson's disease patients, you know, and creating a samplings frame from them. I don't think there is a population list of all patients with Parkinson's disease. And therefore, there will be some bias about the people not included in that list and how does one go about finding those people, et cetera.

I spoiled my own remarks by this morning talking about electronic medical records and data warehouses. And while indeed it is very difficult to get at that data, it's getting easier. I think that will be a huge shift in the next three or four years.

But finding other places where you're more likely to find patients, and actually that leads

me to another example, the one that talks about the AMA master file. And I'm thinking that also undercounts patients, right?

We're highly unlikely to find patients in community-based health centers or in treatment models where patients are more likely to be seen by a general practitioner or who might not be -- or by a practitioner not associated with that disease.

And increasingly, people are not being seen by a doctor at all. They're being seen by a nurse practitioner. They're being seen by other healthcare workers. They're not going to be in that master file. Now again, I don’t know of a better list to go from. But you know, the structure of how healthcare is going today is changing rapidly.

And I guess I'd like to see in the examples there may be just even lists of possible bullet points for examples for people to create on their own, collecting data with new novel methods. We've got FaceTime and Skype and, you know, people

conducting neuropsychological testing remotely. So you don’t actually have to send a neuropsychologist out there to conduct an examination.

I actually sat on a small panel. I think we were in a third of this room, you know, on rare diseases. And the pure expense of sending out the same test administrator to the 300 kids who have the disease all around the world almost made it impossible to conduct the studies.

But the reality is people are having this examiner sit on the other end of a camera while the patient's sitting there, perhaps with someone to hand them the technology.

But they don’t have to go there, saving literally thousands of dollars a day. And then, you know, new untested waters. But they're coming quickly.

There's a lot of federal funding right now into using mobile phones to, again -- passive data collection but also direct and indirect queuing a patient, finding cognitive information. IBM,

Apple, Google all have already done research that's shown they can predict -- they can show people with mild cognitive impairment. They can show people declining based upon the quality of their texting. You know?

So these are passive models of data collection that seem completely foreign on one hand. On the other hand, they're working. They have much better models than we do and they have access to far later -- larger patient samples.

And one last word on that is Steve and I were going back and forth on largescale data collection versus random selection. And I'm not anti, you know, stratified random sampling, getting there.

But the capabilities of getting to large volumes of people, particularly if you can adjust your weight for them for bias, allows all sorts of subgroups to be addressed which we simply didn't have the money to do. And there's access in new ways.

And actually, it can be cheaper to collect 10,000 people than 30, depending upon -- or a

hundred or 200 or 500 -- depending on the methodology. We've got a lot of methodological issues to go over. But these are, you know, new pathways that this discussion document will eventually have to discuss as well.

DR. EGGERS: Thanks so much, Richard. Now, Telba?

DR. IRONY: Hi. I'm going to allude to what Laura Lee said in terms of the examples and the data collection that she mentioned very rightly so, that, you know, this patient information, patient perspective needs to be collected and submitted to the FDA only when it can influence the decisions, at some decision point, if it can sway the decision one way or another, that's important information for the FDA purposes.

So I think the examples could illustrate that in a way and, you know, have an example, for instance, when you will collect patient information to inform the design of a clinical trial. In that case, you will maybe collect information that will tell what are the best

endpoints that are relevant to patients. What is the clinically meaningful difference that you want to detect? So how would you collect that kind of information?

There is another purpose that I see is to inform benefit-risk determinations. For instance, the clinically meaningful difference for a treatment that have very low risk can be different than the clinically meaningful difference for a treatment of high risk. You will want more effect for a high risk treatment than for a low risk treatment.

Now, how do you determine that? It's a very difficult thing to be determined. But the patient can inform that. You know, the patient that lives with the disease can tell if the burden of the disease is so high that they are willing to take more risks. So they can inform the FDA so we will give a very good information on our determination.

So these will be good examples to get in the guidance because, depending on the information you are gathering, you have different ways to collect

it.

Another thing that comes to my mind is labeling. Someone mentioned labeling. How would that kind of information be relevant in labeling, if it's relevant in labeling?

In some cases, it will be, particularly in the cases which will help decision-making by the FDA. In some situations, it might not be relevant for the labeling. So these will be things that might be important to get examples of that.

Other things that come to my mind is examples on rare diseases. You know, because the disease is rare, it's very difficult to collect large samples.

But sometimes, a small sample will be representative just because it's a small population. So these kind of distinctions might be important to get into the collection and in labeling.

Another thing that was alluded here is real-world evidence and it comes to mind, you know, how to collect information from the Web or from a

social media using, for instance, natural language processing and things. You know, this is just foreseeing the future. But it's very well possible, particularly for very well organized patient advocacy groups.

So all these kind of examples will be helpful if they came in the guidance because it will inform people that it's not only actually the guidances are not only intended for patient advocacy groups.

It's intended to industry and it's also intended to the FDA reviewers. So they will learn from the guidance too. So all of this information will be very well taken to be in the guidance.

DR. EGGERS: Thank you, Telba. Now, we have Sally.

MS. OKUN: Thank you. Thank you so much for having me here today to participate in this important panel.

It's very clear that the FDA is not only seeking broad participation for the development of these guidance documents. But we've also heard

frequently today that the FDA is welcoming the opportunity to explore novel ideas for ensuring that drug development is truly patient-focused as we continue into the 21st century.

So overall, the guidance is a comprehensive discussion of traditional research methods for collecting comprehensive and representative input.

In my opinion, the guidance actually can be improved quite a bit by recognizing and integrating nontraditional opportunities for advancing innovation in research.

And by harnessing the emerging and ever evolving 21st century methodologies that actually are already here and being used in many cases, but also that we could begin to push the boundaries for expanding the scope and scale of patient experience data collection methods in analytics.

So some might say that there isn't quite enough experience using these novel data collection models and analytics for regulatory decision-making. You know what? I think that's all the more reason for us to ensure that the

guidance includes these examples of nontraditional approaches, so that these methods can be considered and discussed with the FDA.

They could be potentially tried, if given the right environments, and the experience could be gained and we could begin to learn how best to harness the power of these.

So if I were going to think of a few high level concepts that I'd like to suggest we could be thinking about including in this first guidance, I'd say we need to think about expanding the volume of patient experience data by using online research-focused platforms and Web-based and mobile-enabled networks.

This opens up opportunities to reach much larger numbers of patients using current and rapidly emerging technologies that are really increasingly part of people's everyday lives. Technology approaches support increased efficiency and timeliness and can even improve the targeting for subpopulations and diversity through strategic engagement models.

I would also set the expectation for rigor with novel data collection. You know, just because it's novel doesn't mean we relax our requirements on rigorous methodological considerations.

So it is possible to integrate systematic and methodological processes to collect patient experience data in environments that provide convenience for the patients by fitting into their real-world experiences.

You know, we've actually had a research collaboration with PatientsLikeMe and FDA for the last 18 or 19 months now. And a lot of that work has been spent simply studying the characteristics of this novel patient experience data in order for FDA to better understand how it might be useful for regulatory purposes.

So the work is beginning and the work is actually underway and I think we need to find ways of continuing that to help other researchers start to expand this work.

We need to challenge researchers to explore

new methods to validate patient experience data collected from novel environments.

And I'll use another example that we have done. We had a cohort of 600 consented PatientsLikeMe members with multiple sclerosis and we were able to identify them within a claims data environment and to validate the diagnosis they gave us in that claims data environment.

So it was an opportunity for us to use sort of a novel approach to validating what patient-reported information against what was known in an accepted real world evidence environment.

Encourage innovative study designs that include novel environments where patient experience data can be longitudinally collected. And we heard a lot of that this morning. And I really want to enforce that.

Much of the representativeness of the real world experience of patients happens over time. And much of the experience that patients have don’t happen within the clinical site environment. So we miss a lot of the kinds of things that we

should be collecting on a regular basis. Patient networks can help support a longitudinal design. Virtual trials are another opportunity that we should be exploring.

We've recently done one with the Duke ALS clinic where patients with ALS were able to remain at home, do the data collection, connect with the study sites over the -- excuse me, over the phone or during Skype interviewing.

And then, they only had to go to the clinical environment twice throughout the entire study. The timeliness of it, the convenience for patients was remarkable and the satisfaction was high and retention was also high.

Finally, I would say to encourage collaboration. We've heard that also -- across data collectors and data holders to ensure that gaps in one data source might actually be filled by another collaborator's data source.

Collaboration offers greater efficiency by reducing the number of duplicative studies. We heard Richard talk about the 40 simultaneous

studies being done in fatigue earlier this morning.

So in summary, I would suggest pushing the boundaries beyond traditional methods and analytics does require us to step outside of our comfort zone.

Many sponsors and other stakeholders may be reticent to explore novel patient experience data collection without explicit examples to look to in the guidance. So even if they're nascent, even if they're still emerging, even if we still are learning, they should be at least discussed in the guidance as possibilities.

So I strongly encourage FDA to ensure that the patient-focused drug development guidance are relevant to 21st century patient experiences and inclusive of examples that demonstrate current and rapidly emerging 21st century technologies. Thank you.

DR. EGGERS: Thank you very much, Sally. And finally, we have Elizabeth.

DR. STUART: Great. Thank you so much for

having me. Many of my comments are going to echo other things that we've heard and I want to first say that I agree that having examples in the document will be inordinately helpful in making things concrete.

I serve on a panel for PCORI and I find that often there can be discussions that are very high level and theoretical that people might sort of disagree about different issues. But then, once we sit and talk about a specific case study, there's much broader agreement.

So I think examples sometimes actually help people realize that maybe they actually do really believe the same thing kind of when you get into specifics. So I think examples can really be crucial in that way.

So one of the methods that's talked about in the document is purposive sampling. And I want to posit that I think the selection of examples should be thought of in a purposively sampled kind of way. So we'll use one the approaches that's actually being proposed in general.

So one type of purposive sample is called deliberately heterogeneous sampling. And when you try to do a deliberately heterogeneous sample, you sort of think about what are the factors that matter that we want to make sure we have representativeness over.

And so, I was sort of thinking, well, what are those factors for selecting examples. Some of the things I thought of were the sort of spectrum of the goals of the study, so whether it's at a stage of just measured developments, sort of understanding the course of disease, whether it's for an efficacy endpoint. Those are very different goals. Might want to think about having heterogeneity in those.

Another would be size and heterogeneity of the populations under study. So for example, a rare disease versus a more common disease. Another might be chronic disease versus acute.

We heard earlier examples of sort of some differences that arise based on that sort of type of disease. Similarly, another factor might be

the length of the disease course. Is this something that people have for six months or something they have for five years?

And then, finally, one that's sort of near and dear to my heart is -- especially as a statistician, is sort of how much are you worried about unobserved differences between the sample and the population.

And so, you know, a sample of 30 people that we've heard about might be highly problematic in some scenarios where you're really worried that those people are very self-selected in unobservable ways but might be perfectly fine in another scenario where they really are believed to be representative.

And so, I think, you know, sort of thinking through where does that sample come from. So I just would sort of posit that FDA could sort of think about what are the factors that really should be considered or shown in the examples and then make sure to kind of cover those.

And I think the key is that one size won't fit

all and we need examples that will fit that. And so, then I just wanted to make a couple other points that are more on the sort of sort of slightly bigger picture comments.

First is just to make a sort of obvious point that has been alluded to. If data on a population is actually available, a non-representative sample can be made to look more representative and therefore presumably more generalizable with respect to the observed factors.

So then, there's really two issues we need to think about. One is what factors are observed, and I'll come back to that. And then, two, how worried are we about unobserved?

And that gets back to my comment about 30. A sample size of 30 is much more concerning if we really think that they are just highly different and more motivated or whatever than the rest of the population.

So then, we need to think about what population data is available and what measures or characteristics are available on that population.

So we really ideally would like to be in scenarios where we have good, high quality measures on the sample and the population. And again, I think sort of showing diversity of scenarios like that would be useful in the examples.

I worked in one. I sort of straddle public health and education and public policy and I worked in one example in Head Start, so early childhood education. And I had two datasets, a sample and a population. They each had 400 measures. But only seven of them were measured consistently between those two. That is not a good scenario to be in.

So we need to also move towards models of sort of if you're running a study, try to get comparable data with some population of interest that's already available.

And then, I just want to conclude with two other quick notes that again build on other points. I think it will be important in the examples to show innovative designs. You know, I think there's often -- I work a lot in non-

experimental designs. And sometimes, there's an immediate, like, oh, there's no way we can collect a random sample. And so, people then sort of shut down and go to like the other extreme.

And I think showing specific examples of kind of compromised designs or innovative, maybe two-stage designs, hybrid designs they're sometimes called, can be really useful for sort of raising people's awareness of the possibilities that might exist and sort of not just it's either random or it's not random, but really what are some possibilities between that.

And then, finally, I just want to note that, again, I straddle fields. And these conversations are happening in so many different fields right now. We heard a little earlier about, you know, political polling and the public policy sort of world, economics, online research.

And I would just encourage more meetings like this, that I think do a great job of bringing people from these different fields together because really lots of different areas are

struggling with the same issues. And there's no sense -- there's no reason, you know, we should be in different silos.

DR. EGGERS: Thank you very much. And thank you to all the panelists for giving a lot of great ideas that would take years to fully flesh out.

I want to move now into the discussion and focus it in on a couple of the bullets because I think that collectively you have answered question one about the thoughts and the examples in there. You've given -- and you've certainly answered number four.

When we asked you to think both pitfalls and novel ideas, all of you have jumped to the novel -- the novel approaches. And that's very useful.

So then what I want to focus in on then is the third bullet here about some of the common challenges in study design or implementation or analysis that might be useful to address through additional examples where we flesh out what the situation was, why it might be problematic from a regulatory perspective and how we might address

that challenge.

I'm going to put up a scenario as an example. Now don't worry. This is not springing this on the panelists. They were sent this earlier.

But we're looking for a response to a situation like -- described like this, in a vignette that would accompany -- that could accompany an eventual guidance that spells out a situation that has a methodological limitation or unforeseen challenge to it.

So in this case, the situation that the researchers, for an unspecified study goal, used a probability sampling scheme to send out a survey. But the response rate was low and the submitted report included only the results and demographics of the responders but not information on the non-responders.

So then, this scenario further goes through and outlines what makes that a potential regulatory concern, to main concerns. One is the representativeness of the study participants to the target patient population and then the risk of

nonresponse bias, people who respond may systematically differ from those who do not.

And so, then it gets into some more of the sampling issues about whether this is functionally a nonprobability sample. I think it was Kai who mentioned this weighting adjustment. I don't think that was mentioned as a methodological issue before. But Kai mentioned that earlier today. Anyway, it's a methodological issue.

And then, we thought through some practical solutions, both to increase the participation rate and then to factor in the potential for nonresponse through a pre-specified analysis plan and then through having to consider modifying sampling approaches, if necessary.

So this is the type of information we thought might be useful to illustrate fleshing it out a little bit more and keeping it hypothetical as an appended scenario or a vignette.

So I just -- so understand that we could model lots of situations, including the innovative types of approaches that you have mentioned in your

panel responses, but just as a style and as a first response or first think-aloud to this scenario. I'll open it up for any thoughts on its utility or on what would have to be further explained. Go ahead, April.

DR. NAEGELI: I think scenarios like this are great. They would be perfect. Also taking a step back and thinking about the survey itself, were patients involved in developing the survey.

Did they feel like a valued contributor to it? Was it asking sensitive questions that maybe patients didn't want to necessarily respond to? So doing some pilot testing of that nature would be helpful as well.

DR. EGGERS: Anyone else? Elizabeth? Or no, Sally?

MS. OKUN: I think one of the things that stands out to me is that we don’t know enough really to sort of suggest, you know, how it might improve in some way.

So if surveys were sent out and what method was used to send them out, if there were ways of

being able to sort of have a pre-specified analysis plan, it would really require you to think a little bit about who you were sort of ultimately trying to target.

And I think the scenario itself is useful in sort of breaking things down. But I think it lacks sufficient information to give you enough to sort of sink your teeth into.

So I felt like I was left here feeling like, well, I'm assuming they didn't necessarily use the latest technological approaches to getting the survey out. I'm assuming they maybe didn't put it on an iPhone. I'm assuming that maybe it wasn't something that was going to be convenient and fit into the lives of the persons they were trying to reach.

So those would be my initial reactions, that if we were to put something like this into the document, that it provides sufficient information that really sort of suggests here's -- yes, we could get to a practical solution.

But we have to know a little bit about what

they didn't do particularly well at the start.

DR. EGGERS: Okay. So let me ask you, before we go to Elizabeth, could this be written up? And we get overwhelmed.

So could this be written up in a scenario that is a page to two pages and be useful and still account for the things that you're suggesting?

MS. OKUN: Oh, absolutely. Yeah. I mean, it could still remain bulleted. But it could provide in each bullet just a slight bit more information about the methods that were used and some of the other, you know, kind of thinking that went into it.

I think one of the things also, coming from where I come from, one of the things that we think about and that we integrate into everything we do is really thinking about an overall engagement strategy from start to finish.

And so, that not only includes how do we get the people we want to, you know, respond to what we're trying to have them respond to, but then how do we ultimately figure out, for those people we

didn't get, what is it that we need to figure out to reach them at the next point in time that we're trying to reach them.

So I think, you know, this is the sort of thing that I don’t think researchers think about quite frequently enough, that you're not just trying to recruit people to get at your survey, but you're also trying to learn from the experience of that survey in order to be able to improve the opportunity to gather better data every time you do it again and again.

DR. EGGERS: Okay. And we'll go with Elizabeth?

DR. STUART: Yeah. I think a similar feeling of like I think this could work fleshed out. And some of the things that I would have liked to see fleshed out are first the goal of this survey.

So it wasn't clear to me if this was we're just trying to learn about patients or if it's for, you know, an outcome efficacy, treatment control, effectiveness. And those would be very different considerations, I think.

And then, the other thing I would like to flesh out builds on one of my earlier comments about sort of what do we observe versus what do we not observe on these people and sort of what data is available on the non-respondents -- well, on the respondents and on the non-respondents and maybe even have two sort of sub-scenarios, one where there's very limited data on the non-respondents, which might be common in some situations.

And so, there you might really want to think about sensitivity analyses to assess sensitivity to an unobserved difference versus another scenario where maybe there's really good registry data or some other really high quality sort of baseline data on the non-respondents so then -- like these weighing approaches rely on having high quality, observed variables that you can adjust for.

And so, maybe kind of two scenarios, one where you feel like that's a reasonable assumption and then one where it feels much iffier. And then,

you can cite, you know, there's like the National Research Council recommendations on missing data and it kind of could fit into all of that.

DR. EGGERS: Okay.

DR. STUART: But yeah, I certainly would want those sorts of issues fleshed out more.

DR. EGGERS: Great. We'll go with Telba, if you had some, if Telba had something and then Richard and then Susan.

DR. IRONY: Just had -- yeah, I think it's a little bit more, you know, according to what Elizabeth said because for me -- to me, all these data collection, the purpose, the objective of the survey is fundamental because depending on what is the objective, you know, you might be worried about the bias or not in this case.

And also, fleshing out and giving concrete examples. For instance, let's say that the non-responders are because, you know, people are working. So you get the non-responders are the busy people and the people who respond to survey are the people that are less busy. Does it impact

the disease experience or not?

You know, it comes to missing at random, missing completely at random and missing not at random, all these three things. And in some cases, you can correct for that and in some cases you cannot. There is no way to correct. So these are important.

But you only think about this when you get more concrete examples. So I think one of each would be for instance missing at random, not at random or completely at random, that will be important.

DR. EGGERS: Now, these last two, is this still going to fit into our two-page --

DR. STUART: I think we can honestly, yeah. And part of it might be even just --

DR. GERSHON: I would --

DR. STUART: -- like a little simple -- like I do a lot of work in mental health where depression might be a concern, where you really worry about not missing a random. So even just having a specific here's a scenario where we're really

worried about not missing at random and then some references on where to go --

DR. EGGERS: Yeah. Great.

DR. STUART: -- here's a scenario where probably missing at random is more believable and move forward.

DR. EGGERS: Yeah. All right. Richard, and then we'll go with Susan and then I want to make sure we have some time for Q&A.

DR. GERSHON: So similarly, using really small print, keeping within the two pages, I would actually add a fourth blue band.

DR. EGGERS: Okay.

DR. GERSHON: And that could be how could this situation have been avoided in the first place potentially.

DR. EGGERS: All right.

DR. GERSHON: Because I think actually that would have helped me the most in looking at this. Some of the things we've mentioned before. You've got to have demographics data. Minimum data you need from non-respondents. Otherwise, weighting

falls somewhere between voodoo science and highly respected. And without that minimum demographic set, it is definitely in the voodoo science side.

But that would help people in planning to better realize what they could be going for. And response rates are all over the place nowadays.

You know, people think I've got 11 percent. Well, I'm at the national average for this. There are people who get 70 and 80 percent and there are people who keep people responding continuously for years and others who can't get them to respond later.

So having examples of that and sharing that amongst the community would be helpful as well.

DR. EGGERS: Great. Susan?

DR. MCCUNE: So I really like this approach and I'd like to see a hybrid between kind of the examples that were given already and then taking it to what I see as that next step of being able to take what you've provided as kind of a situation and then -- and I know that there are an enormous number of examples that you could spend

forever going through.

But I think with the examples you have and then some additional examples based on what we've heard today in terms of different diseases, different populations, different rare diseases, you know, all of that, pediatrics, all of the things that we've been talking about today, having some examples of being able to then utilize the practical solutions that we've been talking about in terms of innovative designs and all of the tools that have been so far mentioned today.

And some of those might be very different, depending on the population or the question that you are actually studying or the situation that you've presented.

And I think that would be for me very helpful to understand where I might be able to use a particular practical solution more efficiently than potentially in another case.

DR. EGGERS: Great. Thank you. So working in the novel approaches ideas through some of these more practical, situational-based examples. I'm

going to open it up to see if there's any questions from the floor.

And while I do, you know if you were at our patient-focused drug development meeting earlier, you'd know that we have love show of hands.

So I'm going to ask for a show of hands to say if -- does a scenario like this that takes the concepts and puts them into a story, would that be helpful? Is it worth the effort that it would probably require to do that? Show of hands if that would be helpful to stakeholders like you. Okay. Near most, yes.

So I think then you've been able to give some input, even if you don’t come to the mic. But if you would like to come to the mic and offer something more concrete, feel free. Richard, go ahead.

AUDIENCE QUESTION AND ANSWER

DR. GERSHON: I won't walk over to the mic. Two things. One is perhaps the FDA would entertain people submitting scenarios to help with the burden because frankly people I think in the

audience could -- unfortunately, those of us sitting up here -- really could help come up with some of these. And I'd like to actually respond to someone from the previous session and the Alpha-1 person.

And I hope by my disagreeing with you, you'll actually be appreciative. And that is you indicated that, you know, we're dependent on you representing patient groups. And I'm really struck by this proceeding by wanting to agree with you but then vehemently disagreeing with you.

I think this discussion document indicates that the FDA and researchers are dependent on you. We are dependent on patients.

And I think that this guidance and the -- you know, the predecessor legislation is demonstrating that indeed this process is dependent on patients and maybe hat wasn't a prevailing thought in the past, but it is a prevailing thought now.

DR. EGGERS: Thank you so much. And we'll go here with a question or comment.

DR. GILLESPIE: Okay. Hi. My name is Barbara

Gillespie. I'm an adult nephrologist at the University of North Carolina. I'm at Covance, a CRO that runs clinical trials. I'm also on the board of directors at the Kidney Health Initiative.

You know, I think this is a fantastic meeting. But there are people who are not here in the room because they don't exist. And so, for example, you know, we all know diabetes affects 12 million Americans.

Chronic kidney disease affects 15 million. Half of that is from diabetic kidney disease. But there is no one consolidated diabetic kidney disease patient group that I'm aware of.

So yes, I think the patient advocacy groups in the room, you know, it's important for them to have their say. But for groups like that, who's speaking on their behalf? I would say the same for end-stage renal dialysis patients.

And so, that's kind of, you know, an issue in nephrology that we have to bear and we're trying to deal with. But I have a concern. And you

know, I've worked with sponsors for the last 12 years in developing protocol design, feasibility and executing trials and have always thought it's important to get the patient feedback, even the feedback from study coordinators and dialysis nurses.

I guess what I'm concerned about is the risk that sponsors take. It takes time and money to get patient feedback, a lot of paperwork. And even if you do it electronically, there's still a lot of effort that goes into there.

And it's hard to convince sponsor executives to invest this time and money without clearly defining a return on investment. So hopefully that return on investment will be to support an approval or add to the label.

But what about the risk of the data showing from patient preferences showing it's neutral or even negative or even discordant with the hard outcomes that we're finding and even that prove positive.

For example, fatigue. I'm also part of the

SONG initiative in dialysis patients where we're trying to come up with a standardized set of outcomes. Fatigue is important to patients. It's important to us clinicians.

But it's hard to tell a patient that your fatigue improved by two units and it's statistically significant. What is that really saying to the patient? Especially in something like dialysis?

Fatigue improvement at month one, six and 12 after they start dialysis, there's so many compounding variables. What was their hemoglobin level? Comorbidities? How many times were they in the hospital? We've listed a couple other limitations with gathering patient data and patient preferences.

And so, you know, I looked to the pediatrician there on the panel. In pediatric drug development, there have been regulatory incentives to study kids. And I think it's even a negative -- even if you do a negative trial, that sponsor will still receive a patent exclusivity extension.

So can we think about regulatory incentives for sponsors, given the patient input, for the same scenario? Because I think there is a risk, time, money and a neutral or negative outcome in getting patient preferences.

The other thing I want to point out that, you know, sponsors also have to, and will, invest time and money in doing health economic outcomes research because they want to achieve reimbursement success too, right?

They want to show payers and CMS that this is worth it. So again, what are the regulatory incentives that we can put in place to help sponsors make these decisions and investments?

DR. EGGERS: Thank you. So to tie it back in here, what I'm hearing is a scenario that could address when the findings weren't quite what one had hoped or still learnings but it might not be directly able to support what it was intended to support, either how -- you know, how was that handled or what else could that have been used for or how maybe -- how did it yield a shift in

direction to something that is still useful. So, thank you. Is there anybody -- Sally?

MS. OKUN: I just want to make a quick comment on that.

I think it's critically important that we actually do encourage the reporting of findings that didn't come out as one expected or hoped for because those sorts of negative outcomes actually can help us learn about the kinds of things that maybe were didn't do in ways that might have been better to complement data sources with each other.

But I think it's oftentimes that kind of information that we don't share. So I would encourage that.

DR. EGGERS: Thanks, Sally. We have Theresa.

DR. MULLIN: So following up on Richard's encouraging or mentioning that people could offer examples, I mean, I think it would be very helpful, and to follow up on Sally's point, that we try to include more about nontraditional, and Elizabeth's, to innovative, nontraditional methods.

It probably would be helpful too, since you have a great deal of expertise with those methods, and maybe even giving examples of what would be for you now obvious pitfalls or things to avoid because if we're going to try to encourage the use of nontraditional methods, you don’t want people to get burnt by making mistakes.

And I think, quite frankly, that FDA sees a lot of maybe not great ideas that have been pursued and money's been spent on them.

So to the extent that a guidance can not be looking in the crystal ball and figuring out everything that can work, you know, all that innovation, but examples of what to not do, I mean, some just kind of sensible things from based on your experience of what not to do when you're pursuing novel methods.

DR. EGGERS: We'll go with Meena as our final question.

DR. KHARE: I have a comment from my recent experience on the situation and then you move into the how to improve. But the first line it says,

okay, survey of patients you send out. Again, it goes back to the first session we had. What is your frame where you are getting the data?

And the second bullet says, okay, researchers note that the response rate is low. Why it is low? It's very important to look at it because we have recent experience that I was working on.

It's the same database, same EMA list of frames and we use it in provider surveys. One of them has a very high response rate and also what is the topic, what your objective is because the other one, we had a big problem with unlocatables.

Fifty percent of them, you couldn't locate. People moved, providers, patients. So you have to build in all of that and then figure out why it is low before you go into it and then you look into what information is available and how do you adjust your final estimate.

Are those estimates any good? What is the quality of it? And we struggle with it all the time. And one of them really I was surprised when we started looking. After data collection, I was

involved. And I said, well, why it is low, in teens? And you have the same survey, the same database, another survey has very high response rate.

And then, it turned out to be there were half of them were not locatable. And then, there was an eligibility criteria. That dropped further down. So then, what you're left with is a very, very small sample.

So those things have to be built in when we are trying to improve and maybe it should be done as you're collecting data, at the same time look at it. And then, after the first small sample, and see what's going on.

DR. EGGERS: Great. Thank you.

DR. KHARE: Even with the new technology, that everything is on the social media. But you can't follow up. A lot of providers move, patients move. So mobility is another problem.

DR. EGGERS: Thank you.

DR. KHARE: And cellphone, it's a really big problem because you're -- people move around and

keep the same cellphone. So which area you are sampling from? Is it from New York or California? So, thank you.

DR. EGGERS: Great. Thanks. Any final questions here on the panel from my FDA colleagues? Okay. I do want to thank Megan Moncur who has been sitting down at the end who has been -- I drew the short stick to be up here at the podium. But she has done a tremendous amount of work.

So thank you so much. Did you have any final questions you wanted to ask? Anything come to mind? Oh, okay. All right.

MS. MONCUR: let me try again. Thank you. No, I don't.

DR. EGGERS: All right. We are on time and we will take a 15-minute break and then come for our final session, which will -- our final facilitated session which will identify key themes. So thank you to the panelists for the great suggestions.

(Applause.)

(Whereupon, the foregoing went off the record

at 2:44 p.m., and went back on the record at 3:02 p.m.)

DR. EGGERS: Sorry. If you want to work your way back to your seats, we'll get started in a few minutes. All right. Is everyone working your way back to your seats? Because we are on the last sessions before you can get back on the Beltway or the Metro, which I hope is working more smoothly this afternoon.

Okay. Before we get into our session, we had a new addition to our FDA panel for this afternoon. So I just wanted to let Tejashri introduce yourself.

DR. PUROHIT-SHETH: Sure. I'm Tejashri Purohit-Sheth and I'm from the Office of Tissues and Advanced Therapies in CBER, FDA.

SESSION IV: IDENTIFYING KEY THEMES AND NEXT STEPS

DR. EGGERS: Great. Thank you. Okay. So we are in the final session, identifying key themes and next steps. And we'll start by asking the panelists to introduce themselves. They're not in the order on the slide. But I don’t think anyone

has been on the order of the slide. So it's probably -- I think it's just a random placement. So we'll start with Theresa. We'll start with Elektra. Introduce yourself and then we'll --

DR. PAPADOPOULOS: Hi. I'm Elektra Papadopoulos. I'm associate director for clinical outcome assessments staff in the Office of New Drugs, CDER.

MS. BERLIN: Conny Berlin, from Novartis. I'm the head of qualitative safety and epidemiology.

MS. MCCLEARY: Hi. I'm Kim McCleary. I'm managing director and currently the acting executive director of FasterCures, which is a center of the Milliken Institute.

MS. EREMENCO: Hi. I'm Sonja Eremenco. I'm associated director of the Patient-Reported Outcome Consortium at the Critical Path Institute.

DR. WITTEN: Celia Witten, deputy director for CBER at FDA, the Center for Biologics and Evaluation Research.

DR. EGGERS: Thank you all. Theresa, do you want to introduce yourself?

DR. MULLIN: Theresa Mullin. I direct the Office of Strategic Programs in the FDA Center for Drugs.

DR. EGGERS: Okay. Great. So the purpose of this session is to wrap up what we heard and how we hear our FDA colleagues, what the key message is you're taking away, and our external stakeholder representatives up here, what you're taking away from the meeting today.

But then, we're asking you to add on a few pieces about looking at the overall discussion document and really this discussion document in the context of being the first in a series.

What are your thoughts about it being as a document the right scope, the right direction, the right balance to help stakeholders? And also, what are your key recommendations for FDA moving forward?

So it's a little bit heavier ask for our external stakeholder representatives. But we will start with Theresa to reflect on the key takeaways that you -- that you've heard for today.

MODERATED PANEL DISCUSSION

DR. MULLIN: Okay. Thank you, Sara. So my major takeaways were that I think we did a pretty good job with the discussion draft, trying to be comprehensive enough and make it accessible enough and usable, which is what we set out to do.

But one thing I think I learned today is that I didn't appreciate what a good vantage point FDA has in seeing what looks to us to be sort of an evolution and you might even say revolution in terms of the involvement of patients and the role that patient advocacy groups and others can play in the drug development.

And I think patient groups help to go beyond that period of the ecosystem. And that we've come to learn through the previous five years too that there are evolving approaches. There's a lot of innovation going on. There are modes of collaboration going on that we can't even anticipate yet.

And so, we don’t think that there's a single use case or a single scenario for how a document

like this would be used. We really were trying to make sure that this new and critical player, which is becoming more of a larger and recognized as an important player, also can have an understanding and working with others, but have a good working understanding of the kinds of things that we would be looking to see in a development of endpoints and information that we can use to better understand what matters the most to patients.

So perhaps we need to try to do even a better job. We have worked on this, to set the stage in the beginning of the guidance to convey that, that this is trying to provide the information for across all the stakeholders and including ones that who have not traditionally been in drug development as much as they probably will be going forward. So that's one point.

And my second one was probably related to that, that we were encouraged to be -- that openness to new methods, but making sure that they're going to deliver reliable results. And I think that's something we very much appreciate.

We've been encouraged to consider adding examples with more nontraditional methods or innovative designs and to encourage folks to consider those and maybe come in and talk to us about it before proceeding very far to see if they can get that aligned with what we'd be looking for.

And another area, my third area -- I think Sara mentioned three areas. So I'm on my third one now, that maybe we can also make clearer where we would see that things might be developed that would be sharable, ideally would be sharable.

It's non-proprietary information that would be of interest to the community in a disease area, for example, and maybe others that could be sharable more publicly versus what should be submitted to FDA to support FDA decision-making. It could be the information might be used in both ways.

But some information we would want to see to support decision-making. Others might be very helpful to advance development of drugs in an area

if it were shared with the community. So I'll stop there.

DR. EGGERS: Thank you very much, Theresa. And now, Elektra?

DR. PAPADOPOULOS: So my big three takeaways are, you know, the importance of clearly defining the research objectives for your patient input, the importance of, you know, understanding how the FDA will use the patient experience information when we receive it and the importance for the FDA to remain aware. And so, I'll try to take those each.

So with regard to the research objectives, I think, you know, it's very important to -- and we've heard just to kind of take a step back at the outset before delving into the research and what is it that we want to accomplish, what is the ultimate regulatory use of the research and this is what's really needed to spur investment and incentivize people to undertake this research because it can be obviously resource-intensive.

And so, the idea of starting with the end in

mind is very relevant here and making sure that we're asking the right questions. And so, this is going to take dialogue between the FDA and our external stakeholders and we want this to be collaborative.

We want it to be in the precompetitive setting so that we can have information sharing, minimizing burden to patients, regulators, industry and others and duplication of efforts.

And this is really where the patient organizations play a crucial role as the conveners and supporters of these activities, not to say that patient organizations can do all the work by themselves. No, it's going to take a village.

But they can really play a crucial role in this process. And we want to avoid ultimately the scenario where work has to be redone to -- because we've used a wrong method or a target population for our research question.

So the next one is, you know, there's a big need and desire for our stakeholders to understand what is FDA going to do with this information.

And again, I think once we're clear on this, this will allow groups who are sort of working on similar issues, perhaps in different disease areas, but working on some more sort of issues and research questions to really learn from each other.

And with that, the hope is that with this learning, regulatory submissions will improve in sort of a continuous learning environment. And I think with the website that we're planning to open, this transparency and sharing will really assist in this.

Then, the last one is awareness, awareness. We need to be aware of -- there are innumerable resources and databases, consortia and we've heard several mentioned today that can be leveraged. And we also need to stay aware of the technologies, social media, real-world evidence, mobile technologies, passive and active data, virtual research, et cetera, et cetera.

And so, all of these things, we need to be aware of. We need to make sure that we remain

open to the evolution and we want, you know, to really avoid any implication that we're inflexible or that we're not staying ahead of a really rapidly evolving field and science and technology. And so, I think we need to continue to be aware and to be nimble and adapt to the evolution. And that's all I had.

DR. EGGERS: Thank you, Elektra. And now, Conny?

MS. BERLIN: Okay. So I think, like my speakers before, I would say also to me the workshop has shown how much all the different stakeholders really appreciate FDA's enormous effort here to develop a guidance for patient-focused drug development and how much also such a workshop gives us the opportunity for a very early dialogue and how much and how many new ideas we have got today and which you now have the really hard job to really incorporate this into the guidance, I would think.

I think the guidance has shown us before already and given us a very good idea what a

systematic and factored approach could be for patient-focused drug development.

And I think what has been emphasized, especially today in all the discussions, is the collaborative aspect and how much all the different stakeholders, be it industry or regulators or patients, are really behind that idea of collecting patient experience data and use these data for better decision-making. I think that was really my first takeaway.

And then, my second takeaway, as also said before, is that the high importance of what is really the goal of the patient experience data, how to use these data.

And I guess for me, really the key driving aspect here can be the benefit-risk from FDA because this is for me the final goal. And I think also as you have written in your guidance, we all aim to have very good benefit-risk assessment at time of submission and for the approval.

And I think the benefit-risk can even help us

to identify what are the research questions, what really are our objectives and help us discussing very early what are the first aspects to consider in developing this roadmap.

I think that has been mentioned several times today, that it would be good to have a roadmap for the full development program where we see at what time we might want to use and collect what type of patient experience data for what purpose.

And we have heard different aspects like informing the clinical trial design or patient preference information. And I guess these early discussions will help us then go through the full lifecycle, which also means that it's not the one-time discussion.

But we probably need to have several discussions during the lifecycle. And we need to have that together with the patients. And I think we have heard how much even our patient organizations are encouraged to run their own studies which might be even very important and helpful to not duplicate or replicate studies.

And what I find also really important as a takeaway message here is to maybe even more emphasize the role of the patient in this journey and in running the studies.

That is what we have learned also in the IMI PREFER project which is a public-private partnership to develop recommendations for patient elicitation for benefit-risk assessment.

There, patients tell us very often how -- that they don’t want to be considered only as data providers, but want to play an active part and really be equal partners, which means that they want to be at the table when we discuss the research question, when we discuss the study design because they would know best whether, for instance, a focus group discussion really works for them or whether they would feel much more convenient with individual discussions at the beginning, for instance. Yeah, I guess I stop here and hand over now.

DR. EGGERS: Great. Thanks. Kim?

MS. MCCLEARY: Great. I'll echo a lot of the

other panelists. Thanks to the FDA for this opportunity to sit on this panel and for this workshop and for the extraordinary work that's gone into the guidance and just the embrace of this evolution, as Theresa called it, or maybe even a revolution in the way that patients are reflected in the totality of medical product development and regulatory decision-making.

And I was struck as I was sitting listening to the earlier sessions about just this widening aperture and this opportunity that we're now at with patient perspectives where we've gone, you know, taking kind of a bigger step back from there being really no involvement of patients in settings like this to in the sort of days following the HIV crisis when the HIV activists sort of insisted on a seat at the table and there might be a single patient representative or advocate sitting on an ad com in the scope of a single product decision to with PDUFA-V and the PFDD meetings having kind of a convenience sample, if you will, of people who could come to White Oak

or some other place in the D.C. area for 24 meetings that you all hosted and nine that have been held by externally led groups and hearing maybe a little bit more about sort of the burdens of the condition, the burdens of the therapies, the unmet medical need to now this guidance really shaping how do we collect a more comprehensive and sort of evolving story about what it means to be a patient with a certain diagnosis and all of the things that impact health and outcomes and longevity when you have that diagnosis or perhaps collection of diagnoses, as we were reminded.

I think it's important as we think about this to connect back to something, Theresa, you said very early in the day and that I've heard you say on many other occasions, that one of the really important outcomes of the PFDD meetings was a recognition by FDA of how many times the domains that the patients were talking about in the setting of those meetings were maybe disconnected from the things that they knew sponsors were studying.

And if we think about this guidance, this series of guidances as being a bit of a roadmap to help reduce the frequency with which that occurs and to sort of step back at that level and say, okay, what are we really trying to accomplish.

And we could get way down into the, you know, types of case examples we use. But that's really what this is all about, right? And so, I think about it in that context.

So my second takeaway is really to echo a comment that Annie Kennedy made from the floor about the audience for this document not just being the patient organizations or the sophisticated ones that know to come here on the December 18th workshop. But this is really for all of us.

And also, to clarify that the burden for conducting this type of work that will inform all of these different steps in a long and expensive and time- and resource-intensive process of developing new medical products is a shared burden that we all will face and that, as others have

said, needs to be collaborative.

So I see the great value in this draft guidance and the guidance that will follow as being a platform for sort of level-setting the conversation, for the glossary and the appendices and the methods that are described in it to really give us a shared vernacular and a way of understanding what we're shooting at in terms of collecting this evidence and why we would do it and being real clear in our collaborative initiatives about talking through all of these different aspects.

And for that reason, I see this as being, you know, extremely valuable and well done in terms of the structure of the document itself, starting out at a pretty high level with kind of a series of questions and answers in pretty plain language and then the progression through the document, getting increasingly more academic and detailed in terms of the specific methods and how you would go about collecting this evidence and for what purposes it might be used.

And I think you did a really great job of breaking down the concepts so you don’t need Benicio Del Toro to come in as the code breaker and tell you like what is meant by, you know, this document.

But we did hear maybe from some of our industry colleagues that they thought it was at too high a level for patients. And I'm probably not a good representative of the patient community because I've been in too many of these meetings.

So perhaps it's an opportunity for FDA to involve some of the patients from either the patient rep program or the patient engagement advisory committee or somehow to maybe do a pre-vetting when you do have the draft document itself to make sure that it does have a readability factor for those who may not be as familiar with this language and lingo.

The third takeaway I had is I think one of the greatest challenges that you'll face, in addition to incorporating all of the feedback you'll get and have already gotten, is striking the

appropriate balance between enough detail that we all have kind of a good understanding about what we're shooting at with not being either overly prescriptive to kind of chill the evolution of new methods and nontraditional ways of doing some of this work or to make it appear so complex and daunting that people just say thank you, no, I'm not going to do this. It looks impossible.

And if we got wrapped around, you know, concepts of representativeness and making sure we've got every single perspective captured or eliminating any source of bias or getting to the perfect design, that would certainly just stop us all in our tracks because we'll never quite get there.

And then, I think you've also got the added complexity in every therapeutic area the challenges are going to be somewhat different. Some have a very high velocity of change and a study done one month might be really kind of not needed six months later because you've had a new treatment or a new diagnostic entered the market

and it changes things for patients.

So we can't let the perfect be the enemy of the good I guess is the phrase. And also thinking about this as you really start to walk through how do you get this information to FDA, that there might be some scenarios in which it's not a study-by-study basis.

But you're really trying to create kind of a collection of sources of really, again, going back and understanding what is it like to be a patient with this condition. What are the important choices that they are going to be making?

And it may be more a body of evidence that accumulates over time than just something that's much more of a snapshot, so leaving open that opportunity as well. And with that, I'll turn it over to Sonya.

DR. EGGERS: All right. Thank you so much, Kim. And then, Sonya?

MS. EREMENCO: Hello. Good afternoon. Thank you so much for this opportunity to speak on this panel today. And I really appreciated what the

previous panels have said and the panelists who spoke earlier in the sessions today.

I just -- so I'll touch on some of the key takeaways that I had and also some of kind of related to the fourth question about kind of thinking about the bigger picture and how all the pieces fit together.

So we heard a lot about collaboration. We thought that's a really key point. And myself, coming from the Critical Path Institute, that's kind of our motto as well. We're all about collaboration.

And I kind of saw it in a couple of different ways. One was collaborating around developing perhaps new measures, new instruments, collecting data in a collaborative way. But I also thought of ways to collaborate to reduce the burden on patients.

I think we heard in a couple different sessions that we don’t want to do new data collection all the time for all of our conditions. That's just going to exacerbate the problem that

we've seen in the past with redundant studies and that we really need to find ways to either use data we already have in new ways and perhaps collect data from new sources, like social media.

I think we heard in a couple of different cases, social media can be a source of data. It's a nontraditional source and there are some caveats and challenges and you have to be careful about the authenticity of who's providing that data.

But it's something that could be considered as a way to get a better sense of the patient perspective and the patient experience without having to do the traditional methods. So I think it will be a really important thing for FDA colleagues to think about, you know, how can we incorporate some of these nontraditional methods not just examples in this guidance but as part of the options of methods to use.

I think by putting them in the guidance as options, it kind of gives not just an impression but it kind of makes them more acceptable. Right now, by focusing just on traditional methods, I

think it will make researchers and industry hesitant to use some of these newer nontraditional methods because it's not kind of blessed in the guidance. So it's not kind of seen as acceptable.

So I think that's something that's really important because there is so much existing data out there and there should be ways that we can leverage it and use it moving forward for patient experience data.

So my second point was about technology. I kind of touched on that a little bit. But I want to talk a little bit more about that too. I think we heard it touched on in some of the earlier sessions. But it's not just because it's novel and new and fun.

But clearly, with some segments of the population, that might be the only way we can reach them. We're not going to be able to reach younger people using traditional telephone surveys. You know, we need to find the methods that will match the populations that we're trying to reach. And I think that there could be a

little bit of expansion in the guidance around ways to use technology for the purpose of patient experience data.

And in terms of moving -- kind of moving forward and the bigger picture, one of the things that occurred to me as I was reading the discussion document was really a better understanding of the context of this guidance in terms of how it fits -- you know, how it relates to the PRO guidance, how patient experience data relates to PRO data because I felt like in this current draft, that distinction wasn't really clear or the way that they complement each other wasn't really clear.

And I think that's really important, especially to I would say the researchers and industry who might find the way that it's phrased in this guidance a little bit -- there's a lot of overlap. Let me put it that way.

And I think for us to really understand, you know, where does it fit and kind of which guidance do we need to be looking at when we're working

with either PRO or patient experience data, when we're looking at symptoms and when we're looking at function that really fall into both categories.

So I think maybe adding a little bit more about the context and the background to the guidance and also currently section one outlines the four guidances that are part of this aspect of the PDUFA and the 21st Century Cures.

And I think it will probably be necessary to repeat that outline in all of the guidances just to reiterate here's the structure, here's where the different sections are, here's where to find the information that you might be looking for. So, that's all for me.

DR. EGGERS: All right. Thank you so much, Sonja. And we have Celia.

DR. WITTEN: Yes. Thank you. It's been an interesting day and I'd like to thank all of the participants in this meeting and to the organizers for inviting me. So I will be brief because there's obviously some common themes in these remarks.

But to some extent, some of these may be things that we'll want to address in this guidance and some of them maybe are comments that we want to think about in other parts of this entire project. So they may not speak specifically just to this guidance.

But one relates to the audience and I think that's already been discussed, that this is intended for multiple stakeholder groups, both patient groups and industry and it may be that some further consideration of that, you know, needs to be made or put in the introduction or thought about when the guidance gets developed.

There's been a lot of discussion about the research objectives being important. And I think it's important for a number of reasons. But some of the commenters have also talked about how the data will be used or how it could be used.

And I think that's important when you really can't talk about research objectives without thinking about how you're going to use the data. So I think that we did get the suggestion that

there might be some examples of what the impact of some of these could be and that might be something to consider.

And then, separate questions which may not be for this guidance but certainly are something for us to think about, is how data from one of these studies would be submitted or shared with FDA.

You know, if it's part of a formal submission, I think it's a little more intuitive what we'd expect. But if it's for some other purpose, exactly how do we expect to have that shared with us.

Certainly I think that's important to think about and one of the previous speakers referred to this guidance as an ocean of opportunity, which I think is a good thing. But it also might be good for us to, you know, give some examples that would explain.

As one of the speakers on this panel said, this guidance will probably be helpful and others have said throughout the day this guidance will be helpful hopefully in enhancing collaborations and

hopefully also eliminating duplication of work by establishing a common vernacular for what these studies should be or could be.

And then, the last thing I want to mention is just about examples. So there were two kinds of examples that were discussed during that session and also earlier in the day, methodological examples and examples of the impact of the study, which are really two different things.

But I think they are related. And there was a great example in one of the morning talks, or one of the earlier talks anyway, about quantitative versus qualitative studies, which I think very well incorporated the importance of thinking about your research objectives when you think about formulating your study design.

And maybe that is an important concept that we need to think about a little bit more. So that is all I had to say. Thank you.

DR. EGGERS: All right. Great. Did anyone's comments spur additional thinking by those of you as you heard each of you go through your comments?

Did it spark any new thoughts? Go ahead.

MS. MCCLEARY: So one thing, and we talked about this a bit on our prep call for this session, was a lot of the conversation today just -- I don’t know -- emphasized the need for a communications plan when this draft guidance comes out and maybe it goes into the document itself or along with it in the form of blog posts or something from the commissioner or, you know, to re-explain sort of because others are still catching up with where we all are in this discussion.

And that's going to be really important if we want this to get beyond sort of the early adopters or early majority.

DR. EGGERS: So let me follow up on that. I think this would be for you and Sonya, if you -- even the voice blog has to assume that you're connected to FDA and that you're following along in this.

What are your thoughts on how FDA can connect with people who maybe aren't in this space yet,

particularly for a rare disease or another organization that's maybe focused on other -- on patient support, but not yet focused -- but they can tap into a lot of -- they have a wealth of knowledge. How would we reach out to them?

MS. MCCLEARY: I would suggest for the -- I assume you've kept registration lists for the 24 PFDD meetings, that, you know, blast emails, because they may not get the regular emails from FDA, going out through the patient rep program and the 200 or so people that are part of that as ambassadors to, you know, voice this and then getting out to as many different areas of industry because often it's, you know, regulatory or clinical affairs that come to these kinds of meetings.

And then, you talk to somebody else in the same company and they don’t even know what you're talking about. So I think we just have to kind of take a very broad-based but also targeted approach and engagement for this too.

DR. EGGERS: Great. The same question, we had

-- those of you -- some of you may have participated in the meeting on patient preference information that was held in collaboration with FDA and other academic institutions last week.

And there, we got a comment that there are researchers who work in very similar areas who are qualitative experts or other types, but they're just not in this space. They're not in pharmaceutical development.

Any thought maybe, Sonya, this is for -- oh, I won't put you on the spot -- any thought on how we could reach out to other researchers who could also contribute?

Because I think we're going to find that we need to build capacity in the research community to help with this what we hope is the evolution to come. Any thoughts?

MS. EREMENCO: I guess what occurs to me, and this is kind of related to the earlier question because it could be patient groups, it could be other researchers in other areas, is potentially to go to their conferences, to really seek them

out and either try to present there or make connections that way, network with them and broaden our horizons that way.

DR. EGGERS: Great. Okay. Go ahead, Conny.

MS. BERLIN: Yeah, maybe one thought. I guess the more we strengthen the role of the patient also in the guidance, the more industry will certainly collaborate also and other patient organizations weighing in here. And I guess that would be also one way to communicate messages.

AUDIENCE QUESTION AND ANSWER

DR. EGGERS: Great. I'll open it up to see if there are any questions. You can feel free to come up. Okay.

So I do want to go back to the point about this guidance as the first in a series of guidances. I don’t know if it's the only time we've done it. It's not typical for FDA to put out things in a series. So any more thoughts?

I know -- I think one of you mentioned this. But would anyone else like to follow up on thoughts on how we can best guide stakeholders'

understanding that there's more to come and that this is really laying the groundwork for a lot of future work to follow? Any thoughts? Go ahead, Theresa.

DR. MULLIN: Well, I guess I don’t have a lot of other ideas. I think that, to Kim's point earlier, and it's a very good one about putting together maybe a more complete communications plan involving others including people who focus on communications with the right messaging.

You know, I think we're still dealing with the bandwidth issue frankly in this space in terms of our own expertise in the agency. So I think that kind of slows us down a little bit. But that would have been a really good thing for us to do.

And I think that some of the other channels where I think we just need to in fact get that new story. I mean, we really need to kind of put what do we explain to people. What's the message of what we're doing here? For the next few years, we'll be repeating it and going over it. And that's probably a good way and it's also part of

change management as well is over-communication.

So we're going to have to do that lot better. But at things like DIA, I mean, you could think of some of the large conferences which industry participates a lot and we're going to have to really reinforce the message there. You can think of some of the other large venues where the stakeholders participate and that -- so I think we need a multipronged approach on it and we can do that.

I think the point's well taken too about going further, if we can, on laying out a roadmap. And so, here's where it's both -- we're trying -- I think what we'll try to balance is laying out a roadmap but also trying to be open to innovative approaches.

So it's not like this is the way to do it, like this is the only way to do it because that's contrary to the idea of allowing people to be innovative. But we understand there's a tension there because people really do want to in some ways be told this is the way to do it. So we'll

have to try to figure out how to walk that and balance that.

DR. EGGERS: Go ahead. Yeah.

MS. PALLADINO-KIM: So it actually leads right into something I was going to bring up. So, hi. Lisa Palladino-Kim. I'm from Rutgers University. We have a master's in clinical trial science. I think Conny was bringing it up earlier an then you just mentioned it with the roadmap.

Just FYI, from a high level concept, the Drug Information Association worked and put together an actual patient engagement I guess pictorial. And it actually goes through the whole drug development process and they have the time points of when the patient voice or patient engagement can occur and actually be of benefit.

So that might be something to have a conversation with them and use that as your high level guidance to help develop your roadmap.

DR. EGGERS: Okay. Thank you very much. One thing that hasn't been discussed much today was the glossary of terms. Now, of course, you can

comment in the discussion -- I mean, into the docket that we have available.

But I wanted to put and see if you had any thoughts on the glossary, if you'd refreshed yourself in the last few days, I'd put to the external stakeholders. Was it -- as you read through it, was it useful? Did it resonate with you, the terms? Okay.

MS. BERLIN: I found it very, very useful, very good. So I don't have really comments. I found it very helpful.

DR. EGGERS: Okay. Great. Great.

MS. EREMENCO: I thought it was very useful as well and I think it was good to reference existing definitions from the best glossary and other places rather than creating, you know, new definitions that would just create confusion.

And I think the only thing that struck me was there was one term that wasn't in the guidance that was in the glossary. And it's something I'll probably comment on in the docket just because I think it's a term that probably belongs in this

particular guidance, as well as the future ones. But it was helpful to hear earlier today that it wasn't necessarily meant for just this guidance, but for all of them.

DR. EGGERS: Okay. Thank you. Any other questions from -- go ahead. Yes?

MR. BUSH: Yeah. Hi. Alex Bush, from Syros Pharmaceuticals. We've talked a lot today about the use of surveys and about patient data leading ultimately to an understanding of the disease and then maybe at some point an inclusion or an endpoint.

But it never came up, the role of the patient voice in the way we think about inclusion and exclusion criteria. And I was wondering if that was something that you're considering through the development of these guidances.

DR. MULLIN: I mean, that's part of trial logistics also. So I think that all of this works in together, yes.

MR. BUSH: Okay. Thanks.

DR. EGGERS: Okay. Great. Question?

MR. DEWITT: Thank you. Steve DeWitt, Parkinson's advocate. And I want to thank the committee for all the work that's been done up to this point because there's a lot that you've done and I really appreciate that.

And I did have a question that the young lady from New Jersey just spoke to about the issue of regulations that exist right now on industry on when they can talk to a patient and when they can't.

And so, DIA is taking a step to try to make this little model to help industry understand who they can talk to and when. And I've kind of always felt why couldn't they talk to me now about these subjects and not be so regulated. And I know that there are reasons for it for as far as wanting to be too -- don't want to be too much of an influence.

But I wonder if we took those away, if there'd be more input from the community and the stakeholders without those regulations. Could someone respond to that?

DR. MULLIN: Okay. Well, let me begin by saying I'm not a lawyer at FDA. It's very important.

But I think the kind of interaction that would be of concern would be construed -- would be the kind of talking that would be construed as marketing an unapproved product.

So if it's really early conversations that are really marketing the product and it's unapproved, that that would be objectionable.

The kind of interaction we're talking about here is quite different I think and I think if what we have been saying is if there is -- there are certain kinds of communication that we do not want, would not want and then there are other kinds of communication and really listening that we do want.

And that's what we're trying to cover in these guidances, is what we would like to see. So it's more focusing on what we really hope to see. And a lot of it has to do with asking questions and listening but not marketing a product that's not

been approved for marketing, if you know what I mean. Not promoting a product that's not approved for marketing.

DR. EGGERS: Thank you.

MR. DEWITT: I don’t mean to speak for industry. But industry itself, maybe they don’t want to cross that line.

And so, they would take a more cautious approach and maybe leave out a lot of Q&A that could help advance the treatments more quickly if they didn't want to protect the liability associated with walking that line. And so, it's maybe something to look at for the future.

DR. MULLIN: Yeah, and maybe if they read this guidance, they'll move the line as well.

DR. EGGERS: Go ahead, Kim.

MS. MCCLEARY: And you might think about in the case examples that you're conceiving, maybe there's one that's product -- you know, in a product-specific scenario that illustrates like maybe not where the line is but how close you can get to it because I do think that is a point of

hesitation.

And also, you know, I think there might be some leading ways. And we've had this conversation about using the target product profile as a platform to get early sort of alignment around what are the features and benefits and tradeoffs early on in a development program.

But how much then does that create expectations on the part of the patients who are informing that process? Oh boy, you know, they've designed -- this is going to design a drug that really is what I want to have.

So I do think there are, you know -- it's easy to say we want to foster this. But then, you get down and the devil is in the details, as it always is.

DR. EGGERS: It's an interesting concept of managing patients' expectations about the data being collected and the -- on the opportunities that they could imagine coming from it. Did someone else -- was someone else going to say

something?

MS. BERLIN: I guess, I mean, the more normal it becomes that this is really data which we use in the drug development process, it might be really simplify the process and becoming clearer with the -- I mean, the purpose is then clearer.

And I guess then it becomes hopefully also easier to collect the data. But on the other hand side, maybe you're also aware that there's still quite a -- usually it takes quite a long time to set up all the contracts with the patients and to go through this.

So this is what we have learned already. This is also an information which we get back from the patients. But I guess we can work on this.

DR. EGGERS: Great. Okay. With that, I think we have covered -- I'm not going to say every topic we could have covered in the course of the day. But it has been -- I think we're at the saturation points in terms of topics and variety of thoughts that are out there.

But this isn't the only -- I'll put another

plug in. This isn't the only opportunity you have, especially if you are on the Web and haven't had a chance to put a comment through. The docket, there'll be information coming I think at the end.

But the docket, so your recommendations not just one what's in the guidance document but on how we can make sure that the eventual guidance is as useful to stakeholders as possible, either through examples or communication plans, other ways to reach people will be very helpful.

So I will close the end of this session and we'll move it to Meghana, to Meghana who will do the open public comment. Thank you very much to the panelists for your thoughts.

(Applause.)

OPEN PUBLIC COMMENT

MS. CHALASANI: Hello again. I don’t have slides this time. So there's no room for technical glitches. That was quite embarrassing as a millennial.

So now, we're moving on to the open public

comment session of our workshop. Please keep in mind that FDA will not be responding to your comments during this session, but that they will be transcribed and be a part of the public record.

Since we would like this to be a transparent process, we encourage you to note any financial interests that you have related to your comment. If you do not have such interests, you may state that for the record as well. And if you prefer not to provide this information, you can still provide your comments.

We have collected sign-up before the meeting and during the break. We have nine people signed up. So please be respectful for your other colleagues here and stick to the two-minute limit. We won't have a timer. But I will be keeping track of time. So if you approach the two minutes, I'll start asking you to wrap up.

So I'm first going to run through the order of the speakers, and I'm going to apologize in advance if I mispronounce your name. We have Danielle Friend, Anthony Howell, Steven DeWitt,

Melena Anjikova (ph), Jennifer Madsen, Cheryl Coon, James Valentine, John Davis and Eric Gascho. So with that, I will ask Danielle Friend to come to the mic, please.

DR. FRIEND: Good afternoon. My name is Danielle Friend. I'm the director of science and regulatory affairs with Biotechnology Innovation Organization. BIO is the world's largest trade association representing biotechnology companies across academic institutions, state biotechnology centers and related organizations across the United States and in 30 other nations.

BIO thanks the Food and Drug Administration for the opportunity to provide oral comments at this public workshop. BIO also commends the FDA for its plan for issuance of patient-focused drug development guidance under 21st Century Cures Act Section 3002.

These guidance documents will be important for informing sponsors, patient organizations, academic researchers and healthcare professionals of the FDA's expectations for collection,

analysis, submission and utilization of patient experience data. As the FDA begins drafting guidance on these methodologies, we ask the FDA to consider a couple of points, some of which were mentioned today.

First, we ask the FDA to consider providing clear opportunities to engage with the FDA as stakeholders begin designing strategies and studies to collect patient experience data.

Specifically, BIO requests that the FDA specify when and how sponsors can consult with the FDA during drug development regarding the conduct of studies related to patient experience and the incorporation of patient perspectives into regulatory decisions.

Opportunities to engage with the FDA will be important for ensuring that data collected from patients accurately reflects the current patient population and are appropriate to inform drug development and review.

We also ask for flexibility in approach because we are in the early stages of

incorporating patient experience data into the drug development and review processes, BIO asks that the FDA remain flexible as new approaches are tested, learnings are gathered from experiences and practices evolve.

We also ask the FDA to consider challenges faced by sponsors when determining how to provide patient experience information that is representative of a patient population.

To this end, we ask that the FDA remain flexible as to requirements for representing the range of relevant diversity in patient populations. We also encourage the FDA to promote the use of technology-enabled methodologies for collecting comprehensive and representative input.

Finally, we ask for the allowance of the use of mixed method approaches. BIO asks that the FDA be receptive to the use of both qualitative and quantitative patient experience data for regulatory decision-making.

We also ask that as the FDA begins drafting guidance regarding methodological approaches for

patient-focused drug development, an emphasis be placed on the utilization of the most appropriate methodology as determined by the particular research question at hand.

Thank you again for the opportunity to present our views on collecting comprehensive and representative input for patient-focused drug development.

BIO would like to thank the patient organizations who've developed draft guidance and language for the FDA and provided their valuable input on issues pertaining to patient-focused drug development.

In addition to these comments, today BIO will be submitting comments via the written -- or written comments via the open docket. We also look forward to working with the FDA and patient organizations as well as other stakeholders in the future on questions related to patient-focused drug development. Thank you.

MS. CHALASANI: Thank you, Danielle. Next, we have Anthony Howell.

MR. HOWELL: That's a short walk. Hi. Thank you for organizing and hosting the conversations today. My name is tony Howell and I am the cofounder of rareLife Solutions, which is a health technology company collaborating with advocacy organizations and industry to build novel, online, verified patient communities designed as engaging and methodologically rich opportunities to collect patient experience data from patients, advocates and caregivers.

We've heard the term social media a lot today and we would like the FDA to consider these novel communities as distinct from social media, particularly for orphan conditions.

Verified patient communities are pretty much what they sound like, a discrete online community dedicated to a particular disease or condition, joined by individual patients, advocates and caregivers who are impacted by that particular disease or condition and whose role or status in that community has been verified using voluntary authorization, security tools, documentation,

video uploads and other third party corroboration.

They are distinguished from general population social media sites like Facebook, Twitter, Instagram, Pinterest, et cetera because of the connection among its members. Verified patient communities are dedicated to people coming together who are motivated to make things better regarding that particular condition.

And this connection attenuates in orphan conditions where patients, advocates, caregiver members and their friends and families and support professionals can be some of the most inspirational, knowledgeable and driven people who advance research from the patient's side by, among many things, sharing their experiences from their relevant perspectives.

Verified patient communities are more like registries because of the verification process which in turn elevates the reliability of the data collected. However, verified patient communities differ from registries because they offer a more engaging opportunity by coupling a social

component with immediate acknowledgement of the data contributed. This creates a rewarding, dynamic and altruistic incentive to participate in the research process.

I'd like to briefly discuss the strengths of the verified patient communities with respect to verification which uses antechambers in which information related to the member roll, demographics and patient-reported health information can be corroborated using cross-matching public records, ICD codes, et cetera, even two-way token authorizations used on mobile phones.

Representativeness is addressed because they are easily accessible to the individual through simply signing up online which allows the common or average patient to connect resulting in participation from a broad cross-section of the community and potentially more robust sampling frames and, finally, prospective data collection because they are designed exactly to do this, to collect the data using mixed methods both

immediately and over time using passive and active engagement techniques and social engagement tools built directly into the verified patient community.

We have built and recently launched a verified patient community designed specifically for people impacted by sickle cell disease and it serves as a real-world example about how this data can be collected and considered as a primary source.

So we would like the FDA, in drafting its guidance, to consider including verified patient communities as a defined source and method for collecting patient experience data, distinguished from social media and indicate that data from verified patient communities can be considered primary data.

We will be submitting additional specific suggestions to the public document -- docket, sorry. Thank you for your time and consideration.

MS. CHALASANI: Thank you, Tony. Next, we have Steve DeWitt.

MR. DEWITT: I'd like to yield my time to

Karlin Schroeder from the Parkinson's Advocacy Community and if she has a second left, I'll fill it in. But I don’t think she will.

MS. CHALASANI: Okay. Sounds good.

MS. SCHROEDER: So, Steve and I actually work together. I'm Karlin Schroeder and the director of community engagement of the Parkinson's Foundation. And I'm happy to be here with a group of people with Parkinson's who are advocates, so Steve Dewitt, Kevin Clark and Gary Farfel (ph) are here today.

I coordinate our Parkinson's advocates and research program at the Parkinson's Foundation. We train people with Parkinson's and their care partners in how to team up with researchers in industry, academia and government to design clinical trials.

And I did want to just build on what Steve said but also on some of the things we heard earlier today. I think the methods of collecting patient experience data and the methods of patient engagement and research may overlap in a lot of

areas but are two different things that are complementary of each other.

So I think the speaker from Novartis had said, you know, it's not just giving the survey to collect information from patients about their experience. But it's helping patients actually -- and allowing patients to actually help design that survey.

And that is sometimes where we find hesitation from our industry partners is going to that next level. It takes more time upfront. But you're probably going to have a better survey in the end.

You'll have better data collected, less missing data, better retention because patients actually helped design that survey and helped determine what questions to ask and how to phrase those questions.

And I think maybe that's a little bit of what Steve was getting at. And I think too that what we have found is that, you know, we would really like to see encouragement again from FDA on how to do that patient engagement and research piece of

it, so going to the next level.

Coalitions like the Drug Information Association, the Clinical Trials Transformation Initiative and Patient-Focused Medicines Development are all working on best practices for patient engagement in research and I think that ultimately, you know, having that supported by FDA would be very helpful. I think I'll leave it at that. Thank you.

MS. CHALASANI: Thank you. Next, we have Melena Anjikova. Sorry.

MS. ANJIKOVA: It's not an easy name. My name is Melena Anjikova and I'm a senior research scientist at Evidera, a research organization. And today, I would like to make a comment from our patient-centered research group which reflects our first impression from reading the draft guidelines.

So, first, we want to thank the agency for the tremendous amount of effort to prepare for this first public meeting to discuss the patient-focused drug development guidance. We do

recognize the agency has led a number of innovative patient-centered efforts over the past decade, including the growth and expansion of the patient representative program, the patient network, voice of the patient meetings, device patient preference initiative and also, most recently, the establishment of the patient advisory board.

These and other efforts have communicated a vision for a paradigm of drug development where patients are truly at the center of the design and evaluation of medical products. The establishment of the patient-focused drug development guidance is a critical and important next step to communicate this vision and drive change.

In the first guidance, which will set the stage for the series of other guidance on drug development, we do recommend the agency outline a framework for the use of patient experience data in medical product development.

As stakeholders navigate this new paradigm, we urge the agency to consider a clear mechanism for

stakeholders to engage with the agency in the context of both precompetitive and the NDA submissions. Thank you.

MS. CHALASANI: Thank you. Next, we have Jennifer Madsen.

MS. MADSEN: Hi. I'm Jen Madsen. I'm with Food Allergy Research and Education. Thank you for the opportunity to share our comments on the topic of patient-focused drug development. I represent Food Allergy Research and Education, the leading organization offering life, health and hope to the 15 million Americans living with food allergies.

Food allergies affect 1 in 13 children. That's two in every classroom. And the number is increasing rapidly, with 50 percent growth from 1997 to 2011.

Food allergy is a life-altering and potentially life-threatening disease in which the body's immune system mistakenly targets a harmless food protein, an allergen, as a threat and attacks it. This causes an allergic reaction which can

range from mild to severe. Anaphylaxis is a severe allergic reaction that comes on quickly and may cause death.

An estimated 40 percent of children with food allergies have experienced a severe or life-threatening reaction. And a recent study by FARE Health -- not associated with the fair -- found that emergency room visits for anaphylaxis have skyrocketed, growing by nearly 400 percent in the past decade.

Anaphylaxis often begins within minutes after a person eats a problem food. In some cases, symptoms may begin hours later. Those symptoms affect one or more of several body systems -- the lungs, heart, throat, mouth, skin and gut.

We're learning that food allergies are a constellation of disorders involving epigenetic changes to the immune system, the human microbiome, environmental changes and increasing exposure to allergens over the lifespan.

Many factors have contributed to changing human immunity over the last 50 years, including

higher use of vaccines, antibiotics and Cesarean sections and the lack of exposure to breast milk, parasites, sunlight and allergenic foods.

Research that FARE is funding at 30 centers across the country who collectively treat about 80,000 patients is helping us understand the molecular mechanisms of allergic reactions and identify potential targets for new immunotherapies.

Two companies are currently in Phase III trials developing immunotherapies, one oral and another delivered for a patch for peanut allergy.

We are pleased to see this evolution of food allergy, which previously has been a disease with no therapeutic options other than avoiding the problem food and carrying epinephrine, which can save lives but does not prevent future reactions.

From the data we've seen so far, it's apparent that these products probably won't work for every patient with a food allergy. But that's not surprising and, in our view, products that work for some patients, even if not for all of them,

still should be approved by the agency.

Peanut allergies are the most common type of food allergy and we believe there may be multiple molecular mechanisms driving their allergic response to peanuts. There are seven more allergen candidates and some of those like tree nuts and fish contain multiple species, different antigens.

Assuming we can characterize the antigen's impact on the immune system at the molecular level and find molecules that block the response, it's entirely possible that we could be in a position to treat allegories to multiple foods with the same treatment. This would be an exciting breakthrough for patients who are allergic to multipole foods.

Just as FDA has recently approved a drug based on a tumor's biomarker without regard to tumor -- the tumor's original location, FARE hopes that the agency will consider a similar personalized medicine approach with respect to food allergy immunotherapies. Drugs that target a specific

cytokine, regardless of the food that triggered the cytokine's production, should not require clinical trials for each food individually.

We're also continually challenged by a lack of biomarkers that can be used as endpoints in clinical trials. Currently the only definitive diagnostic test for food allergy is an oral food challenge which involves giving the patient the very food they're allergic to and waiting to see what happens. Fear of food challenges limits enrollment in clinical trials and slows down the pace of scientific discovery.

We hope to engage in dialogue with FDA to find more patient friendly endpoints.

MS. CHALASANI: Thank you, Jen.

MS. MADSEN: Thank you very much.

MS. CHALASANI: Thank you. Thank you. Next, we have Cheryl Coon.

DR. COON: Hello. I'm Cheryl Coon. I'm a consultant to the pharmaceutical industry. I'm a principal at Outcometrix. The discussion document and then the discussion itself today took a deep

dive into methods for generating patient-centered data.

But what's missing is the big picture of why we're collecting the data and how it's going to be used. Several folks mentioned today the sponsor perspective and at least two people asked about the incentive for sponsors to undertake such work.

You have representatives from the outcomes team at different pharmaceutical companies represented here today. And they'll be going back to their teams having to convince their clinical development team or regulatory leads that these activities are valuable.

So the guidance would be more useful for convincing sponsors to use these methods if guidance number one went into detail into what questions these methods would answer and what decisions would be based on these data.

Is it for internal purposes when designing a clinical trial protocol? Or is it for submission to the FDA to support the appropriateness of an endpoint hierarchy to patients? Going back to the

slide that Theresa Mullin presented this morning on the drug development timeline, where in the timeline would these data be used?

Would it be at a Type C meeting? Would it be at an end of Phase II meeting? Where are these touchpoints between the sponsors and the FDA to submit these type of data?

And then, this could all be made more concrete if incorporated into the examples throughout the document of the type of conversations and decisions that will be made after the data are analyzed. Thank you.

MS. CHALASANI: Thank you. Next, we have James Valentine.

MR. VALENTINE: Good afternoon. My name is James Valentine and I am a drug development regulatory attorney. However, before I was ever practicing law, I was at FDA working on pre-PDUFA-V and pre-21st Century Cures approaches to incorporating patient input into the agency's regulatory decision-making.

I now represent over 20 patient advocacy

organizations, as well as numerous medical product developers to help them provide patient experience data to FDA and have utilized almost every method highlighted in the discussion document to do so. I commend the agency for this very thoughtful document, especially providing a broad range of tools for the PFDD toolbox.

Today, I would like to raise two points that I feel should be considered in developing this PFDD guidance. First, the discussion document, as well as the panel one and two discussions, called for clear research goals and objectives.

I agree that this is critical, as it informs who do you ask and how do you collect it. However, before stakeholders can set their research objectives, it would be important to have insights into what FDA's regulatory needs are and the agency's thoughts about the needs of the drug development enterprise.

Therefore, the guidance should not only provide decision-making factors to match research questions to "fit for purpose" research methods,

but also do the same between common research questions and the areas of drug development and FDA decision-making that the answers to those questions could help inform.

This would be an area ripe for examples based off the agency's experiences from working with those patient advocacy organizations and sponsors who have been the tip of the spear, piloting the methods under consideration.

Second, I have had the pleasure of being involved in 13 patient-focused drug development meetings, both FDA-hosted and externally led, several that I've moderated.

What I've observed is that much of FDA's learnings about patient experiences and preferences come from FDA representatives' participation in the in-person meeting.

While the voice of the patient reports and draft benefit-risk frameworks are valuable for memorializing the input and help FDA reviewers reference that patient experience data at the time of decision-making, it is impossible for the full

context of a patient's own words to be communicated in a summary report.

So while the discussion document provides methods for in-person input, the PFDD guidance should also include externally led PFDD meetings and should encourage FDA officials to attend these meetings so they have a venue to hear directly from actual patients and caregivers as one way to receive patient experience data, another tool in the toolbox.

Thank you for the opportunity to share some initial thoughts. I look forward to submitting some more comprehensive written comments to the docket.

MS. CHALASANI: Thank you, James. Next, we have John Davis. John Davis? No? Okay, next and finally we have Eric Gascho.

MR. GASCHO: Good afternoon. My name is Eric Gascho. I'm the vice president -- it's okay. I've been called worse. I'm the vice president of policy and government affairs for the National Health Council and I would really like to thank

FDA for a very thoughtful set of documents that were put out.

It is clear that the agency is valuing the patient perspective and really will see the voice of the patient become a much more integral part of your work over the course of the next five years, and it already has been. So really excited about that.

Much of the focus today has been on the discussion document. But I also want to commend you on the glossary. We think that it's really important to be all singing from the same songbook and starting out with a set of commonly accepted nomenclature to make sure that all the documents are consistent throughout the process.

One thing that I want to highlight from the document is about leveraging third party templates, checklists and guidances and updating the approach as you go on. I think this is really important for a few reasons. I think it shows two themes that are prevalent throughout the document.

One is a collaborative approach with the

community. We think it's really important not creating the wheel. And two, it shows that the FDA really understands that this is an evolving science and will be -- the processes will be evolving as the science evolves as well. So, commend you there.

A few things I want to highlight, and much of what I planned on talking about has been covered today. But one is on the fact that this is not going into the methods for COAs and for patient preferences.

And you referenced the patient preference work that was done by CDRH. And it's still not clear if this is CDER formally acknowledging that document. So certainly more clarity there we think would be really important.

And one other thing that was mentioned earlier was about the -- about FDA labels. Wanted to point out, while I understand that the key audience for FDA labels are patients and providers, to really understand that there are other decision-makers who use those as well,

namely for coverage and payment and value determinations and really understanding that if not on the label, there needs to be additional documentation to really make it clear how the patient perspective was used in decision-making we think will make their decision-making much easier and have the voice of the patient injected into that as well.

So thank you. We will obviously be submitting written comments, including a set of recommendations that come from all of our members. So, thank you.

MS. CHALASANI: Thank you, Eric. Now, I'd like to invite Laura Lee Johnson for closing remarks.

CLOSING REMARKS

DR. JOHNSON: Thank you, everybody. So most of what we heard today and what we are trying to focus on is that these documents are pragmatic. What's being proposed is feasible and user-friendly. And apologies to anyone who thought we were going to try to put everything on the patient

groups.

But one thing I want you all to note also as an apology in advance that the draft guidance comes out this way. Our actual template, the title says guidance for industry. If you look really hard, it's guidance for FDA staff and industry.

So do not be dissuaded and think that the information we're putting out is only for those few stakeholder groups. As many have pointed out, this is for a much wider range of stakeholders and that is part of what we are focusing and emphasizing here.

We also want to emphasize that every situation is unique and nothing is perfect. But you know, I don’t have the slide that I use in some of my presentations where I have a picture of a limbo stick that's maybe three inches off the ground. Like I'm not sure how the person is even able to get underneath it.

But then, also you have those high jumps and pole vaults. And usually our work, what we see is

going to fall somewhere in between there. But we need do to have some boundaries. It can't be so perfect, everything that's necessary and decided that nobody can ever achieve it because, yes, that's never -- we're not going to make any progress. But also, there does need to be a floor.

And so, that's what we are trying to work on and there's been a huge description today of the many different types of patient experience data, the many types of stakeholders. And also, the many different ways to collect that information and data. We heard the word hybrid quite a bit and I think that we'll probably be seeing that work its way into the guidance also.

But also, really that collaborative part and that a huge emphasis on ground preparation for the building of whatever is to come and to make sure that that prep is solid enough that when people start living in and working in that building, that it's going to stand up to the tests.

But there's not just one approach. I ask you

all to please send us your examples. We can try to think of examples to use in the guidance. But we're also trying to think of, well, who's going to get mad at us, like how can we kind of hide all of the good and the bad.

So if you all have specific examples we can put in or that maybe get shared in a common area, that is also useful. And that's true also for any templates, checklists, other documents that people have found useful. If your organizations are willing to share, we can try to find and facilitate a sharing place for that.

So you know, I mentioned this morning on behalf of Elektra, but also we had more than 30 different FDA people working on different working groups for this across not only the Center for Drugs and Center for Biologics.

But we also have a collaboration with our other centers at FDA. So CDER and CBER are the people covered under that PDUFA commitment later. But we do not work in isolation. We work in a large group effort across multiple different

centers beyond that.

So our questions to you, I'm going to go into a little more detail than what others have, is in fact down to what is that level of detail. We can't write a textbook.

But how do we balance he detail and comprehensiveness in that usability and that user friendliness? Is it okay with what we had for this workshop today? Is it something that we need to add an additional layer? And if you think an additional layer is needed, please tell us what it should be and how to present it.

Should it be in an appendix? Where should it go? What should be there? Or you can say this is great, don’t change it. Just slap a cover page on it and go. That's an okay comment too, wherever you think it's necessary.

What is the document structure for this first guidance? Do you like how we broke it out for this workshop where it's really kind of three documents related together? Do you want one thing that's cohesive in a single area? So let us know

about that.

Is there missing content? Is there corrections to the current content that we have? Is it clear FDA's open to discussion of the methods described in other methods?

So I hear some folks saying yes, it's clear you're open. And other folks are like, I'm still worried about my regulatory group inside my company. So talk a little bit about that and how you think we can kind of solution these issues.

Now, another focus and point I want to bring up here, we talked about the glossary. So there was a meeting I was at and they brought up something called the devil's dictionary where the definition of a dictionary of a malevolent literary device for cramping the growth of a language and making it hard and inelastic.

This is clearly not our intent. So think about are the proposed draft definitions clear and do they really serve to facilitate the dialogue. What I thought I heard today was yes. But again, make sure that we're not backing out way into

something that will make life more difficult instead of a solid good path forward.

What are the most important time points? Cheryl Coon brought this up and I was like, oh good, that's on my slide. What are the time points where FDA input could be maximally helpful?

So for those of you all who are creating this information, for those of you all who are working in organizations that might be using it and for anybody else, what are the touchpoints that you would like to see the most? Let us know those.

So we have our internal thoughts on this. But you may come up with something that could be even more useful or that we could elaborate on more. Are there any other additional external resources for us to consider?

But also, if you have any information, documents, thoughts, comments, anything else to share, please submit it -- I'm going to emphasize the word quickly here -- to the public docket for this meeting.

And also, please share this with other

groups in different ways. So I know before I came to the U.S. government, I knew everything there was about this Federal Register and the notification process, which is I didn't know it existed at all.

So please, if there are groups that you think may not have heard about this, please share this with them and help us also be able to broaden because this is the first of four workshops that we'll be holding underneath this part of that commitment so that we can have robust interactions in the future too.

Now, this morning, Pujita and others mentioned our due date is Friday, February 16th at 11:59 p.m. Eastern. But this is our new difficulty, which is we now have to get our first guidance on the street probably June of 2018.

It's a long process to go from we think the draft is ready to actually publishing the draft, which means if you can submit your comments in the next, say, two to three weeks, there's a far higher likelihood we are going to be able to use

it as we are actually getting that draft guidance ready to go.

So we had the option. We could say there's only a 30-day comment period. But we realized there are a lot of holidays and vacations perhaps planned in the next few weeks. So we went with a 60-day comment period.

We will do our best if you submit it at 11:58 p.m. Eastern on the 16th of February to include your thoughts in the draft. But understand we also have a lot of review responsibilities.

Everybody involved with this, this is something we do because it's passionate for us. But we also carry full review loads as well. So we will try. But it might be that it makes it into a final guidance. It might be that it gets rolled into other guidances as well.

So how do you actually do this? So you have this picture here. And when I checked at the break, we still only had zero comments received. So please, start submitting them. You click on this little button.

So if you see kind of the link to the Federal Register notice, this is the page. You click on comment now. When you click on comment now, you're going to get a page that looks like this.

And you literally just put in your comment. You can upload files. You can put in your name and contact information on behalf a third party, select different things. But it's actually now a pretty nice Web form that folks can use.

So again, our draft guidance, which will also have a federal comment period through this same type of docket, is expected to go out June 2018. And we will have another Federal Register notice and another comment period. You will probably be hearing about that in a lot of different ways. And we hope that you will expand on that.

But one of our key takeaways that I have and that we hope is present in the documents -- and if not, let us know -- there's not just one approach. This is not just about patient-reported outcomes and that we want a lot of people to be involved and we hope that you will send us your examples

and your practices so that we can include them as well.

Unless my FDA colleagues have other comments or thoughts? All right. Thank you very much and have a great day.

(Applause.)

(Whereupon, the meeting was concluded at 4:26 p.m.)

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I, IRENE GRAY, 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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12/27/2017

DATE BENJAMIN GRAHAM

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