UNITED STATES FOOD & DRUG ADMINISTRATION

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Public Meeting on CDER Standard Core Sets: Clinical Outcome Assessments and Endpoints Pilot Grant Program

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FDA Great Room, Building 31
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P R O C E E D I N G S

MEENA SAVANI: All right, we're going to go ahead and get started. Welcome to everyone who joined us today. Before we officially kick things off, just our standard disclaimer language. Friendly reminder that the views expressed in the following presentations are not necessarily those of the individual speakers and do not represent an official FDA position.

And now, the warm and friendly welcome. Good morning, everyone. My name is Meena Savani. I'm with CDER's Patient-Focused Drug Development staff within the Office of the CDER Director here at FDA. And I'd like to welcome everyone to this morning's public meeting to support the -- for CDER's pilot grant program, which FDA developed to support the development of publicly available core sets of clinical outcome assessments and the related endpoints.

We appreciate everyone who's joining us in the room here in person. We also have a number of folks who are joining us through the webcast. So

welcome to them as well and thank you to all of you for being a part of this meeting.

During today's meeting, just as a quick overview, Robyn Bent from the FDA will provide an overview of the grant's program, specifically the background, the purpose, and the cooperative agreement structure. We will then have a presentation from each one of our grantees who are funded under this grant program, and they'll share their development plans, specifically in the areas of migraine, physical function, and acute pain in infants and young children. We're then going to kind of round out the day with a panel discussion with panelists from FDA, each one of the grantee teams, as well as a patient representative.

Following each one of the grantee presentations, as well as the panel discussion, we will have an opportunity for audience members to express any comments or questions to -- and you can direct yourselves to one of the microphones on both sides of the tables. And if there is time, we will also be entertaining questions through the webcast.

Before we get started, just wanted to also remind everyone that we encourage you to submit any comments or questions also to our public docket.

And a few housekeeping items before I turn the mic over to Robyn. A recording of this meeting and transcript will be available and archived on our public website. We do have a 15-minute break scheduled around 9:45. But if you do need to step outside to stretch or to grab a quick snack at the kiosk, we welcome you to do so throughout the meeting, and we do plan to wrap up around noon.

And there is also a kiosk, if you didn't see it yet, right out here in the hallway in the main lobby where you can also grab snacks or beverages. Bathrooms are down the hall. So if you go out here, make a right, you'll see them on your left at the end of the hallway. And if you're looking for internet access, the Wi-Fi password was on the first slide. But if you didn't catch it, there's also a sign right outside at the front lobby that you can use to get the password.

I would now like to introduce Robyn

Bent to the podium for her presentation. Thank you.

ROBYN BENT: All right. Thank you, Meena. Good morning, everyone. I am Robyn Bent. I'm the Director of the CDER Patient-Focused Drug Development Program and the FDA Program Officer for the Standard Core Clinical Outcome Assessments and their Related Endpoints Pilot Grant Program. I think we're going to need to work on a slightly shorter name.

I want to start by saying how much we really appreciate you being here today. The goal of this meeting is to hear from stakeholders, both during the question and answer period, as well as in the public docket so that these standard core sets of clinical outcome assessments are developed, the identified concept COAs and endpoints reflect what is most important and relevant to patients, and support regulatory and potentially other stakeholder decision making.

This program only started this fall, so we're still early in the process. This meeting is really going to focus a bit more on what we're

planning to do than on what we've done, and we plan to have meetings twice a year to get feedback. And we anticipate that in the future, there'll be much more opportunity for stakeholders to review deliverables and provide that feedback.

So I'm happy today to provide you with a high-level overview of the grant program, why FDA felt it's needed, how it's currently structured, and what we hope to accomplish.

I'm going to start with a little history. Back in 2013, the FDA started holding disease-specific public meetings that strengthened our understanding of disease and treatment burden. These were our patient-focused drug development meetings, and we realized that these meetings provided an important opportunity to hear directly from patients, patient advocates and caregivers about the symptoms that matter most to them, the impact the disease has on patients' daily lives, and patients' experiences with currently available treatments.

These meetings reinforced that patients with chronic serious disease and their caregivers

really are the experts on what it's like to live with their condition. We learned that the chief complaints heard in PFDD meetings were often being factored explicitly into drug development plans, and that often they weren't being measured in clinical trials.

We also heard that patients want to be as active as possible in the work to develop and evaluate new treatments. So building on what we learned and continue to learn from those meetings, we're looking ahead to enhancing incorporation of patient input into drug development and evaluation.

This will bring us to our vision for incorporating patient input as standard practice: We want to ensure confidence in the reliability and accuracy of patient experienced data for regulatory decision making; we want to reduce regulatory uncertainty for the sponsor by consistency applying standards; and we want to promote rapid and consistent adoption of new guidance, processes and resources through good communication, both internal and external to FDA. And finally, we hope to see sustained incorporate of patients' experience in drug

development and decision making, make it a standard practice.

We have multiple efforts underway to help with this vision becoming reality. In the interest of time, I'm only going to touch on two during this talk.

So one way we are working on incorporating patient input as standard practice is by providing guidance on methodologically sound ways to collect and use patient experience data so that it can be used to inform drug development. We have a series of four guidance documents, each of which is accompanied by a workshop to inform its development. We've published the first two guidance documents, held a public workshop to inform the development of the third guidance.

And tomorrow in this very room, we'll be holding a public meeting to hear from stakeholders regarding guidance four, which will provide guidance on incorporating clinical outcome assessments into endpoints for regulatory decision making. We would encourage all of you to attend. On-site registration

will be available, and the meeting will also be webcast.

Another way we are working to encourage the incorporation of patient input into regulatory decision-making is through the establishment of the Standard Core Clinical Outcome Assessments and their Related Endpoints Grant Program. As patient focused drug development efforts began maturing, we noticed that there are currently little -- there's currently little coordination in efforts to develop COAs, including within a given disease area.

There's a great deal of duplication of efforts and a diversity of measures; proprietary tools are being developed at great costs, but then they are limited in affordability and sustainability. FDA reviewers may currently receive multiple independent COAs for review, each of which takes time to understand and evaluation. And we're also seeing variable quality of the tools and resulting data that has the potential to limit the tool's utility for regulatory decision making.

So FDA's grant program will enable

development of standard core sets of measures of disease burden and treatment burden for a given area that will be made publicly available. A standard core set can include different types of COAs and their related endpoints that assess a minimum list of impacts that matter most to patients; are likely to demonstrate change, including differences in trial arms related to disease burden, treatment burden and, if applicable, physical function, and should be reported in a clinical trial.

FDA expects grantees to conduct a well-managed, transparent, and methodologically sound process that provides for consistent application of appropriate methods, consideration and use of vetted publicly available measures, milestone workshops engaging key stakeholders, and milestone work products that are made publicly available.

So in mid-September, we awarded three of these grants, and you'll hear more about each of them in a moment. We are really excited to be working with our grantee teams. We're very impressed with the strong teams they've put together. They all have a

combination of expertise in clinical areas, COA methodologies, and a strong commitment to including the patient community as they develop the core sets.

To touch a little bit on the administrative portion of the grants, these grants are funded under a cooperative agreement that has the FDA and the grantee team guided by the grant PI, who is ultimately responsible, working together towards a common goal. Within the FDA, we have multiple internal stakeholders involved. These stakeholders include our clinical review divisions, our COA staff, our biostatisticians, and anyone else who may be interested in the success of this program.

These grants are funded using a two-phased approach: the first phase is the UG-3 phase, which is a one- to two-year phase focusing on planning activities; the second phase is the UH-3 phase, which is the implemental phase where the COA sets will be developed and validated. A high-level review will take place between the first and second phase to ensure that the projects are moving in the right direction.

We've also designed into the grant multiple opportunities for stakeholder input. And as I mentioned, we'll be holding twice yearly public meetings with an opportunity for stakeholders to ask questions and provide feedback, both as part of the meetings or by submitting feedback to the public docket. Each grantee has put together an external technical advisory committee made up of disease-specific experts, COA experts, biostatisticians, patient experts, and other technical experts as appropriate who oversee and monitor each specific project.

And because we realize that many trials are multi-regional or are used by multiple health authorities to make decisions, we have convened a scientific policy board to bring a global perspective to the standard core COA development process. The board is currently made up of representatives from the FDA, NIH, AHRQ, CMS, the VA, and the HLWPMDA in Japan and EMA in Europe, and we anticipate that this will expand.

In closing, I would like to thank you

all for giving your time to this project. It's something that's very important to the FDA, and we are looking forward to collaborating with excellent teams, and we look forward to your feedback because we understand that we can't do this in a vacuum. Here is a link to the additional information on the COA grant page in case you have some spare time and would like to do some reading. Thank you all for your attention.

And at this time, I would like to invite Dr. Kanecia Zimmerman of Duke University to the podium to discuss the clinical outcome assessments for acute pain therapeutics in infants and young children, COA-APTIC grant. Thank you.

KANECIA ZIMMERMAN: Good morning. On behalf of the COA-APTIC team and my colleague Dr. Bryce Reeve, we are really excited to be here today and to have the opportunity to present. We're really excited that we were one of the awardees and hope that we get to learn a lot from you guys as we move forward.

Over the next several minutes, we hope to tell you a little bit more about why we're

motivated to do this project, what are goals really are for this project, give you an overview of our team members, and the aims and milestones throughout the phases. We also hope to tell you a little bit about the stakeholder engagement plan that we have planned.

So many of you are already aware, pain among infants and young children is disproportionately underrecognized and undertreated. There are a number of reasons for this: one is that few medications to treat pain in this population are actually FDA labeled or EMA labeled. A lot of it has to do with the fact that we have difficulty doing clinical trials in children period, let alone in this particular population.

There are a number of reasons for not having the efficacy and safety information: one is that we can't really just take the information from adults and translate it to children. That's because we know that there is immaturity, and children are rapidly growing and rapidly developing over time. They have rapidly changing systems of metabolism, elimination, and even the receptors. So the drugs may

not work the same in adults as they do in children and even older children as they do in infants.

There are also many ethical limitations in conducting clinical trials in children. Can you imagine not being able to consent a child, yet not giving them pain medication because you want to test whether or not the drug is efficacious and want to make sure that you have a placebo arm. It really isn't something that we can actually do.

The other problem is that these children can't really talk to us; therefore, we don't really know if this is coming from pain or is it coming from a wet diaper or just general irritation. So these are some of the limitations that have kind of plagued this area to date.

We believe that really high-quality COAs and standardized well-justified endpoints can help mitigate some of the limitations of the current clinical trials. Although many people have done a lot of work in this area and we definitely will stand on their backs, to date, there are no well-accepted core set of COAs or endpoints for this particular

population.

So our goal as a COA-APTIC team is to identify or develop core sets of high-quality COAs and endpoints for assessment of acute pain and other relevant outcomes for use in clinical trials of pain therapeutics in infants and young children.

We are really fortunate to have, I think, a really strong team with expertise both in the clinical realm, in the measurement realm, and even in dissemination. I lead the clinical team at Duke. Bryce Reeve, my colleague, leads the measurement team. And then we have the Duke Clinical Research Institute communications team, who is involved in dissemination. I'm really pleased to have Emily (indiscernible) and Courtney Mann here today as our team members as well.

We have convened an external technical advisory committee really made up of a diverse group of people. We're super-excited about the opportunity to work with people who can think outside of the box, which I think is really needed within the context of this space. We have three parent advocates who are very excited to share their stories about children

with sickle cell disease and being a parent of a patient with osteogenesis imperfecta or congenital heart disease.

We're pleased to have Robyn as our regulatory expert. Ernest Kopecky, who is the vice president of TEVA will serve in an industry role. Amy Ohmer and Leanne West come from the International Children's Advisory Network and will be very important in thinking about how we do advocacy and how we think about patient advocacy and how we implement this in the future.

Dr. Frank Rockhold is an expert in biostatistics. He also has done a lot of returner results work, as well as data sharing and data standards, so will be very helpful in thinking about endpoints in general.

Dr. Bonnie Stevens and Dr. Gary Walco are really forces within this particular area. Dr. Bonnie Stevens, in particular, has focused a lot on neonatal pain, and Dr. Gary Walco has been the co-chair of pediatric pain research consortium within Action, within I'll talk about a little bit later.

Dr. David Warner is a practicing pediatric anesthesiologist who really will help us really understand some of the nuances in that particular space. And I mentioned Leanne West with iCAN.

So together, we intend to really put together the scientific pieces to make sure that people are excited and able to invest in pediatric trials of acute pain therapeutics, particularly for this population.

We are fortunate to be able to leverage a number of resources that are led by Duke teams. The Pediatric Trials Network is a network that is sponsored by the NICHD. Under BBCA legislation, NICHD was really charged to create an infrastructure for investigators to conduct clinical trials that improve pediatric labeling and child health.

I am chair of the steering committee for the Pediatric Trials Network and oversee the day-to-day activities of this network. And I'm really pleased to say that we have conducted more than a hundred clinical studies -- or we have more than a

hundred clinical sites, have more than 40 clinical studies, and multiple collaborators really across the globe. We've studied in more than 18 therapeutic areas, enrolled more than 8,000 children, submitted 26 packets to the FDA for labeling update and have resulted in 11 label changes. So we really think this is a strong foundation for being able to connect with sites and being able to connect with patients.

We have sites in 43 states. The coordinating center is at Duke, as I mentioned before. The Duke Center for Health Measurement also is a gem, we think, at Duke. The Center for Health Measurement is led by Bryce, and it partners with clinical researchers and healthcare providers to bring patient and caregiver voices really into care planning, treatment decisions, and health policy.

We have many methodological specialties, including psychometrics, statistics, qualitative research, health preferences, stakeholder engagement, and we evaluate people from pediatrics to geriatrics across therapeutic areas.

The goal of the Center for Health

Measurement, regardless of COA-APTIC, is really to engage multiple stakeholders to determine endpoint models and outcome measures, and to select or design COAs to use in research studies or healthcare settings. They are very interested in using stated preference methods to capture patients and caregivers' concerns, values, and preferences. So together, I think we really have a very strong core.

We are also fortunate. There have been people in this space already that we can work with and we can kind of learn from the thoughts that they've already put together. The analgesic, anesthetic, and addiction clinical trial translations, innovations, opportunities and networks for action has formed a consensus meeting or previously formed a consensus meeting to think about clinical trial designs and models for analgesic medications in neonates, infants and toddler, actually up to age 18. But really provided some guidance in this group that we think will be very helpful.

Pediatric impact group is a pediatric initiative on methods, measurement and pain assessment

in clinical trials that has really thought a lot about core outcome domains to consider when designing clinical trials in this age group. They have focused a lot on children who are older, but have also provided some guidance for the younger group as well.

So with that foundation, we have a plan, a very fairly ambitious detailed plan here. I'll go through all of these in the next couple of slides.

So in year one, we really want to identify outcomes important to stakeholders in the context of pediatric acute pain. We also are very interested in making sure ETAC kind of trains each other, that everyone is up to speed on what things mean and that we're speaking the same language. We have a number of ways that will do this. We will do a literature review for the outcomes. We will do concept elicitation to really identify the outcomes that are important to people, and then the external technical advisory we'll talk a little bit more about.

So the literature review really primarily for this phase will focus on outcomes and

endpoints that are used to evaluate (indiscernible) for acute pain and/or distress in infants and young children and really focus on the zero to less than 3-year-old age range.

We believe that as a byproduct of some of the things that we'll pulling, we will also gather information on COAs that have been used in the past to assess the identified outcomes and endpoints. We will get some idea of what people think by way of did you identify the outcome as a primary, secondary, or exploratory outcome; what is important to you based on those things. Are there -- is there heterogeneity in the outcomes and the endpoints that have been used kind of across ages, across populations, et cetera. And then how have people in the past differentiated pain expression and behaviors from other distress expression and behaviors, so cry or movement and things of that nature.

The concept elicitation interviews, we intend to do one-on-one interviews with at least 24 clinicians and 36 caregivers. We will recruiting from PTN sites, such that we will really have an emphasis

on geographic, socioeconomic and demographic diversity. We want to make sure that we're representing everyone and everyone's voices. We're hoping to have equal representation of infants and young children, ranging from the zero to 36-month age range and will likely also concentrate on the zero to two-month age as well within this particular group.

Some questions that we intend to ask, for example, would be: how does a child who is zero to less than 3 years of age express pain, or how does your child in this age range express pain; how do you actually determine the severity or intensity, via their behaviors or their movements, their vocalizations or cry, or maybe even their facial expression; how can you actually tell the difference between pain and other types of distress. That goes to you mom, or that goes to you, you know, clinician. And then how do you know when an intervention for pain is successful; what is your goal for success?

As I mentioned, we're also very interested in this phase of making sure everyone's on the same page. As I mentioned as well, our ETAC is

very diverse and a number of people have not even stepped in this space at all, so it's going to be very, very important that we, you know, speak the same language. We will have our ETAC train on perioperative pain management and assessment, talk about the long-term effects of acute pain experience and quality of life so people really understand why in the world we might be doing this. Thinking about how you develop outcomes and endpoints in clinical trials.

There will be opportunities to engage patients, stakeholders, and research and practice, and we really want to learn about what those -- what has worked before, even outside of this space. What is the parental perception of the child pain experience? And what is the role of industry or what does industry even think about this space at all; are they interested, how do they think they should move forward or we should move forward. What is the current state of pain assessment based on people and experts who already have kind of been there, and what are the challenges and next steps that we haven't thought of before?

So in AIM two -- or year two, we hope to then identify the characteristics of COAs for each outcome once we have identified our list of outcomes. We then will concentrate on evaluating the quality for each of these COAs. And as we go through the process, we intend to identify where the gaps are; we will design the UH-3 phase based on the gaps.

In the UH-3 phase, we really hope that we will do some implementation, that we'll do qualitative and quantitative evaluation in order to really provide some additional evidence for the COAs that we've picked for the outcomes that we've identified that are important to people. We will intend to provide the documentation to support this and make it publicly available.

Throughout this process, we have a plan for engaging our stakeholders, both through our ETAC, through our respective teams with the PTN, as well as the Center for Health Measurement. We're going to use the websites that are already there because a lot of people already come to them and visit them and are very interested in what we're doing. We intend to

disseminate this information through scientific and public meetings, through publications of course, and then collaboration with stakeholders. We're fortunate that we are already in talks with Action and the Impact Group to see how we might be able to interweave our efforts.

Thank you again for the opportunity to present today. I'm happy to take any questions, and you are more than welcome to contact any of us moving forward. Is there anything from the Webix?

MEENA SAVANI: None at this time.

KANECIA ZIMMERMAN: Okay, thank you.

ROBYN BENT: Thank you so much, Dr. Zimmerman. I would now like to invite Dr. Richard Lipton of Albert Einstein College of Medicine to the podium to talk about the Migraine Clinical Outcome Assessment System Grant Program, or MiCOAs.

RICHARD LIPTON: Well, thank you. So the program that I'm going to present is a little bit different than the other two programs you're going to be hearing, in the sense that we're focusing on a disease, rather on a symptom. And because of that,

I'm going to spend just a few minutes talking about migraine, which I know, although I spend much of my life thinking about migraine, that is not true for most of the people in the room.

So migraine is certainly an extraordinarily disorder by any standard. Twelve percent of the global population has migraine. Estimates from the World Health Organization Global Burden of Disease Program estimates that there are a billion people in the world who have this condition.

And, of course, like many conditions, migraine is characterized by a relatively broad spectrum of severity. At one end of the spectrum, there are people who have attacks less than once a month that respond well to over-the-counter medications and don't produce disability; and at the other end of the spectrum, there are people who have migraine attacks almost every day who are completely disabled by headache, unable to work, unable to engage in family life and so forth.

So migraine is a disorder characterized by brain sensitivity. It's a genetic disorder. It's

a disorder that's characterized by a group of symptoms that travel together in various combinations in people who have the disorder. Pain is the most obvious and the most disabling symptom of migraine, and the pain is usually one sides, pulsatile, exacerbated by physical activity.

The pain is inevitably accompanied by other features, and the migraine-defining features that are part of the international classification of headache disorders include nausea or vomiting, photophobia, sensitivity to light, and phonophobia, sensitivity to sound, as well as auras where auras are neurologic symptoms that typically evolve slowly and last between 15 minutes and an hour. And any given person with migraine may have various sets of these symptoms.

Of course, one important hallmark of migraine is that it's a chronic disorder with episodic attacks. And by that, I mean the most prominent and disabling feature of migraine occurs during attacks. But between attacks, people have an enduring predisposition to attacks and actually have

disability, functional limitations, anxiety, difficulty with planning between attacks as well.

According to the Global Burden of Disease, migraine is the world's second leading cause of disability, as measured by the metric disability adjusted life years. It disrupts health-related quality of life. Part of the reason that migraine is so disabling is that it's a condition that typically begins in adolescence or early adult life, and people with more severe forms of migraine may have the disorder throughout their life span during their peak productive years.

One estimate of the cost of migraine in the United States is at a cost about $20 billion per year. This is an older estimate that includes both direct and indirect costs, and estimates are often much higher. Unlike most disease advocates, I selected a low end estimate rather than the highest estimate I could find, so I would consider this a lower bound estimate.

So like other chronic disorders with episodic attacks, treatment of migraine is generally

divided into two categories: acute treatments, which are given at the time of the attack to relieve pain and restore function; and preventive treatments, which are given independent of the timing of attacks to reduce the frequency and severity of attacks and perhaps to reduce medication overuse.

So since 1990, development of treatments for migraine has been tremendously successful. So I was thinking about the number of drugs that have been approved for migraine since 1990, and it's seven triptans, two NSIDS, three devices, and one new drug in a class called ditans; and on the preventive side, there have been two anti-epilepsy drugs, three monoclonal antibodies, and several devices that have been approved.

So there's been a tremendous expansion of therapies for migraine on the one hand, but on the other hand, we're continuing to use the same endpoints that have been used throughout my rather long career in this field.

So when it comes to measuring acute treatment effects, the typical regulatory endpoints

focus on pain and on the symptoms associated with pain. So although the trip- -- and generally the way these trials are done is patients are asked to wait until pain is moderate or severe. And they then take a treatment, have an electronic diary and record pain and associated symptoms at relatively frequent intervals over the first couple of hours, and then much less frequent intervals after that.

And in these studies, patients are typically allowed to rescue two hours after taking their therapy. The typical primary -- one typical primary endpoint is pain freedom two hours after a drug is delivered, and that is certainly a regulatory endpoint that served the field well on the one hand. But on the other hand, I've never seen a patient who says, well, what I really care about is what my level of pain is at two hours and I don't care what happens before that and after that, so we may be leaving information on the table.

We also measure most bothersome symptom, which is a patient selected endpoint, selected from among nausea, sensitivity to sound and

sensitivity to light. And the second co-primary endpoint in most recent migraine trials has been freedom from the most bothersome symptom at two hours. We also look at sustained pain freedom; does the pain go away and stay away? And there are some PROs that are used for acute treatment trials, either to assess the benefits of individual attacks or to assess the longer-term benefit of treating multiple attacks over time.

The challenges are that many of these endpoints were really developed without a patient voice. Most regulatory trials focus on a single attack where people treat multiple attacks in the real world. When we prescribe an acute medication, patients use it over and over again. And regulatory endpoint -- primary regulatory endpoints certainly don't measure consistency of treatment effect, focuses on a single point of time when time, of course, matters, and relatively little attention is given to disability and quality of life.

On the prevention side, the usual primary endpoint has changed from baseline in monthly

migraine days or monthly headache days. This is dichotomized into a 50 percent responder rate, which is the proportion of people whose headache frequency is reduced by 50 percent or more over one month or three months.

We heard in meetings yesterday with Eric Bastings and Nicholas Kozer that they see a major unmet need in the migraine space or measures that will allow us to better assess disability or functional status in the context of regulatory prevention trials, and the team certainly agrees that that is one very important area of unmet need.

The challenges in prevention are endpoints that, again, the endpoints were largely developed without a patient voice, that defining migraine and headache days is difficult, that much of the benefit of prevention goes unmeasured in the regulatory endpoints, and that for the most part disability and quality of life are not attended to.

So our objective, and this slide projects rather dark, but our objective is to develop clinical trial endpoints for patients -- with patients

and for patients. So the aims then of the MiCOAs project in phase one are: to build a team of advisors, which we've done; to develop an initial list of endpoints that have been used, and we've completed that task; to conduct a systematic literature review of all the clinical trials that have been conducted on migraine on the acute and prevention side, and based on that literature reviewed, refine our list of endpoints that have been used in the past.

And then to talk to people with migraine and make recommendations for what are the things -- what things are the most important things to measure. From there, we will talk to people with migraine about how we can best capture the recommended endpoints in a way that makes sense to patients. We plan to conduct two rounds of data collection, one for acute treatment and one for preventive treatment, to study the psychometric quality of the measures that we develop and to establish those measures. And then finally, our goal is to make the measures we develop available to people who want to use them.

One of our partners in this process is

an organization called CHAMP, the Coalition for Headache and Migraine Patients. This is an organization that brought together something like 40 separate patient organizations. And their goals are to support people with headache, migraine and cluster, to bring together stakeholders to more effectively help people, and to identify unmet needs for those with headache disorders, and to work to better support patients and caregivers.

So this group reaches more than a million people with migraine. And one of the members of our ETAC is Katie Golden and she is a representative of CHAMP, and you will be hearing more from her a little bit later this morning.

So as we try to develop clinical trial endpoints with patients, for patients, patients and people with migraine are being incorporated into this process at various stages. So in AIM three, we're going to do qualitative studies focused on better understanding what endpoints make sense to patients.

In AIM four, we'll do more qualitative work focusing on the development of a new endpoint or

new endpoints. And there are many endpoints out there, so we're certainly not interested in making change just for the sake of making change. And we will carefully evaluate the tools that have been developed, and to the extent that they're fit for purpose, we'll be conservative. To the extent that what we hear from patients mandates change, then we'll make those changes.

A couple of areas of migraine burden that have not been well measured that were highlighted in our discussions with FDA yesterday were the cognitive burden of migraine. So it turns out that throughout the migraine attack, many people have cognitive problems. And the other thing that was emphasized by FDA yesterday, which I hear from patients very often, is about what's called the interictal burden of migraine, the burden between attacks.

And so, those are two areas where we particularly feel that additional development may be needed, and we will test that hypothesis in the qualitative work that we do.

And then in AIM five, we'll do two quantitative studies to refine measures as needed to ensure that we have reliable fit-for-purpose measures. And as I mentioned already, Katie Golden, who is a patient advocate, is part of our ETAC.

So our goal then is to develop endpoints and their measures that accurately reflect patients' experience using patient input and collaboration and the best available psychometric methods. And with that, I'd like to stop, thank you for your attention, and see if there are any questions.

MEENA SAVANI: We do have a question from the web. The question is: why do you think that existing migraine COAs are not fit for purpose?

RICHARD LIPTON: Well, you know, so I don't want to prejudge what we hear from focus groups. There are a number of measures that are out there. I've, you know, worked on many of them over the past 30 years and, you know, I'm not here to criticize existing measures.

The issue is ensuring that the measures

that we recommend really reflect the patient voice. So some of the measures have a three-month recall interval, and that may be an interval that's too long to be credible; some of them have a one-month recall interval, and that may be stretching the period over which a patient with migraine can report their experience; some of them are daily measures. One major issue is distinguishing ictal and interictal burden. Another major issue is making sure we capture all of the domains that are important to patients, including cognition.

So, you know, I'm not here to criticize the PROs that have been developed. Our purpose is to validate those PROs, listening carefully to the patient voice, and we hope confirm the utility of what's out there or build on the utility of what's out there by refining it.

PAUL: Hello, Paul (indiscernible), Meditation Solutions. I'm curious to your thoughts around specifically for acute measurement, the actual burden on the patients of just reporting it at that time. We recently just finished some usability

testing of an electronic solution for capturing data from patients. And some of them reported concerns around actually interacting with an electronic device while in the midst of a migraine, and I suspect that could extend to paper and pencil as well potentially being challenging. Just curious to your thoughts on that.

RICHARD LIPTON: Yeah. So, you know, so one of the hallmarks of migraine is sensitivity to light and sound, so in most migraine trials, data is captured using electronic diaries. And so, the task we give patients, both in acute and preventive studies, is listen to the alarm go off on your diary, then tell us how much your head hurts while you look at a brightly lit screen. So, yeah, so there are challenges. I mean, obviously, the advantage of real-time data capture is that it circumvents the recall issues that have people recall their experience.

You know, one approach is to use a daily measure where people record their experience over the course of the day. The most common approach is to use daily diaries with multiple assessments per

day. And we will talk to patients about how they feel about interacting with their smart phones or with their computer screens to try to get a handle on that. I think it's an important issue. Other questions?

Well, if not, on behalf of the MiCOAs team, I want to say --

MEENA SAVANI: We have one more question, sorry, and then you can wrap up.

RICHARD LIPTON: Okay.

MEENA SAVANI: The last question is: most trials submitted to the U.S. include international sites. Sometimes COAs developed in the U.S. do not work the same way outside the U.S. How are the projects, including information from patients outside the U.S.?

RICHARD LIPTON: Yeah. So the scope of our focus groups and qualitative research will be limited to the U.S. We're well aware that drug development often occurs on an international basis, and we're interested in developing measures that will meet regulatory standards of FDA, but also regulatory standards of other agencies.

There is a meeting later today that includes representatives of regulatory agencies outside the U.S. We're going to do an evaluation of the measures we develop for translatability, but actually doing translation and validation in languages other than English is outside the scope of what we're going to do.

WOMAN: (indiscernible) from Genentech. A quick question. You mentioned function, and in the spirit of co-concept because functions of interest for industry. Do you plan on interacting with the other group working on function so that we won't have a migraine instrument between function, but who would have a co-concept between function across different (indiscernible) area? What is the plan for your function part of measurement?

RICHARD LIPTON: Well, so, just as in measurement of quality of life, there are generic and disease specific measures. In measuring functional status, one can envision generic and disease specific measures. The group developing measures of disability are very much taking an approach that's focused on

developing a generic measure that will work across a range of diseases.

Our focus is very much on developing a disease specific measure. You know, obviously an advantage of disease specific measures is that we might be able to be more sensitive to particular problems that are very burdensome in migraine. The advantage of having a disease -- a generic measure is that you can compare functional status in disability across diseases on a common yardstick. To the extent that the measure works equally well across a range of diseases, we will certainly interact with the disability group.

My co-PI on this project, R.J. Wirth, has worked with the disability group extensively. I've not had that privilege, but we will certainly endeavor to learn from them and keep those two perspectives in mind. But our goals are really quite different because we're focusing on a disease and they're focusing on functional status, each of which has advantages and disadvantages, I would say.

WOMAN: Thank you.

MEENA SAVANI: And we do have another question. Many times, research includes patients as the people we get information from, and others work toward more partnership. How do you envision patients will be engaged in your study design and information dissemination?

RICHARD LIPTON: Right. Well, so, you know, we do have a patient advocate on our advisory board. We do plan on running multiple focus groups and some surveys that involve patients to ensure the patient voice is represented at multiple stages in the process. And we hope that our patient advocacy partners will, with their broad reach, will play a major role in disseminating our findings.

We're planning on developing a website of our own to make the measures that emerge from this process accessible. We're hoping to publish the systematic reviews that we do on the way to developing a final measure, and we're open to other ideas if the questioner has any.

MEENA SAVANI: And another question that we also welcome anyone from the audience to

comment on as it's more general. What areas do you think would benefit from development of COA core outcome sets? So more of a general question.

RICHARD LIPTON: Yeah. Well, so from my highly biased perspective, no area is more important than migraine. But, you know, yeah, I don't know. I will open that. I mean, obviously, there's a need in many areas. I think, you know, Alzheimer's would be a great area for additional development.

And I think the sort of, you know, the fascinating thing to me about this pilot project, and I think the wisdom of the people who set this up, is that built into this are two competing strategies: one is focusing on a domain of measurement, like pain or functional status, and the other is focusing on a disease. And, you know, ultimately, those approaches need to converge as we measure domains in people with particular diseases. And I don't know if anyone else has something to add to that.

R.J. WIRTH: If I could, it's outside the scope of the migraine. It's R.J. Wirth, I'm with the migraine project. But I think finding an area

that could incorporate wearables of some kind would be really interesting, just to figure out -- I mean, that sort of landscape right now is so diverse and there's no really clear structure about how do you build an endpoint around a wearable device that's sort of well-accepted and well-established. So something like Parkinson's or some other area that would allow us to sort of explore that more, I think would be great.

RICHARD LIPTON: Any other questions? Well, if not, thank you so much for your attention and for this opportunity.

ROBYN BENT: Okay, so thank you very much, Dr. Lipton. And my apologies to the people online, but I think that we're going to, instead of taking a break that was scheduled after Dr. Lipton's talk, I think we're going to move straight into the NUCOAT teams talk, so that we'll just add a little bit of extra time to our panel discussion if that's something that evolves organically.

So right now, I would like to invite Dr. Sara Shaunfield from Northwestern University to the podium to discuss the Northwestern University

Clinical Outcome Team Assessment Grant Program, or NUCOAT.

SARA SHAUNFIELD: Hi, thank you. Sara Shaunfield here. I'm here to present on behalf of my team members for the Northwestern University Clinical Outcome Assessment Team Grant Program, which we bovinely refer to NUCOAT. I'm presenting on behalf of our principal investigator, David Cella, who is actually in Japan today, so I am very excited to be here and share this with you.

The main objective of NUCOAT is to refine and test a set of cross-cutting measures for physical function that can capture a range of physical function impact from mile to severe, and that are appropriate for use in chronic conditions and rare disorders.

You may be asking yourself why physical function is important. Disease-related symptoms and treatment side effects have a great impact on one's ability to function and lead a normal life. With physical symptoms, normal is often defined by one's ability to move about freely and to engage in

activities of daily living. So we feel that this provides a good opportunity for a cross-cutting measure of physical function across diseases and will have impact for a lot of patients.

So I'm going to start by introducing our team, and then I'll give an overview of our UG-3 aims, the organizational structure and committee membership, as well as some of the measurement systems that will form the foundation of the work that we'll be doing, and then we'll dive into some of the details of the project.

So here we have our team. At the top, we have the members of the Northwestern University. David Cella there is the principal investigator. And across the Northwestern University team, we have a range of expertise in the development and validation and application of patient reported outcome measures and performance outcomes measures, and specifically, the measurement systems that form the basis of this work.

In addition to the Northwestern team, we also have representatives from the National

Organization for Rare Disorders, NORD; representing them, we have Vanessa Boulanger and Allison Seebald, who are very informative and helpful throughout this decision making and planning process. We also have representation from Aging in Motion with Jack Guralnik, and the Alliance for Aging Research from Ryan Carney. And these bring perspectives of physical function, epidemiology and policy.

And this is, we'll dig into this a little bit later, but these are just a preview of some of the different stakeholders that we have involved in this. And you'll see that we have valuable perspectives from consultants and stakeholders, ranging from payors, regulators, pharmaceutical, patient and caregiver representatives, and then patient reported and performance outcome measure expertise.

So as we've discussed today, the project is divided into two phases, the UG-3 and the UH-3. For the UG-3 AIMs, I'm going to talk about the three AIMs that we've proposed.

So for the first AIM, we're going to

convene stakeholders, including patients, care partners, clinicians, measurement experts, payors, regulators and industry representatives around the topic of physical function. And when we're talking about physical function, we're talking -- we are defining it as one's ability to carry out activities that require physical capability. And this can involve anything from daily self-care activities to more vigorous activities that would require movement, strength and endurance.

For our second AIM, we are proposing six model conditions based upon this planning and exploratory work here in this UG-3 phase. So at the end of this, we'll have -- we will be able to propose six model conditions. We want to propose three sarcopenia and three rare disorders in which we can test and measure cross-cutting clinical outcome assessments of physical function that cover a range of type and severity of limitation, and we'll also identify gaps in an of our proposed measures.

I think it's important to here to note that for sarcopenia is defined as an accelerated

wasting of muscle; it's just kind of a general definition. And sarcopenia can be associated with a number of things and can occur on its own with aging or is often associated with certain chronic conditions.

Our third AIM is to propose interim plans and final plans for refining and testing the physical function performance outcomes, based on the promised physical function item bank and physical function performance outcomes based on NIH Toolbox and the short performance physical battery, which I will provide an overview here shortly.

So digging in a little bit into our milestones to complete these AIMs. So the first AIM was to convene the stakeholders. And so, here, we're going to motivate, facilitate and retain active participation and involvement, but first we had to establish our committees. As the other groups have done, we've established and nominated participants for our external technical advisory committee or ETAC. We also have assembled a stakeholder engagement group and a clinical expert panel, and I'll provide an overview

of these members here briefly.

Additionally, we'll establish a project website and semination venues through publication and provide preliminary summaries of physical function assessment options.

The second AIM, we will propose the six model conditions to evaluate physical function. In order to get there, we proposed to conduct literature reviews of the impact of physical function across these different conditions, and also looking at the existing patient reported outcomes and performance measures that have been used to evaluate physical function in these conditions. Looking at both patient reported -- I said that. I'm sorry.

In addition to the literature review, we will conduct what are some targeted scoping interviews where we'll explore the range of physical function impact and severity across the different conditions, and then also identify similarities and differences to help inform our decision of which of the conditions we'll select for the UH-3 phase so that we can be sure that we have cross-cutting measures

that can apply to all conditions.

And then finally -- or next, we'll present a gap analysis to the stakeholder engagement group and the clinical expert panel. We'll propose an implementation plan and a final list of conditions. And then finally, we'll develop a sustainability plan for our clinical outcome assessment dissemination and maintenance.

For the third AIM of UG-3, we will prepare and present our plan for refining and testing our clinical outcome assessment measures. We'll use feedback from all of our stakeholder groups to guide a well-defined physical function concept definition and the validation process and plans for UH-3. As part of this AIM, we'll develop the protocol for refinement and validation, and we'll develop and submit the revised materials so that, hopefully, we will be able to continue this work in the latter years.

So now I'm going to talk to you and show you our organizational chart. In this, you'll see that we have Northwestern University. And above that, we have our scientific policy board and program

steering committee. And then to the left, we have the external technical advisory committee, which consists of FTAF program officers and five experts that I'll show you shortly that we nominated. And these three committees are going to have substantial oversight and input throughout the phases, providing redirection as possible and helping us to navigate some of the challenges of developing cross-cutting clinical outcome assessments of physical function in these range of conditions.

And then below Northwestern University, you'll see we have our stakeholder engagement group and our clinical expert panel. These also have substantial input in the processes and procedures and will review materials and provide their input before we implement any sort of study -- implement the studies.

And then below that, we have our quantitative teams and our qualitative methods teams, and these are the teams that will be conducting the proposed work.

So here, we have our committee

membership. For our clinical and expert panel, you'll see that we have seven clinicians and experts in rehabilitation and clinical psychology, physical-occupational therapy, and kinesiology. Our stakeholder engagement group is comprised of experts in rare disorders, pharmaceutical industry, patients, caregivers, and payors. And our external technical advisory committee, those that we have nominated to this position, are five experts in patient-reported outcome science, cross-cutting -- cross-cultural validation, statistics, and regulatory strategy.

So next, I'll provide background on the measurement systems on which our work is based. So health measures was funded by the NIH, and today is a repository and distribution center for patient-reported outcome measures and performance outcome measures. We have, within health measures, it houses four measurement systems and they assess physical, mental, social health symptoms, wellbeing, physical function, social function, sensory and cognitive function in individuals aged 3 to 85.

One of the benefits of health measures

is its flexible administration using short forms and computer adaptive tests, which means essentially that the computer will tailor the questions that you receive based upon your responses, and then performance tests of function.

The health measures also provides a common metric across the different measurement systems and health conditions and is comparable to the U.S. population. These measurement systems are appropriate for use in clinical research, regulatory practice, and educational settings.

These are just an overview of the four measurement system, but for time sake, I'm going to focus on the two highlighted, but the others, we have Neuro-QoL and ASKME. But the highlighted ones, we have PROMIS, which stands for patient-reported outcomes measurement information system, which is a self- and parent-report set of measures for global, physical, mental and social health for adults and children in the general population and for those living with a chronic condition.

For this particular project, we're

focusing on the physical function item bank, which is a bank of 165 items that's appropriate for a range of conditions and assesses mobility, upper extremity and central body function.

Next, the NIH Toolbox, on the other hand -- so PROMIS is a self-report, so it would be, like, pen and paper or computer administrated. And then the NIH Toolbox is a performance test; you're actually performing those activities. And so, NIH Toolbox is a performance test of cognitive, motor and sensory function and emotion in adults and children, again, in the general population and for those living with a chronic condition.

And for this particular proposal, we'd be focusing on the motor battery, which assesses dexterity, grip strength, balance, gait speed and endurance.

Finally, we have the short performance physical battery, which is a brief set of performance tasks that includes assessments of usual gait speed, balance tests, and tests of lower extremity, which involves raising and standing from a chair. They're

very brief, takes about 10 minutes, and is really good for assessing low end of physical function.

The SPVB has been linked to patients' perceptions of function and disability. It was developed at the National Institutes of Aging, and one of our co-investigators on the grant was involved in the validation efforts of the project. And it's also free from royalty and permission fees.

Okay, so now that we've provided the background, here we have just a visual depiction of the project overview. Above the dotted line is the plans for UG-3, and then below, we have UH-3, and then I'll use this to kind of guide us through the rest of the discussion.

So as we talked about, in order to identify the conditions, we are going to conduct literature reviews and scoping interviews. So for the scoping interviews, the plan is to explore a range of physical function limitations, severity, and health related quality of life impact for the candidate conditions.

So in collaboration with our expert

panel members and the FDA, we've selected six (indiscernible) conditions that are comorbid with sarcopenia, including heart failure, COPD, advanced cancer, hip fracture, Parkinson's disease, and osteoarthritis. We're still working out the fifth rare condition, rare disorder. But currently, we've decided upon achondroplasia, osteogenesis imperfecta, Guillain Barre, fibro dysplasia, and the next one is unknown at this point.

Findings of these scoping interviews will complement our gap analysis and literature review and help us to inform the selection of six of out of this 11 set of conditions for a cross-cutting physical function COA.

So just a brief overview of some of our procedures. As I said, these are targeted scoping interviews. We are going to conduct approximately three interviews with adult patients within each of these conditions, so we expect to conduct around 33 interviews. And within the interview, we will elicit the symptoms and treatment side effects that drive physical function limitations, and we're going to be

sure to capture the full range of physical function limitations through probes to make sure that we're not missing any instrumental activities of daily living, mobility, dexterity, axial function, and we're also going to probe about use of assistive technologies and devices.

Our data analysis plan is we will conduct a frenetic analysis of the physical function limitations for each condition separately; within this, we're also looking at the subdomains, axial mobility, dexterity. And once we have our list of physical function limitations, we will correlate that with the severity and health-related quality of life importance ratings, and compare those across conditions so that it will help us to select our ultimate six conditions for UH-3.

For our literature review, the plan is to identify and describe the impacts of the candidate conditions, both rare disorders and sarcopenic conditions, on the spectrum of physical function. And, again, we'll be looking at anticipated severity, as much as we are able to tell from the literature

review to inform these decisions. We're also going to conduct a measure scan to identify existing patient-reported outcomes and performance outcomes, but assess these outcomes within these different contexts so that we can include this evidence and support our decision for a core set of COAs.

As we've all discussed, there's a lot of stakeholder engagement, and I wanted to briefly discuss with you our plans for engaging stakeholders and for motivating them. So as we said, AIM one is to convene stakeholders, care partners, patients, clinicians, experts, payors, regulators. And the goal of this is to motivate, facilitate and retain active participation with all of these stakeholder groups throughout this process.

In order to do this, we are going to follow the principles set forth by PCORI for stakeholder engagement, in which we will emphasize reciprocal relationships. So we'll establish clear expectations of the roles and decision-making authority of all partners. We will foster a co-learning environment where researchers and

stakeholders understand one another's needs and share ownership of research activities. We will develop a partnership with our stakeholders by showing that we value and respect the time and contribution of all of our stakeholders, and we're committed to diversity and inclusion. And then also, we will emphasize trust, honesty and transparency through collaborative decision making and information sharing.

In order to achieve these goals and to follow these standards, we will evaluate the engagement process throughout this project in order to maximize contributions from all stakeholders. To do this, we will use in-house data collection tools to document stakeholder participation and contribution. Right now, we're looking at using Microsoft Teams and we're learning about all of the functionality for managing that, and I think that that's going to be a good opportunity to get some involvement of all of our stakeholders and some communication.

Collect feedback on engagement using brief surveys following each stakeholder meeting. And then quarterly, the team and stakeholder

representatives will review the data, and then discuss whether any modifications need to be made and then implementing those.

So now we're moving into the UH-3. For UH-3, of course, there's a lot of planning that's going on in the first two years. But currently, the plan is to produce a physical function patient-reported outcome measure from mixed methods research and the PROMIS physical function item bank, which will include three short forms for mild, moderate and severe physical function impairment and a full-range physical function form.

The second AIM is to produce a physical function outcome or performance outcome measure derived from the NIH Toolbox and the SPVB that's optimized for responsiveness to conditions that affect physical function.

And t hen the final AIM of UH-3 is to validate the physical function pro and performance outcome and three longitudinal studies: one that addresses mild or moderate physical function impairment, another that addresses moderate or severe,

and then one that addresses the full range of physical function impairment.

So generally our expected approach is that this will involve mixed methods. The qualitative aspects will involve concept elicitation interviews with patients in each of the final six selected conditions, development of conceptual models, and cognitive interviews of selected items or preexisting measures. We'll also incorporate mixed methods in the short form development. We plan to look at calibrations, because these are existing item banks, so that it can help inform some item selection throughout that process.

And then finally, we will evaluate the pro instruments and performance outcomes through quantitative means using IRT calibrations and validation studies.

Does anyone have any questions? The webcast?

MEENA SAVANI: We do have some webcast questions. And in the meantime, the audience members are also fee to walk up to the mic so we can rotate

back and forth. The question: are the PIs of these grants collaborating at all with the Critical Path Institute, or are they completely independent?

SARA SHAUNFIELD: I can't speak for the other grants. But for ours in particular, we have two representatives, Stephen Koons and Sonya Eremenco, from the Critical Path Institute as our stakeholder group.

MEENA SAVANI: Thank you. And another question: how are you planning to assess saturation? Three interviews per condition is a very small sample size.

SARA SHAUNFIELD: I agree. So given the scope of the work and looking at the conditions, these aren't intended to be concepts elicitation interviews. Essentially, we are just trying to get a sense of the severity of the physical function limitations, the importance to quality of life of those different limitations, and the types of limitations experienced, upper extremity and mobility, so that this can help to inform those decisions in selecting those six conditions.

And once we have selected those six conditions, we will conduct up to 21 interviews until we've reached saturation, and we define saturation as conducting interviews until no new concepts have emerged over three consecutive interviews.

MEENA SAVANI: Another question related to sampling. With regards to the sample of 33 patients across six conditions, could you comment on how this is going to reflect the principal of sample representation to be able to generalize the findings as described in the draft PFDD Guidance 1.

SARA SHAUNFIELD: That's a very good question. I would -- so I would say with such a small sample size, we can't get -- obviously cannot get a diverse population. We're, again, just trying to get a range of the physical function impacts and severities. And I welcome any members of my team to add to my response, and we can also get back to you on that question.

WOMAN: So since sampling representativeness is dear to my heart. I think, though, that there's -- we're not going to have

prefect versus if you only have people that are only at Northwestern University and they're all white and they are all upper middle class or upper class. Like, there's ways to have representativeness. And so, is that, like, kind of how are you reaching out to try to have some diversity, even though it may not, you know, it's not going to look like the CDC national health interview survey.

SARA SHAUNFIELD: And we're talking about the scoping interviews --

WOMAN: Yes.

SARA SHAUNFIELD: -- not the concept solicitation? So I think this is a really good point that you've raised because, again, three interviews is a very small number. But we are working with NORD, so I think this is something important for us to consider to get a diverse, or as diverse as we can. Through initial aspects of literature, we can identify aspects of the population that would be important to sample in this very small sample. And then once we've selected conditions, we can certain expound upon that for the concept solicitation interviews in the second phase.

Any other questions?

STEPHEN COONS: Stephen Coons from the Critical Path Institute. And I didn't seed that question, by any means, about the interaction with the Critical Path Institute, but I'm the executive director of the patient-reported outcome consortium. But also, we recently got a seed grant from FDA to establish a rare disease clinical outcome assessment consortium.

And one of the things that we're trying to do in that consortium, or will be doing once it's established, is identifying measures that are at the domain level for the most part -- physical function, pain, fatigue, et cetera -- where peritus, which is a symptom, but an important one across a variety of rare diseases, and we are very interested in collaborating, obviously, with this initiative at Northwestern. And certainly Bryce and his team work in pain in infants because so many of the rare diseases that we're going to be dealing with do involve infants and children.

So the point is, there's a lot of interaction with these groups and will be in the

future, so I want to just assure everyone that CPATH, the Critical Path Institute, is very much wanting to collaborate and willing to collaborate and has discussion collaborations regarding what is being done in these three studies specifically. Not much in the migraine area at this point because that's very specific to that disease, but we are interested very much, particularly in the Northwestern and Duke initiative.

Well, physical function, yes, is certainly one. But I mentioned peritus because that has come up as an important area within rare diseases. But, yes, physical function, fatigue, a number of domains that will be useful to assess across multiple rare diseases. The problem is there are 6,000 to 7,000 rare diseases, and we can't have disease-specific measures for every one of those diseases. So we have to find measures that could be used across multiple diseases as endpoint measures in clinical trials, so it's one of the things we're going to be working on.

SARA SHAUNFIELD: Thank you for that.

Are there any other questions?

MEENA SAVANI: A question from the webcast. As it relates to the model conditions in AIM two of UG-3, could the most common cause of physical limitation in the U.S., obesity, also be included? It seems to be a missed opportunity to not assess this condition that impacts over a third of the U.S. population. Thank you for considering addition of obesity as a potential model condition.

SARA SHAUNFIELD: You know, honestly, I thank you for your comment and your question. I think -- I hadn't even considered obesity. I think that's a really important in terms of physical function. I think that I wouldn't be able to make that decision here, but I would need to confer with my team, but we can certainly have those discussions.

MEENA SAVANI: Another question: why focus on sarcopenia?

SARA SHAUNFIELD: The sarcopenia is something that's experience -- will eventually be experienced by every one of us in terms of aging, and it's also associated with a lot of chronic conditions.

Sarcopenia is something that isn't well defined, which creates a lot of challenge for us in this space and that we'll be figuring out as we go. And there's a lot of discussion on what constitutes sarcopenia, how do you measure it. And it is an important physical outcome and it's important for these conditions that are undergoing regulatory review, and important for new drugs and new treatments to be developed. So we hope that we're on the cutting edge of helping to move this effort forward.

ROBYN BENT: Thank you.

SARA SHAUNFIELD: Thank you.

ROBYN BENT: Okay, thank you so much, Dr. Shaunfield. We are not going to take a 15-minute break and reconvene at 10:15. Thank you.

(Break)

ROBYN BENT: And at this point, I'll just ask all panelists to come up to the panel. Okay, welcome back. I hope everybody enjoyed the break. And we're going to add -- just before we start with the panel presentation, we're just going to add a small plug for people to submit any feedback or

comments to the public docket, which is open until January 6th.

And now, we're going to move on to the panel discussion. We are fortunate today to be joined by several members of the FDA staff, a representative from each one of our grantee teams, and one of our patient experts. At this time, I'm going to ask each of the panel participants to provide a brief introduction of themselves before we launch into the panel discussion.

Please note that at the end of the panel discussion, we've reserved approximately 20 minutes for questions from the audience, both in the room and online. Thank you.

KANECIA ZIMMERMAN: I'm Kanecia Zimmerman from the COA-APTIC team at Duke.

HEATHER BENZ: Heather Benz, Center for Biologics Evaluation and Research.

KATIE GOLDEN: Good morning, my name is Katie Golden. I'm a patient advocate living with chronic migraine disease.

LAURA LEE JOHNSON: I'm Laura Lee

Johnson and I'm in the Office of Biostatistics in the Center for Drug Evaluation and Research.

ELEKTRA PAPADOPOULOS: Good morning. I'm Elektra Papadopoulos, and I lead the Division of Clinical Outcome Assessments and Office of New Drugs, CDER.

DEVIN PEIPERT: Devin Peipert from Northwestern University, representing the NUCOAT team.

MICHELLE TARVER: I am Michelle Tarver. I'm the Director of Patience Science and Engagement at the Center for Devices and Radiological Health.

R.J. WIRTH: Hi, I'm R.J. Wirth. I'm one of the PIs for the MiCOA project, as well as managing partner of Vector Psychometric Group.

ROBYN BENT: Wonderful. Thank you very much. To kick our questions off, I'm going to start with what I hope to be an easy question, which is directed mostly to the grantees. But I'd also really be interested in feedback from Katie as far as why did you want to be part of this program for the grantees, why did you apply. And maybe you wouldn't mind starting, R.J.?

R.J. WIRTH: Happy to. It is a simple question, I think, but it's -- I don't know how we could not have wanted to be part of the program. You know, as Richard mentioned earlier during his presentation, migraine is such a impactful disease. You know, not just the number of people that experience it; it's the degree in which it impacts peoples' lives. And, you know, so many people are affected to the point where, you know, it's hard to work, it impacts your social life, whether or not they can go to their, you know, kid's wedding becomes an issue.

And while there's a lot of interest and new treatments and currently, it seems like it's sort of a prime time in migraine, right? There's a lot of interest in new treatment. There really hasn't been, in recent years, a ton of new work in endpoints and outcomes. And we've been talking about it now for, you know, a couple of years at least, if not more, about how nice it would be to have the time and the resources to dig in and really explore what's out there and understand what's out there. And while

there are some new developments, you know, try to better understand what's being developed.

And when we saw this opportunity come by, and especially when it mentioned migraine specifically in the RFP, we just -- we though, you know, we had to do this. And, thankfully, FDA agreed or else it would have been very awkward with me coming up here to talk otherwise. But, I mean, it really was just something, that we think there's a real need. And if we're thoughtful and, you know, with the team that we have put together and with the collaboration at FDA, hopefully, we can make a real impact on this industry and, hopefully, help patients, so I think we had to do it.

DEVIN PEIPERT: It's Devin from the NUCOAT team here. I think one thing, you know, that we responded to specifically was the opportunity to locate a thru-line across a number of, you know, potentially diverse but also, you know, similar conditions and find a way to measure important outcomes across those.

So we've, you know, our team works a

lot with PROMIS and Neuro-QoL and Toolbox and measurement systems that address a number of chronic conditions and we feel that are appropriate in that there really is a commonality across some of those conditions that can be measured very well. And this was an opportunity to leverage that to the benefit, you know, we think of industry, of patients and regulators to help systematize and bring together, you know, using the efforts that went into all those measurement systems through the, you know, the NIH funding and other sources that went into those.

KANECIA ZIMMERMAN: So I'm a pediatric intensivist, also a clinical trialist. And as a clinical trialist, children are so often forgotten, and that's the reason I want to be a clinical trialist, because I feel like we really have to kind of fill those holes. And a lot of the time, children are so often forgotten because it's hard, it's really difficult, and I think I mentioned that earlier.

And one of the reasons that things are difficult is because we don't have the right tools to be able to actually measure things, and that was

really a motivating factor. As a pediatric intensivist standing at the bedside of a child and not really knowing what's happening or how I should be treating them, it's frustrating. And it's frustrating to me as a clinician, it's frustrating to parents, and that really is the motivation -- my motivation and certainly for moving forward.

I'm thrilled to have a team who can help me and partner to be able to measure things and to apply the correct methodology to make sure that we can do this correctly.

KATIE GOLDEN: I have to say thank you. The reason I put my sunglasses on is because the screens right here and the background is white. And actually, that's something for everybody who is working on one of these grants, especially for migraine. That hurt my eyes and it could induce an attack, so thank you that was recognized. I really appreciate it, and I might stay movie star style for a little while longer. But that is part of my everyday life and I'm not the only one.

So I had an episodic migraine with

aura. My first attack was when I was 5 years old, and I was episodic, meaning clinical definition 15 days a month, headache days a month or less -- or 14 or less. And right before my 30th birthday, I had a migraine attack as normal, as there was nothing different about it, except that it never stopped. And I was the youngest vice president in my company in commercial real estate financing, and I eventually had to stop working because the migraine still has not stopped.

It's a disease, and it's on such a wide, wide spectrum. So whether or not you have it or you know somebody who has it, what they experience and what I experience can be extremely different. And so, I'm sitting here telling you that I have -- in eight, almost nine years -- I have not had a pain-free moment. And you might not believe me because I'm wearing movie star sunglasses and, you know, I've curled my hair and I put my makeup on and I put a dress on, you know, I look decent.

But I think just in general, when you think about disability, I don't look like I'm disabled. The government has agreed with me that I am

disabled. And some of the things, especially with the study on children, you know, they can't verbalize it. You may not be able to see it, the pain that they have. And so, invisible illnesses and, for me, getting the public to understand.

And then also, I'm just excited that NIH and FDA is also interested in, with the public, in making changes. And in doing so and including the patient voice, I think that the public will get that so many people are walking around, you know. There could be -- I'm sure that there are a lot of you right now who have chronic pain and I couldn't tell. But it is extremely disabling, and I'm just excited for the opportunity to share and, hopefully, we all can learn from each other. Thanks.

ROBYN BENT: Thank you. And actually, I think moving on, I think you've kind of touched on it, but I'm going to ask you maybe a direct question about why would -- like, in your opinion, why would patients want core outcome sets; what benefits do you think they could potentially have patients?

KATIE GOLDEN: I like visuals,

especially -- yeah, so this this bag here has all of my medications in it. And that includes for migraine, it includes rescue medications, so when my attacks get really, really bad, I can take. It's also preventative medications. It also includes vitamins and supplements and extra -- so there's a lot of different stuff in there. And it not only includes oral tablets, but it also includes syringes and glass vials that I have to break and get shots to give to myself.

So my point in showing you this -- and it's rather heavy -- I have to travel with this. And if I'm -- I mean, I'm staying at a hotel nearby, but I may need something in this during this meeting. So the real point is that I think all patients don't want -- we would love to be able to lighten this load. And so, if we can change the clinical outcomes so that they are geared to what patients care about, you know. This is just an extreme example, like, we don't want to take all of these, you know? I don't think any patient does. I can elaborate, but that is just one thing. That if follow-up questions, please feel free.

ELEKTRA PAPADOPOULOS: Sorry. I just wanted to say how much we appreciate your involvement and these efforts and the patient perspective is so critical. And I think some other things that we often hear from patients are that the clinical trial eligibility criteria can be very restrictive. And, you know, to have outcome assessment that could be potentially applicable to broader population. I mean, you mentioned that you have continual pain. And so, you know, it's --

KATIE GOLDEN: So to that point in particular. Yes, I've never been part of a clinical trial because there are so many. And, you know, I understand, you know, having the controlled studies; they're necessary to make sure that whatever treatment you're working on that, you know, you get the pure unbiased outcome that you need.

However, the real world, you know, there's a new class of medications for prevention of migraine that came out last year. And, you know, it's not required of the pharma companies or, you know, in FDA approval process -- correct me if I'm wrong --

that, you know, the real-world case studies of how a new drug will interact with something that I'm already taking.

For instance, if I'm taking a new CGRP inhibitor medication and I'm also using Botox for prevention of migraine, there weren't studies done on that. And so, there were some healthcare providers who were comfortable with just adding it on, adding the new CGRP on, and then many said, no, you can only do one or the other, and then insurance companies decided also, you can do one or the other.

So that is something that I, and many other patients, have experienced and that's really, really frustrating. And so, the real-world evidence, it really is important, you know. I know that the process to get to approval is very long. But for patients, a lot of women who are pregnant who have chronic migraine while they're pregnant, and we don't totally know yet if that's -- you know, if there's a risk there. And so, that's just one example of a real-world bringing those two things together, and so women are hesitant, as they should be.

But those are the kinds of things that patients care about, outside of, hey, there's this great new drug, that's awesome. And the label may say the only side effects are constipation and injection site irritation. Yet, I do know of other patients who are on these medications, and hair is falling out, they're having other abdominal pain and symptoms. And that's because, you know, in the real world, they're adding it on to and they have comorbidity. So, you know, the amalgamation of all of these, plus something new, plus their daily life isn't studied.

So that's something that is very important because a lot of patients who aren't really clued in and don't have support, the migraine community is very large but very connected. But some people in taking a brand-new medication, no matter what disease area it is, that they will -- they might say, oh, well, it's not listed. Is this side effect -- is this a side effect, is this just something new, am I crazy, do I even tell my doctor? So, yeah, I mean, patients struggle with that, and I hope that answers your question.

LAURA LEE JOHNSON: And I might work off of that a little bit because actually a lot of what you just said reminds of part of what we heard, even thinking about the oncology community. And actually, I think we have people from our Oncology Center of Excellence who would answer this a little bit better than I do, and they can correct me if I get this wrong. But a lot of -- one reason that NIH had built up the peer CTCIE, which was a patient-reported set of actually systematically asking about adverse events, and a lot of this really gets to tolerability.

And what they wanted to do is say, as you're doing trials, like, you know, a lot of times in many of these grants and the funding has been focused on efficacy, but a lot of this is also safety and understanding the tolerability. And right now, much of that information outside of it, it was, like, efficacy people have an idea, like, I need to have a fixed way that I'm measuring this in everybody.

KATIE GOLDEN: It doesn't work that way.

LAURA LEE JOHNSON: And it doesn't work

that way. But then there's the safety part is, you know, the clinician decides to write it down during the trial. And then we've got folks like our medical officers, they're trying to sift through this and try to decide is there a signal here that then goes on a label that then your doctor looks at or you see it online as you're trying to do and look about what treatments do I have and what do I want to do.

And so, part of the good part of this core outcome sets is to really say, okay, what is it that at base we are going to try to measure. And the goal would be to say, hopefully, trials would say we've got something and now we can plug it in. We're going to say, like, what it's good for. Maybe it doesn't exactly for your product, but to say this is already kind of -- we've got a lot of information, we've got a lot of evidence, we've got a lot of background.

Because right now, what happens many times is each individual sponsor for their particular molecule or what have you goes in, they have you sit in front of those screens and there is all of these

panels and focus groups. And it's not that a new tool and more development will never have to happen, but do we have to redo it every single time for something that is, in fact, pretty consistent.

And so, from an entire efficiency and systems standpoint, that's part of what I think is really beneficial of having those core outcome sets and what we're looking for here, because we've heard it from everybody -- from the patients, from the sponsors, from lots of different groups. But it's also to remember that many of these elements you've brought up, like, that may be brought in.

And I think an important part of having that patient involvement is, you know, the tools that we learned and we held dear because people have used them for the last 5, 10 or, in some cases, 75 years, may not be what we should be using right now. And so, where should we be moving forward?

KATIE GOLDEN: And another point to add on to that is, in particular in the migraine area, we have had experience where individual sponsors have, within their individual drug development programs,

develop, you know, very similar tools. But really, you know, what is the efficiency in that? And so, that's part of the goal here is to have a uniform tool that could be used across. Yet, and I recognize that sometimes we do need to have individual, you know. But where there's an opportunity to collaborate and to have common tools where we can compare apples-to-apples and have common metrics to really allow informed decision making with prescribers and patients and have intelligent choices there.

MICHELLE TARVER: If I could just chime in really quickly. You know, we're talking about drugs, but also in the device realm. I mean, there are new challenges that exist in devices. And devices are things that are implanted in patients, so there's a different calculus that goes into determining, am I going to take the risk of something that's experimental and is going to stay with me potentially for the rest of my life.

So how we assess safety in that context is maybe different than how you do it for a drug. So having a core set of outcomes that assesses one of

those concepts, it's also important for that condition, allows industry to focus their efforts in developing what may be the gap and filling that in, instead of repeating the exact same thing over and over again.

HEATHER BENZ: This is relevant for biologics as well. We have a variety of rare conditions that often show up with products, conditions for pediatric patients, conditions with a variety of adverse events. And particularly where there are small patient populations, the patients are begging for efficiency. You know, please tell the sponsors that the trials will be quick and easy to design so that they will do them.

So we see a real need for efficiency so that patients have increased access, not only to products already under development, but products that are in the pipeline or that could be in the pipeline were there enough efficiency.

ELEKTRA PAPADOPOULOS: That's a great point, and that's true across the board. Lowering some of those barriers for development is a key goal.

ROBYN BENT: Great, thank you. I think we'll now move on to the next question because I want to make sure that we get to it. And this one, I'm going to kind of aim initially at you, Elektra. It seems like there are a lot of efforts related to clinical outcome assessments going on across CDER. Can you talk a little bit about these efforts and how they are similar and how they are different? And then we'll move on after that to our representatives from CDER and CDRH and ask them about their programs as well. Thank you.

ELEKTRA PAPADOPOULOS: Certainly, and thank you for that question; that's an important question. And I think, you know, I'll give sort of a long-winded question because I have to provide some background. I know many of the people in the audience are already familiar with some of these efforts.

But I first wanted to highlight the drug development tool qualification effort and to remind ourselves. Drug development tools are materials, methods or measures that could potentially facilitate drug development. And so, included in this

definition are, of course, clinical outcome assessments, as well as biomarkers. We also have in our program animal models for use under the animal rule, but today, we're obviously going to focus on the clinical outcome assessments.

So really, what is qualification? It's a conclusion and it's based on a formal regulatory process that, within a particular a particular context and view, so it's very context specific, that the tool can be relied upon to have a specific interpretation and application in medical product development and regulatory review.

And so, FDA has established qualification programs to support drug development, took development. And as we'll hear, the Center for Biologics and CDER share programs, a joint program, and CDRH, in addition, has a parallel qualification program for medical device development tools.

And so, you know, we've heard expressed very well earlier, you know, the goals of the core clinical outcome assessment program, which is very similar in that we want to have publicly available

tools, tools that can be used in clinical trials that have been vetted with the agency and have buy-in from plurality of stakeholders, and that can be used in multi-national trials. So, you know, there are a lot of, you know, common goals, and these programs are not mutually exclusive and could really complement each other very nicely.

But I also do want to emphasize some of the differences between the programs. They are distinct programmatically, so there are different processes. The drug development tool program is a well-established program; it's been in existence for many years. And recently, with 21st Century Cures Act, it has been formalized and is now part of our mandate, and we also expect upcoming guidance outlining the process of this qualification.

The core clinical outcome assessment program, of course, as we've heard is in its infancy. It's a pilot program and so, we're obviously still learning. And it's also a grant program, so it's different in funding. The drug development tool program is not a grant program. And so, one of the

more content issues is that the core clinical outcome assessment program is a little bit broader in focus; it's focused more globally around comprehensive sets of measures, as well as endpoints.

And these can be, as we've heard with the case of migraine, in a particular disease area or, in some cases and how we've defined it for the purpose of this program, could cross-relevant disease areas that share common domains, such as physical functioning or certain symptoms. And so, you know, as we discussed, this has great advantages also in allowing us to, you know, compare across products of similar classes potentially.

And so, you know, it's really our hope and our goal that the tools and endpoints will be able to satisfy multiple stakeholders because we know that drug development is really multi-national. And it's very important to also remember health technology assessors in this process, and so, we need to pay very close attention to tools that can be able to be translated for multiple languages, as well as culture groups. Consensus development in this regard is also

going to be very critical with the development of core outcome sets. We need to have consensus on common sets that can satisfy these stakeholders, and so we're going to be pulling in a broad range of stakeholders, as we've heard earlier.

The other key thing is, you know, qualification is really focused on an individual tool, so it's a tool that's for a particular context of use. And so, each qualification project is associated with only one tool, it's not a set of tools, and they are important to fill these critical measurement gaps, however. So before we take anything into the qualification program, we ask ourselves, is there a drug development need, is there an unmet need here, and so that's very important.

But, you know, at the end of the day, the measures and endpoints in both of these programs need to be fit for purpose. And so, we're going to be reviewing evidence in both cases, and the core measurement principles are going to be applicable across, so our standards are going to be maintained with any of the measures coming out of these programs.

Both of these programs are voluntary. So drug developers, rest assured, you will also -- we will also continue to interact with you around clinical outcome assessments within your individual drug development programs. So that is also a key part of our day job here at FDA.

So I just wanted to say in closing that, you know, we envision that these two programs will be complementary, not mutually exclusive, and that the learnings can be applied across both because measurement excellence is really shared across these programs. Both programs will be looking to leverage existing tools and learnings and not reinvent the wheel, so those are very important.

We're very committed to the success of each of these programs and the multidisciplinary nature, so it's not only, you know, the measurement folks, but clinical and biostats all coming together. And we're committed to sustaining the programs and maintaining them because it's not just about the initial development, but also maintaining these over time.

And so, finally, you know, really our ultimate goal is the sustainable incorporation of patient voice in clinical outcome assessment and drug development. And so, I think that sort of recaps the key features of our efforts.

ROBYN BENT: KATIE GOLDEN: Thank you.

KATIE GOLDEN: Is it okay if I just very quickly mention something?

ROBYN BENT: All right.

KATIE GOLDEN: And also before I do that, is it okay, because the patient community lives online -- is it okay, I've got my phone here for me to hit go live. They'll just see me, and I've redirected them to watch this. If I can't, that's totally okay. I'm trying to get more patients to watch because this is really -- a lot of us are very, very excited about this.

ROBYN BENT: I think you can go ahead and try it. If we find that there's any sort of interference or something like that.

KATIE GOLDEN: Oh, sure.

ROBYN BENT: And it's also streaming

live for you as well.

KATIE GOLDEN: Sometimes when they go live, I've got the link for them to watch the whole thing so I can probably do it in a few minutes. Because I know you guys care, I mean, I'm here as a patient, but there are so many that could be here right now and could say the exact same thing.

I want to mention to your point, you mentioned having -- trying to find a tool that kind of works, and I wanted to clarify. Finding a clinical outcome tool that -- you were specifically saying that about for each disease area or across all disease areas. Can you clarify that for me?

ELEKTRA PAPADOPOULOS: Okay, yes. So in the case of migraine, the goal is to identify a set within the disease area of migraine. And however, you know, for the purpose of this grant, we've also expressed interest in tools that could be used to measure common symptoms or impacts or functioning that span across disease areas.

KATIE GOLDEN: So I will -- thank you for the clarification, so that I make sure my comments

are germane to this.

KATIE GOLDEN: Thank you for the clarification so that I make sure that my comments are germane to this. And so, you may want to think about starting with -- there are a ton of, you know, apps that you can use, that patients use, that you could look at, and there are lots of patients who have also, you know, kept daily diaries. And their input earlier on probably is going to save a lot of heartache and a lot of frustration.

And this isn't just for migraine, you know, and the other areas as well, because I just recently had a conversation, and somebody mentioned just, how were you in the last, you know, seven days or the month? And keeping a headache diary or using an app, that screen time, that can be difficult. Or, like, if you're having a really horrible attack, I can't go into -- you know, technology is great, but I can't do this. And if it's 30 questions that I need to answer once a week or once a day, you're not going to get the information that you need. There are probably some other ways to get the information that

you need, and so I would just suggest to everybody, like, you kind of start with them as well -- start with patients instead of building it first.

MICHELLE TARVER: So, this is Michelle. I think that, you know, your point is very well founded. I mean, I think that a concern that we have, especially as we're moving into an era where we're using more real-world data to inform our regulatory decisions as well as integrating that information into our healthcare plans -- I'm a clinician as well -- it's important that we deliver tools to patients that are going to be completed. Otherwise, missing data is not useful data, no matter how well developed a tool is. So, I think a pragmatic approach to integration of that information is absolutely spot on.

Also, to your point about apps, there's a lot of work happening. Our center works on mobile applications, as well as other digital health technologies, and how do we best capture other pieces of information that may be complementary, that reflect how a patient is feeling and functioning? I think that is really a critical space when a patient cannot

report, I think both for the pediatric situation as well as for somebody in the middle of a crisis. How do you collect information about that in real time? And I think that there's a lot of work and interest in exploring that, so I do think that you bring up kind of that next horizon. Where do we go next?

I think for the CORE grant, I think it's critical to our efforts. We have not only a guidance document that's been final for a number of years about using real-world data as real-world evidence in regulatory decision making, and using that information to expand our label indications, as well as for premarket and post-market monitoring of medical devices. We want to make sure we get the patient perspective, but what we've been seeing is that the questionnaires are too long. They're too difficult to collect, so we can't incorporate it into our regulatory decision making.

And developing core outcomes that are pragmatic and practical will help us have a better understanding over the total product lifecycle of medical devices, as well as biologics and drugs.

R.J. WIRTH: And, could I just build on that for a moment? While it's not a goal, necessarily, of this grant process, and you know, we've had a lot of conversations already within our team about how important it is for what's being developed here, if possible, to be able to port that into other arenas so it can be used in, you know, within clinics. It can be used in other areas to get us not just on a common metric, but if we can use, if not the exact same tool, having some sort of linking, some sort of system that will allow us to easily incorporate real-world data, allow us to easily incorporate data directly from the clinic and have a better understanding -- you know, with regard to some of the points that came up earlier -- have a better understanding about, you know, what types of interactions are occurring; have a better understanding of how people are feeling when they're not in this very structured clinical trial.

So, while I know it wasn't the goal of the granting process, you know, I hope we're -- and knowing the other teams, I'm sure we are all thinking

about not just what can we do for clinical trials, but how can we build something that's useful outside of the clinical trial to allow us to have a better understanding of just patient experience across the board.

LAURA LEE JOHNSON: And I also want to bring up to the point, because hopefully -- I'm glad that we are recording this, because this is our plan language summary now for guidance to -- of the guidance series. Which, in many ways, part of what we've been trying to talk about, and I was glad that Michelle mentioned the 2009 final PRO guidance that her center, Heather's, and then our center all signed onto. And we all say, at the core, you start with the patient. Don't develop something and then throw it at them, just get some math off of it, and you're done.

But I think the important part that also, to reiterate, we've been saying like, what novel ways could you collect information? And, you know, I know for years, I put every single thing that I ate and drank into one of those apps. And so, that's information that can then be leveraged, and then other

folks that are doing other types of daily diaries, does it take a lot more work to go through those transcripts and more free-flowing information? It could.

But also, sometimes that's where we are in order to try to do and leverage information, especially if you're thinking about, hey, I need to go talk to FDA and say that the fact that people need to answer within -- or talk within your own company -- we need everybody to answer this questionnaire within a two-hour window. Well, for our disease, that's not going to work. Here's the justification for the window. You now are bringing in that evidence to provide that justification.

So, there are a lot of ways to creatively leverage information, not only in the core outcome arena, but also in trying to really define and set up clinical trials that are going to be useful and feasible at the end of the day.

DEVIN PEIPERT: Yeah, I'd like to just add that, you know, our team from NUCORE couldn't agree more. I think even looking at something like

the concept of physical function, it may be one of the sort of core health concepts that we think we understand very well, but those of you who heard Sarah from our team talk earlier heard that we're going to be doing a great deal of qualitative work. And, even though I'm a quantitative researcher, I'm on the math part, I'm probably most excited about that element because I think it's going to give us the opportunity to look at, across this range of conditions, what's the common element that can be measured well from the patients' perspective that's a good therapeutic target in that area, and then push that into the measures. And we know how to do that, but I think there's going to be a lot of new knowledge coming out there, which should be very exciting for everyone.

ROBYN BENT: Great, thank you very much. I'm going to bring the question -- I think this was a really, really great conversation. I'm just going to bring us back a little bit to hearing about the different efforts that CBER and CDRH have work going in the COA realm. And so, I don't know if -- Heather, do you want to start?

HEATHER BENZ: Sure, thank you. So, in CBER, we do partner with CDRH and do leverage the qualified Drug Development Tools and other ongoing programs there.

So, in addition, we have funded a number of studies related to COA development, with the goals of helping those patients with rare diseases and rare pediatric diseases that I mentioned earlier. They include research aimed at improving our design of clinical trials so that, for rare diseases, maybe you don't need as many patients in the control arm if we can have ongoing natural history studies with robust, built-in COAs. We're demonstrating that project with NORD, the National Organization for Rare Disorders.

We're also working closely with IBM to build COAs into apps and into our ability to use a variety of real-world evidence collected from a variety of data partners across the U.S. It's important for us to include the patient perspective in that data to provide context and to elevate the patient voice any time we're looking at safety data.

And then, we've heard a little bit

about pain and function here. There have been a number of challenges for products that are intended to alleviate pain and improve function, and we're conducting research intended to improve our understanding of how those interact, and also, improve our understanding of what matters to patients about that dual axis of pain and function, so that when we see products, for example, that alleviate pain but may not meet their endpoint on function, how do we consider that, and how would patients with relevant disorders ask us to consider that?

KATIE GOLDEN: Could I make a comment? And, please, if I talk too much and we're short on time, please tell me to stop. But just for something for everybody to kind of think of is you brought up the function and the disability and the daily burden. Every disease area has their own set of issues and daily things that they have to deal with. Just, I think that I'm here so that I can kind of give a better picture, at least in my experience with my disease and my comorbidities, of what my day is actually like.

So, I'm trying to be very short. I think the general public thinks, oh, you have a migraine. It's just like a hangover. Take Tylenol and you'll be fine or -- sorry, shouldn't name brand names, but you all know what I mean. And, you know, if you don't have migraine or you don't know somebody who does, hasn't seen somebody go through that, you don't really understand.

So, in my absolute worst, worst day, I will go -- actually, I will describe a flareup, as I would call it, that I had last year. I didn't leave my apartment, even to go to the lobby to get my mail, for a month. Luckily, my amazing partner in my life and the love of my life, he is also the head of CHAMP, the Coalition for Headache and Migraine Patients. He doesn't have migraine, but I was episodic when we met and became chronic, daily, over that time.

So, something like that, I mean, I'm lucky that he was supportive and I had that. He was able to go do the grocery shopping and go downstairs and get the mail. And it's not just about being, oh, I'm nauseous, oh, there's head pain, I'm sensitive to

light and sound. It's so much more than that, and I'm going to get real, and I'm going to be graphic, because I think just in general, the public doesn't realize this. And I think also, just in all the disease areas, that you have to understand the daily life.

So, you know, I could be puking all day long. I could get numbness and tingling in my fingers, and so I can't write. Or, sometimes I'm able to look on a screen, and other times, just even the thought of looking at it is horrible, even if I'm not having a flareup. And some of the other things are the cognitive impairment. I'm definitely, you don't know me, but I'm definitely pausing right now because I'm trying to find the exact right words to convey what I'm saying, and I may totally blank on something during this.

That's my daily life, and it's not just me. While you're having an attack, that can be the case. Or, if you are chronic, which actually, it's estimated about 4 million Americans are considered chronic, where they have 15 or more headache days a

month.

And the ability to work, or not work actually, we all try to kind of -- I just grin and bear it and work through it, because we want to do the best job that we absolutely can. But, you know, employers don't always get that. The fluorescent lights that I see every day, I need accommodations. So, either I can wear sunglasses, or we need to ask to have a policy in place where people don't wear perfume or cologne, because the smell of that can -- you know, certain smells, and everybody is different with the smells -- that's going to cause something.

So, there's things that you may be doing that you don't even realize can hurt somebody that you're coming in contact with. So, I think that, yeah, I'll stop there, because I will ramble when I can't find my words, so cut me off.

ROBYN BENT: No, but think it's really important to hear from you, and I think that that really kind of emphasizes the importance of the qualitative research, to make sure that we're measuring the things that really matter to you, and

not the things that we think matter to you, that we're hearing from people. So, I think that it's very helpful to just kind of reinforce that we're kind of starting down what I think is a good path. And I know that as you provide feedback for the COAs and stuff, I think it's certainly clear that your participation is going to add strength to the process, so thank you.

And now, I'd like to just to Michelle to hear about the CDRH efforts underway. Thank you.

MICHELLE TARVER: Sure. And so, I think I've already alluded a little bit to how devices are different in terms of the level of invasiveness, as well as what they are targeting to do. We have a lot of research efforts also underway. Our focus has really been on the safety aspect for multiple devices, because surgery, in and of itself, is one thing, but the actual device being in place elicits some challenges, as well as gives some opportunities for patients that may not have been available with other treatments.

And so, we've got some work that we've been doing, particularly in the ophthalmic space, that

we're excited about, because it's not just developing a tool that can capture safety outcomes or how a patient is living with their condition, but also using different methodologic approaches to try to streamline that process. And we've been taking advantage of existing registry platforms. Right now, the IRIS platform is probably the largest registry in the United States. It sees about 40 million patients that are housed in that registry with various medical conditions, from the pediatric all the way to conditions that affect our older adults. And in that registry, they're using that as a sampling frame to identify patients that we can do the validation and work that's necessary to support a newly developed PRO measure, identify them, and deploy. And our clinicians are really excited about that in that space, because they want something that they can integrate into their clinical care, so we're exploring how we can do that.

And I do think that's the new horizon. As healthcare providers, I know increasingly, PRO measures are being mentioned in preferred practice

guidelines. So, it's becoming part of our daily care paradigms in many situations, for orthopedics, where we look at physical function; for joint replacement surgeries; or you're looking at intraocular lenses. I can't always measure some aspects of it. I need you to tell me the quality of the vision. And so, with that in mind, we are funding research that can help answer those questions.

The other thing we've been looking at is in rare diseases, particularly things where the tools we have currently bottom out. We can't measure visual acuity in a patient who has light perception vision. And I think this is something we have in common with the biologics group, where we see new tools or new treatments that are coming to market, or want to come to market, but we don't have good ways to measure how well they work. And so, not only are we looking at just the patient-reported outcome measures, but can we look at performance tasks that really do simulate their real-world experience so that we can see observable changes in that?

And so, we are working now with the

Foundation for Fighting Blindness, looking at retinitis pigmentosa, which is a rare condition, and figuring out ways that we can develop supportive information to help support those tools and help further device development processes, as well as I know they have an intention as well for it to be used in drug development programs as well.

And then, the last thing I'd like to talk about is, while we've alluded to it a number of different times, the digital health technology space is really an exciting and new space, but it does present some new challenges and questions that we don't have great answers to right now. Our team has been working. Our digital health is run out of our center, and they've been working with lot of different entities. We have a precertification program that is a partnership, basically saying, we can't keep up with the iterative cycles that happen with each app or online tool, but can we at least have confidence in the company that is providing those tools, and then evaluating that in the post-market, how well it's performing. But a lot of those tools incorporates PRO

measures as part of them, as well as sensor data and other things, and integrate that. So, better understanding how to do that, I think, is one of the areas that we're also interested in looking at in our center.

ROBYN BENT: That's great. That's really exciting and I thank you for sharing that with us, because I always feel like sometimes, I learn more at these public meetings than I learn form our internal meetings. I love to hear about things like that.

I was wondering now if we could kind of move into a little bit of a different sphere and maybe start with a question for people who are actually performing clinical trials. And I think that what I'd really like to hear about, I think it would be helpful to know is, if you've ever felt that you must use multiple different COAs that measure similar concepts in a clinical trial to satisfy different stakeholders, such as payers, regulators, or clinicians. And, if so, what are your thoughts on how this might be a more efficient process, and how can the clinical outcome

assessment's core sets help.

KANECIA ZIMMERMAN: I'm happy to start. So, the answer to your first question is, absolutely. We've talked a lot here about feasibility. I think almost every person on this panel has mentioned that in the last couple of minutes. And we should also think, really, about burden, burden on patients, burden on families, burden on sites. Clinical trials are extremely expensive. They are difficult to conduct, and it is a privilege for us to be able to conduct them and for people to be enrolled into our trials. And so, we really need to be extremely mindful about every step and every decision that we make, particularly in special populations, be it pediatrics or rare diseases, because we want those people to come back for the next drug that we're trying to evaluate, so we really, really need to be mindful of that.

I think one of the ways that we might be able to condense the multiple measures from multiple stakeholders is rally to get upfront consensus, which I think I'm happy, as a part of this

program, not only having our teams talk to the stakeholders individually, but also having the stakeholders talk to each other about the things that really are important, knowing that we all are invested in the same thing in the end, so how do we actually get there?

KATIE GOLDEN: Something that you just mentioned is making sure that you reach special populations, and so I'm going to go just a little bit further. Special populations, and I think you'd probably agree, also means during clinical trials, there are so many -- you need to try to have gender -- for migraine, there are actual gender differences in how women and men experience migraine. You need to have a wide range, depending on what it is you're studying. Migraine is not just a middle-aged white woman problem. Those are the women that actually seek treatment, but those who don't -- you know, migraine doesn't discriminate, so it is all age ranges, and it does affect every race and ethnicity.

And there are also areas, rural areas where, one, they may not have a doctor; two, if they

do want to and can participate in a clinical trial, getting them to the site to actually be there, actually I know that there's a few nonprofit organizations that help bring patients to those sites. But there are so many access barriers for patients outside of what they're able -- sorry, the word -- exclusions. Outside of exclusions, there are a lot of barriers for patients to participate. And they want to, and so, just, yeah, think about it.

And actually, not just think about it; it is incredibly important that their voices and their -- that they're included. And I just want to say thank you to -- I've not been in one, and thank you to all the people that have. Because, you know, I wouldn't be where I am today if people 30, 20, 10, 5 years ago weren't in a clinical trial. So, those people are -- they're real people. They have real stories, and they aren't a number. So, thanks to everybody who's done that, and thank you all who are in this field and doing this work, because I wouldn't be where I am today if you guys collectively hadn't pushed things forward. So, I'll leave it at that.

ROBYN BENT: Thank you. Did you want to --

R.J. WIRTH: You know, obviously, as sort of my role is often working with sponsors who are making the ultimate decisions about what goes in, but I do think we often see essentially multiple COAs asking the same questions about the same constructs. And I think part of it is the fear that, when the trial's done, they don't want to have forgotten something and go to an FDA meeting and say, oh, well, do you have this particular thing? And they go, oh, my God, now we need to do another study.

So, I think a lot of it's just sort of unease with, or not having the confidence that when they're done, they'll have everything they need. So, I think in many ways, this program -- and, again, what's different as opposed to a qualification program, where we have a measure that, all right, well you can feel confident about this measure, talking about a set of endpoints and being able to walk into and start a new trial, and understanding like, this set of things is what people are going to want to see

at the end of the day. And if you have something else that you're interested in, you could always add things if you can justify the added burden on the patients that are in your trial. But I think it will go a long way in sort of easing concerns that we're forgetting something.

So, I hope to see hopefully a lot less redundancy moving forward, and hopefully, that will make for more efficient clinical trials.

KATIE GOLDEN: Very quickly, R.J., I think that people who are in clinical trials, they may not get feedback after they're done. You know, did I get a placebo? Once it's FDA approved or at some point, you know, they invested a lot of their time that they didn't have to. You know, you want something out of them, but like, what do I get in return? You know, I would want to know how I compared to others, the other groups in the study. Did I get a placebo? And it's also very hard when somebody's in a trial and it is working for them, and then the trial ends and they can't get that medication anymore unless it is considered a lifesaving type of treatment. And

so, that is something that patients -- we want feedback, and we want to feel like we are involved and that our time is valued and it's not just one way.

ROBYN BENT: I think that's a very valid point that I think definitely bears significant consideration, because, I mean, I think all of us would expect that patients are making a lot of effort to participate in the trials, and we certainly appreciate their efforts.

So, moving on maybe, unless anybody had anything else to add for this question, I'd like to move on to maybe the next question, which is, can people on the panel discuss how core outcome sets can be maintained and updated to reflect new information, such as disease knowledge, measurement science, et cetera?

DEVIN PEIPERT: Yeah, I'll go ahead and start. So, I think one of the nice things about this program in particular is, I know that every grantee is enthusiastic about bringing in some of the updates in our ability to measure patients' function, health, pain, et cetera very well that have occurred, probably

since many of the COAs that are currently in trials were developed. We've learned a lot about how to do that, both in terms of efficiency, but as well as in terms of creating flexible measures that can adapt over time and can be added to or modified, as we learn about diseases.

I'm thinking about things like item response theory, which is a technical term, but it's an approach that allows us to add in new information, account for new information, expand the range of people we can measure over time, without changing fundamental or core aspects of the measures themselves, so that you can add in that new element over time when new information comes up. When you bring it into the real-world space, you may need a different level of physical functioning that you wanted to measure in your trial, without necessarily changing the underlying metric there and have scores that are comparable, and a standard and a benchmark that could be comparable over the course of time.

So, you know, the chance to bring that into this environment and into trials is really

exciting and I think will be really beneficial. And so, this is where I think we have an opportunity to shine in that regard.

R.J. WIRTH: Yeah, and I think something really nice about all three of the project teams here is that -- and I'm just going to speak for you. You know, I think we all sort of understand that these assessment tools have shelf lives. I think for a long time, somebody made something, you feel like, okay, "it's validated." It's rubber stamped, and you throw it out in the world, and it just goes forever, and that's just not the way assessment works, right?

They need to be maintained. We need to get new data. We need to make sure that, as the world changes, and as people's interaction with the world changes, that the assessments can also change with them. And with the tools that are available and I think the knowledge that are on all three teams, and the experience that are on all three teams, we can hopefully all develop assessments, or refine assessments, that puts it within a framework in which we can continually come back and sort of check in and

make sure that the assessments are behaving the way that they were designed to behave, that are updated when they need to be updated. And as our knowledge of a disease, or as people's way, how they interact with the world changes, that we can make those adjustments without losing the ability to interpret those measures, without losing the ability to have backwards compatibility.

And, like I said, I think one of the nicest things about -- you know, when I learned who the other grantees were is that I know them, which is nice, and I've worked with them before, and we've all collaborated. And I think we all have an understanding that, when we do this work, that it has to be something that's sustainable and something we can come back to.

How we do that, I think, is going to depend a little bit on sort of what we're doing. Hopefully, sponsors and users of the assessment tools will be willing to share data, even if it's not something we publish on, but to allow the scale developers to go in and do this maintenance work and

make sure that we don't lose the precision that we're developing from the tool. So, any sponsors out there, keep that in mind.

KATIE GOLDEN: Just, very quickly, it's a great point, R.J. I don't know how you exactly do this, but for some diseases, it changes over your lifetime. The way you experience it, for the patient, changes. Your body changes, and so, you know, chemical makeup -- and I'm not just talking about women. Everybody ages, and so, if there's a way early on to maybe include somehow those potential changes and figuring that out -- yeah. So, I think you raise a good point, and that's just kind of a nugget to think about.

ROBYN BENT: Thank you. So, at this point, we're going to move on to the audience question-and-answer period. We had anticipated that we would have lots and lots of audience questions, and so we kind of broke the question-and-answer period up first, so that if we had any patient stakeholders who wanted to ask questions, we wanted to make sure that we heard from them. So, at his point, if we have any

people who would self-identify as patient stakeholders who would like to ask any questions, please feel free to do so. Just come to one of the mics, either in the center or on the side of the room. And then, once we make it through the questions in the room, we'll turn to the internet.

Okay, so we will turn to the internet. Do we have any questions?

WOMAN 1: General Q&A.

ROBYN BENT: Okay, well, so it sounds like we're going to move straight to the general question-and-answer period, which is also wonderful. And so, if anybody in the room has any questions for our panelists, please feel free to come up to the microphones now and share your questions. Or, if you're feeling a little bit shy, we can start with the web questions and then move on to the people in the room.

KATIE GOLDEN: If you don't have questions, while I was doing -- I'm still doing the Facebook live, and so I have just one or two things that patients who are watching this right now have

said.

One gentleman said, I can't watch much longer because I'm in the middle of a seven-day migraine and he has to go out to get medication because he lives alone, and that's very, very painful for him, especially right now. And so, that is daily life. One, it was too long for him to be able to watch on the screen. Two, he's got to go get a medication, and it's extremely difficult for him to do that.

And I felt like there was one other. Let me just look real quick. Somebody else said that it's been 12 years and has had a continuous migraine. So, I just -- yeah, those two just really stood out. So, if anybody on Facebook is still watching, I'll try and look if you have questions as well.

MEENA SAVANI: Thank you for those insights. So, from the web, the first question, the COMET Initiative has a database published and ongoing core outcome sets. One of the purposes of this database is to avoid unnecessary duplication of efforts for core outcome set developers. Have you

considered registering this work for COS developers? And for FDA staff, would you recommend doing this?

R.J. WIRTH: This is R.J. from the MiCOAs. We're aware of it and have had some very brief interactions with that group. I don't think we've made it far enough along in this process yet -- I mean, we're just a couple months into the project itself -- to have a serious conversation about registering. I think we first sort of want to get our feet under us and get to a point in which we have a better sense of where we're going to end up. And then, from there, we'll hopefully have a little more breathing room where we can sit down and have a better understanding of sort of their role.

I'm not very familiar with their organization, but it's obviously something that we'll try to learn more about and look into. But I would love to hear from others who have had experience with them or from FDA and whether or not they have any experience.

LAURA LEE JOHNSON: So, we are aware of COMET. That may be part of the question. And I

think, also, there are a lot of other similar types of initiatives. They're all different, but kind of similar, as we were talking about, some of the COAs as well.

And one of the elements here for our focus was to make sure that that regulatory need was going to be attended to. And so, I think we would encourage folks to be looking at COMET and looking at some of these other organizations that kind of try to house what are these core outcome sets or other elements like that, so it is an organic process.

But it's also important to note that, you know, there are a lot of different ways to get after core outcome sets. But, also, one thing we're very interested in is the endpoint and making sure that for us, for our sister agencies that many times have different takes but are looking at those exact same clinical trials that are being run, just from a different perspective, and also the international regulators. So, I think a lot of these groups that have been involved with COMET have actually thought about this, but there is some variety.

ROBYN BENT: Okay, Meena, do we have another question?

MEENA SAVANI: Another question from online: How will FDA ensure that core COAs developed via this program are consistent with draft guidances and that review divisions are engaged such that the deliverables can support product development?

LAURA LEE JOHNSON: So, as our grantees can attest, they've been assigned officers. So, clinical said yes. After the review cycles were done, clinical had to agree, like we're still invested, we're putting forward our time and money. And, you know, a lot of the groups that are involved, like we're really short staffed, but we've all committed to saying that we think this is important enough, as a stakeholder, for the hours that our staff have to put in looking at the 30 different COAs coming in on different investigational new drug programs, can we lower that down, can we gain some efficiency, that we've made that commitment.

So, each of these programs has clinical staff involved, statistical staff involved, clinical

outcome assessment staff involved. We're pulling in a lot of different people, and so that is part of that mandate that we have to also make sure that, yes, we're interested. Everybody should know for your area what those guidances are; we're looking at that, so that level of what we also have for expectations as we're thinking about tools -- again, FDA has put a lot of not only our person power, but also our money, into this. And part of that is to make sure that we, at the end, to the best of our ability -- I mean, we're not doing the exact work, but to the best of our ability, that we can inform and make sure that we're seeing the type of evidence that we need in order to be able to use these tools longer term.

And we also have our sister centers that we then also pull in, say hey, are we in alignment? But most of our guidance is related to patient-focused drug development, clinical outcome assessments and the like. We do this as the three centers, so we align. You know, good science is good science, and so that's an important alignment that we all have. We have slightly different regs, but we

work that out.

R.J. WIRTH: As one of the grantees, I think that's one of the nicest parts about this program is the interaction. And I was surprised by just how much there is. Take that as you will.

But, no, seriously, we have monthly calls, we have meetings. And as Laura Lee was saying, it's not even just sitting on the phone with one person. It's a group of people that are all very interested in the project and how they turn out. So, we have the statisticians; for our group, we have many people from neurology; we have the COA staff online, so there's really a constant dialogue.

What's great about that, not just are we developing something that we can have confidence in at the end of the day that will be acceptable, but given the level of interaction and the frequency of it, we're able to course correct very quickly. You know, it's not waiting after two years, handing in a dossier, then kind of going, okay, now I have to go out and run another trial. You know, we can get on the phone and say, we're thinking about doing this,

and have them go, well, you might want to think about that more. Okay. And I think we're going to be able to get a lot more done in a much more efficient manner, given the level and frequency of communications, because we can make sure we're heading in the right direction in almost a continuous way.

ROBYN BENT: Thank you. Elektra, did you want to add something?

ELEKTRA PAPADOPOULOS: No, I think the areas that were initially put out with the RFA, with the announcement, were areas that have unmet need, and so we had buy-in even before going out with the announcement. And so, there was a very strong commitment to that.

ROBYN BENT: Okay, thank you. I think we have one more question from the web.

MEENA SAVANI: We have one more question, and I believe it builds off of a point Elektra had made earlier in the panel discussion. But, does the FDA expect that, once developed -- let's say in about five years -- the core concepts will then need to go through the DDT process for a specific

therapeutic area?

ELEKTRA PAPADOPOULOS: So, no, they do not need to go through the DDT process because they will be vetted, as was mentioned, throughout the development of the core outcome set with the agency using the multidisciplinary approach, using the good measurement principles that the agency has articulated. So, essentially, they will be -- our expectation and our goal is that they will meet the standards of fitness for purpose. It's just a different program, and so they would not need to go through that.

Now, they could. If they wanted, they could achieve qualification, but we don't see the need for that right now.

ROBYN BENT: Great, thank you. Do we have any questions in the room? It looks like we do.

WOMAN 2: I want to thank everyone for the commitment to patient involvement in this and the idea behind it. I saw a lot of great expertise listed on the slides who are part of the three programs being done.

One thing I don't think I heard as much about is expertise specifically in core outcome set development. I know some of the names on there do have it, but certainly COMET, ICHOM, some of these other places, they all use a slightly different methodology. I think I was reading an article yesterday in a review of common articles where just the definition of an endpoint in all of their review ranged across disease areas from 12 to 5,776 different endpoints that were used in these different disease areas.

So, a lot of researcher discretion on the definition of what makes an endpoint. Do you include the timing of it? Do you include -- and the idea of the concepts, whether or not you would have multiple assessments that would be considered in what's approved as opposed to one that's being recommended, those sorts of things are all highly dependent on the makeup of your committees and groups. Is there people who have that expertise and have been developing core outcome sets for many, many years to have those lessons learned from what they've done as

they've gone through other disease areas that are going to be part of the advising committees?

R.J. WIRTH: Well, this time, I won't speak for the other programs. I don't think we have anyone on our advisory committee or internally that has had a sort of career looking at core outcome sets. We do have a lot of experience in developing endpoint, endpoint models and developing assessments, for us, both within pharmaceutical and device, as well as in a lot of other areas. So, I think there's extensive experience and knowledge and know-how when it comes to thinking about endpoints, and then the conversations with the FDA to make sure that they're sort of in line with their expectations. And there's a lot of experience in developing assessment tools that we can have confidence map onto those endpoints.

But, for our group specifically, there is not somebody who has sort of had that career path. But, again, I don't know about the other ones.

DEVIN PEIPERT: No, this is Devin from NUCORE. Similar kind of statement, and I would echo something that Laura Lee said earlier where I think

the focus is on, what are the needs of trialists and people conducting trials and industry as they develop new products, in terms of the outcomes, whether that's an individual measure and a set of measures and combinations. I mean, I think some of that stuff comes through, in our experience, in different ways. But I think the focus is on growing out of that field and knowing what those experiences are from different perspectives, more so than maybe some of the career core outcome set folks.

WOMAN 3: So, I guess I'll third what Devin and R.J. are saying. I mean, I think that we would all be open to others' opinions, and we want to make sure that we're kind of covering the gamut of what's available. So, you know, we are certainly willing to listen and be collaborative in this space.

KATIE GOLDEN: I just wanted to add that, because there are three different groups and I think that the dialogue has already started, you need to use each other, because you all have different learnings. So, you know, just consult each other. You're all right here, so, yeah.

LAURA LEE JOHNSON: And so, I also want to point out that there is a lot of methodology. There are these different groups, as you mentioned, and others as well. Some groups end up focusing more on, when they say a core outcome set, they really start talking more about concepts. And one thing that has been a struggle for us at FDA and for other regulators is -- and it's something that, in fact, one of the reasons we have the qualification program was to say -- because, we need the exact tool, and so it's important to have the right concepts, so you've got to start there. But then, how exactly is it being measured? Because what may seem to be a small change can actually have major ramifications about how this is going to work in a trial.

And it's also, when we're trying to think about how do we gain even more efficiency, is thinking about, okay, how should it or should it not be used in a trial, and what's the endpoint? So, part of our discussion at the Guidance for Public Workshop for our patient-focused drug development -- that's tomorrow, if you want to spend another day watching

White Oak Live. But there also are certain elements that become restricted when you work for the federal government, and one is, for FDA and NIH, we actually have something called the BEST glossary. And so, it's Biomarkers, EndpointS, and other Tools. So, that is where the two organizations -- we're required by Congress, if I remember right -- to get together and have, like, this is the definition that you're going to use for certain things.

And so, while it is a living document and it's on the National Library of Medicine's website, there are certain parts -- and also, we have ICH. We have other guidelines and guidances that we do have to follow. And so, that is something that we are also taking into account as we're looking at and guiding these programs. But that's not to say -- and I think we've consulted with groups that in fact have that science of the core outcomes set, and not just -- so it's the S and not the A that we're looking at, and that's something that we will keep in mind.

But if people have thoughts, if you all have recommendations, as was mentioned at the

beginning, there is a docket to this meeting. But to say, you know, based on what we heard, we think these principles maybe aren't being adhered to. Can you please look at this? Here's who to contact, things like that. And so, you know, the substantive feedback we can get through the docket, and this is the other reason that we're having these meetings a couple of times a year is to say, hey, here's transparency of what's going on, where we are. Give us feedback. And that's not me here at FDA, but everybody here and all of their organizations to say, okay, what's the feedback you have for us?

Again, maybe there will be a little bit more course correction that happens if that's what's necessary, or for folks to say, hey, this is how you navigate these groups. It's an important feedback mechanism that we have and we encourage you all to use.

ROBYN BENT: Okay, I thank you all, and I want to take this opportunity -- we are kind of out of time for the panel conversation at this point, but I think it was a really informative panel. And at

this point, we're just going to move on to our closing remarks, because it has been an exceptional -- oops, I should have looked at all the slides we had.

So, we're going to move on to the closing remarks. It really has been an exceptional day and a wonderful way for us to kick off our COA grant program, by having this open public discussion. And I'd like to so much thank everybody for staying until the end. It's been very, very much appreciated, and I really would just like to say thank you to everyone who participated in person and on the web, and who have come from long distances; all of our panelists, our grantees, many of whom reworked their scheduled in order to be here today. We very much appreciate it.

For all of the feedback that we've received, it will be taken back, discussed, and very seriously considered. I also wanted to thank everybody here at the FDA involved in both the planning of this meeting and those participating in the grant program, not only the staff of the patient-focused drug development team who have worked

enormously long hours to prepare for this meeting, but also the clinical review divisions, the Clinical Outcome Assessment staff, and the Office of Biostatistics staff, CDRH and CBER, all of whom have committed to this effort on top of an already heavy workload. And I really think it speaks to how important we at FDA feel this effort is.

I want to share that our leadership, at the highest levels, has been extremely supportive of these efforts, and I want to quote Dr. Woodcock, our center director, saying that patients really are the true experts in their disease. And our hope is that, with the development of these core outcome sets, we can harness this expertise and incorporate it more sustainable into the drug development process.

I can highlight some of the key themes from the meeting, but I think it's really been done well up until now. So, we heard about all of the grant programs. We heard about the importance of incorporating diverse patient populations. We've heard and discussed a desire a little bit to include more digital health technologies, but we also need to

consider the impacts of those on the patients who will be using them. We heard from Katie about the burden that patients struggle with on a daily basis and the impacts that multiple things, including insurance, have on her treatment choices.

We heard that what we've been doing isn't always what we should be doing, but that we really need to think about why we're doing things. Some things we're doing great; some things we can improve. We've heard about all of the exciting projects related to COAs across the FDA and the importance of stakeholder involvement, and the importance of fitness for purpose and measurement excellence. And we've heard about how the core sets will continue to evolve as disease knowledge and measurement science changes.

So, again, just a resounding thanks to everyone who participated, and I would like to take this opportunity to remind you that, if you were unable to ask a question or if you have feedback that you'd like to share with us, the public docket will be open until January 6th. Please submit your comments.

We hope to see you tomorrow at the guidance (indiscernible) workshop, and thank you very much. Please, safe travels home.

(Whereupon, at 11:49 a.m. the proceeding was concluded.)

CERTIFICATE OF NOTARY PUBLIC

I, MICHAEL FARKAS, the officer before whom the foregoing proceedings were taken, do hereby certify that any witness(es) in the foregoing proceedings, prior to testifying, were duly sworn; that the proceedings were recorded by me and thereafter reduced to typewriting by a qualified transcriptionist; that said digital audio recording of said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

MICHAEL FARKAS

Notary Public in and for the

STATE OF MARYLAND

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I, SONYA LEDANSKI HYDE, do hereby certify that this transcript was prepared from the digital audio recording of the foregoing proceeding, that said transcript is a true and accurate record of the proceedings to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

SONYA LEDANSKI HYDE

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