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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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MEDICAL DEVICES VIRTUAL PUBLIC MEETING - PATIENT-REPORTED OUTCOMES (PROS) AND MEDICAL DEVICE EVALUATION: FROM CONCEPTION TO IMPLEMENTATION

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Via Videoconference

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M E E T I N G

(8:00 a.m.)

DR. CALDWELL: Welcome to the Center for Devices and Radiological Health Public Meeting - Patient-Reported Outcomes and Medical Device Evaluation: From Concept to Implementation.

My name is Dr. Brittany Caldwell and I am a Senior Health Science Advisor in the Office of Strategic Programs and Technology Innovation, Center for Devices and Radiological Health.

Before we get started with our formal program for today, I will explain a few logistical and housekeeping items. Your webcast view should contain two smaller windows, one with our speaker view and the other with the presentation slide. By clicking on one of the smaller windows, you can enlarge it.

We will be using the CrowdCompass AttendeeHub app throughout this meeting. The app, and its corresponding online event guide accessible through a web browser, will allow for live question and answer during sessions in addition to housing our agenda for today, speaker bios, and additional PRO resources. To ask questions from the app, scroll to the "Live Q&A" header in the session. Tap submit a question now, type your question, and tap submit when you're finished. Questions can be up to 250 characters. You can ask your question any time between an hour before the session starts and a half hour after it finishes. To ask questions from the webcast window, click on the thought bubble icon on the session page. Type your question into the question interface and hit submit.

To access media content, please download the app by going to your respective app store and search for "CrowdCompass AttendeeHub." Once you download the app, you can search for the event, Patient Input in Medical Device Studies. You can then download and begin using the event app. Alternatively, you can also access the app from a computer by

visiting the URL crowd.cc/ptinputmeddev2020. That's crowd.cc/pt -- for patient -- inputmeddev2020. Once you have accessed the meeting, you can choose to log in. If you log in to the app or online event guide, you can access additional features to enhance networking by joining the attendee list, messaging fellow attendees, posting on a discussion board, and taking notes during the meeting. To log in, go to the bottom of the screen and click on the profile tab, enter your first name, last name, and e-mail. You will be e-mailed a verification code that can be entered on the next screen.

A bit of additional housekeeping information for you. All attendees will be muted throughout the entire webcast. The FDA studio will be monitoring for any technical problems throughout the day and will work to address problems, should they arise.

We encourage all speakers to ask questions and hope you will find the meeting engaging and informational. To ask a question, you can click the bubble icon in the webcast window or use the live Q&A feature in our app. Please note, due to time constraints, some questions may not be answered during the session.

Today we have a packed agenda with five exciting sessions for you. After our introduction, we will start our day with the session on the Importance of patient-reported outcomes, followed by a panel on incorporating PRO instruments in the healthcare system. At noon, we'll take a 30-minute lunch break. In the afternoon, we will start with the panel session on bridging PRO instruments with examples of ensuring relevancy across demographics, followed by a panel on developing PRO instruments when one does not exist. At 2:30 Eastern time, we will take a 15-minute break before an exciting panel discussion on multistakeholder collaborations for instrument development. We'll end the day with closing remarks from Dr. Michelle Tarver, Director of the Patient Science and Engagement Program at CDRH.

And now, I'd like to welcome Dr. Bill Maisel to give introductory remarks. Dr. Maisel

is the Director of the Office of Product Evaluation and Quality at the Center for Devices and Radiological Health and is the Center's Chief Medical Officer.

Dr. Maisel.

DR. MAISEL: Great. Well, thank you so much and good morning. On behalf of FDA and the Center for Devices and Radiological Health, I'd like to welcome you to today's virtual public meeting on patient-reported outcomes and medical device evaluation.

Patients are at the heart of what we do, they are at the core of our mission. All of the work that we do to support medical device development, evaluation, and monitoring is done with patients in mind. We cannot over-emphasize the importance of including the patient voice during the design, evaluation, and monitoring of medical devices, including the collection and use of information directly from patients about their medical condition and health status.

We've taken numerous steps to ensure that patients remain at the forefront of our decision making. The patient's voice is so important that in 2016 and 2017, we initiated our Partner with Patients Strategic Priority to promote a culture of meaningful patient engagement by CDRH and we established the Patient Science and Engagement Program.

It's important to us that our staff are not only scientists and engineers and clinicians and statisticians and consumer safety officers, they are also mothers and sisters and brothers and parents, they are patients themselves and caregivers, and we have made a point of ensuring that nearly every single CDRH staff person, particularly those that review medical product submissions, engage in meaningful patient interactions. The patient voice is so critical to the work that we do.

We created the Patient Engagement Advisory Committee, or PEAC, FDA's first advisory committee focused exclusively on patients. We formed it to ensure that patients' needs and experiences are considered in FDA's work. We've held annual meetings since

2017 on topics such as patient-generated health data, patient perspectives on cybersecurity in medical devices, and patient engagement in medical device clinical trials. In some cases, the feedback we received at the advisory committee has led to new or modified policies, such as when we issued draft guidance last September on patient engagement in the design and conduct of medical device clinical investigations. The next meeting of the Patient Engagement Advisory Committee is scheduled for October 22nd and will focus on artificial intelligence and machine learning.

We engage with patients as part of our daily business at CDRH. You may have attended one of our workshops or public meetings, like the one today, where patients are participants not only as attendees, but also as speakers and panelists. Patients are part of the development teams for our regulatory science research studies and offer their perspective and expertise as we work collaboratively to identify and develop solutions to challenging issues. Patients also take time out of their lives to share with us what it's like to live with their condition through our town hall meetings and office-level patient engagement events. Our most recent one was about 3 weeks ago and focused on how patients interact with digital health technologies like wearable devices.

Patient input is important to us at CDRH across the total product life cycle. As you may know, in 2019 CDRH reorganized its structure to implement our Office of Product Evaluation and Quality. We combined our pre-market programs and our post-market program functions along product lines, enabling us to seamlessly leverage knowledge, including patient perspectives, across the total product life cycle.

We've also taken steps to better incorporate the patient's voice into our policies and decision making through expanded use of patient-reported outcomes. PROs are particularly important because they are measurements based on a report that comes directly from the patient about the status of their health condition. The patient's response is not amended,

it's not modified, it's not interpreted by a clinician or anyone else. PRO measures can be used to rate pain intensity, measure the severity of visual symptoms, assess the effects of a treatment on a patient's activities of daily living, or measure a number of other important outcomes meaningful to patients.

Our staff see PROs and other clinical outcome assessments in the many submissions they review with clinical studies and, in fact, over 50% of submissions we review have consistently contained patient-reported outcomes.

We've worked to transparently communicate available and relevant patient perspective data considered during our review of submissions. We've consistently provided this information in our externally facing summaries. We've also issued a report on PROs containing case studies and published an associated compendium to assist in the selection or development of appropriate PRO measures.

But our work does not end there. Just last month we released a draft guidance document focused on the principles of PRO instruments used in medical device evaluation. The guidance is intended to help increase consistency and transparency around PRO instrument use. The document is open for comment until October 30th and we'd welcome your feedback and comments on the document.

Additionally, we're working with other medical product centers to bring the patient voice to bear in medical product evaluation through our involvement in the Patient-Focused Drug Development guidance series.

I provided a whirlwind tour of some of the many patient-focused activities that are at the heart of what we do. Hopefully, you agree that capturing the patient's voice in the work we do is of paramount importance. As you'll hear throughout the day, we're working as a Center to outline approaches to create efficiencies in the development of reliable, well-defined, and relevant PRO instruments while at the same time applying a least burdensome

approach. Today you'll be hearing examples of PRO use across different product areas. Many of these examples would not have been possible without close collaboration between government, patients, industry, and academic partners. PROs are one important way that we can capture outcomes that are important to patients. Future medical devices addressing patient needs can be enhanced not only by innovative product designs, but also through use of innovative clinical study tools, such as PROs, that capture the patient's voice.

We're grateful for your attendance and participation in today's public meeting and we look forward to a productive day. Thank you.

DR. CALDWELL: Thank you, Dr. Maisel, for the introduction to our discussion on the importance of patient perspective in medical device review.

I'd like to now introduce our first session this morning, the Importance of Patient-Reported Outcomes. We will first hear from Mr. Paul Conway, the Chair for Policy and Global Affairs for the American Association of Kidney Patients, on the patient perspective of the importance of PROs. We'll then hear the industry perspective from Dr. Kendra Hileman, Vice President and Global Head of Clinical Research and Development at Alcon. Finally, we'll hear the regulatory perspective from Dr. Fraser Bocell, a clinical outcome assessment reviewer at CDRH, and Dr. Christina Webber, a biomedical engineer, on the Partnerships to Advance Innovation and Regulatory Science Team at CDRH.

Paul, I'll hand it to you to start off with the patient perspective.

MR. CONWAY: Great. And thank you very much. My name is Paul Conway and I serve as the Chair of the Patient Engagement Advisory Committee of the FDA, and I'd like to thank the FDA for this session today and tell you that, as a patient, this is one of the most optimistic topics, in my opinion, because the closer you bring government to people and especially to patients, the better policy you get, and I don't think there's any better example of that than what FDA's been able to lead on over the past many years.

I think it's important to start the discussion with what did the world look like before patient-reported outcomes became embedded into federal policy and federal decision making. And really, the landscape at that period of time was much more patchwork in terms of where the interest rested to incorporate those types of concerns. You would have different sectors of professionals within the government or within industry who were very interested in this, but it really was tucked away, a patchwork approach to patient-reported outcomes. I think people understood intuitively that they could get data, but until it was formalized, it was very much one of those situations where patients had to be real fighters to get their perspective across.

Here you see a graphic that our organization has used quite frequently when patients have felt like this because, at the end of the day, patients know that their experience matters, but trying to communicate that to professionals is often very hard. So, what you had, sometimes, was a situation where people who were not patients would represent the patient perspective at the table. Some of these would be lobbyists, some of them would be special interests. And patients themselves, I think, would get very frustrated about this because they were trying to find their own voice, but most importantly, an avenue that was available to them. Next slide.

So in this next slide what you'll see is an interesting kind of situation that I think, if you're a patient, people have been involved in. You're sitting there and you hear a lot of different medical terms and the science behind how a therapy is being applied to you may be discussed, but what you might want to communicate and how you feel, as a unique insight, you know it matters to you and you have professionals that know it matters to you but you just have to say sometimes, “well, wait a second, this does not make me feel good, this does not make me more effective, this does not let me go back to work; in fact, it's making me feel sicker” or “hey, by the way, I've noticed this, I think it's important because

other patients I've talked to have seen it as important." So you have a situation now where PROs matter not just to patients, I believe, but also to the professionals who are treating them, and what has happened here is with the advent of PROs introduced into the policy structure, you now actually have validation that patient insights or what patients thought may actually be correct and they had greater value and so now you have patients and professionals working together to advance this to the FDA.

If you take a look at the bottom point here, I think it's probably the most important because I think, as patients in general, I think they're very idealistic. If you suffer, your idealistic notion is you don't want somebody else to have to suffer and so your instinct is to try to help improve the lives of others. As PROs in the policy structure for those that are developed, there's a better avenue to express your idealism and to be involved to try to help those who have not suffered and try to intervene earlier and try to get your insights there so that perhaps it can impact people in a much more positive way, people that you will never meet. And that's, I think, one of the most promising things about PROs. Next slide.

So, in this next slide, if you take a look at the language on the slide behind us, this is Secretary of Health and Human Services, Alex Azar, if you take a look at that it says, basically, how to change how government does business. And this has -- the introduction of PRO data and putting patients at the table, has fundamentally changed the terrain for policymakers, not just because it gives them substance and truth to the fact that they're trying to do more patient-centered policies, but what it has done for the government, I believe, and for industry, is it has shown a very clear path that there are clear expectations, a clear set of guardrails, for how this data will be incorporated. What it does is it eliminates the random approach or the patchwork type of approach to policymaking and the expectations for industry and has made it much clearer that not only are the patient

insights valued, but they are valued as a matter of policymaking. And when you elevate an element like that into the policy process, it has very dynamic changes that it triggers and we'll take a look at those here in a second. Next slide.

You'll see here on the train that at the same time that the FDA was advancing patient-reported outcome data, other forces on the larger terrain of policy were beginning to make changes. But when this PRO type of effort began and unique patient preference insight data was also being collected, it introduced a new era of research, the science behind a new generation of scientists and medical professionals who are interested in capturing unique patient insights.

You had other agencies, that had been somewhat moving in this direction, began formalizing their own processes for bringing patients to the table. Some of the really tremendous ones are the National Institutes of Health with the Kidney Precision Medicine Project, DoD, HRSA, CDC, CMS, all of these agencies have formalized their processes because they know that on the FDA side of the operation, these are valued, these have been validated and they are now part of official decision making and deliberations across the product development life cycle.

You have the Patient-Centered Outcomes Research Institute that is funding research. Our organization happens to have been involved in all 17 of the studies that PCORI has done on kidney care and kidney innovation.

But what you see is this critical mass now across the landscape, not just in government, but also among stakeholders and this is very important. You have major organizations like the American Society of Nephrology also bringing patients in, having them be part of clinical journals, having them be part of planning for Kidney Week, the largest kidney meeting in the world; we have patients at the table presenting their perspectives as unique and talking about how they're impacting innovation, really transformative things

that have happened in the past 4 or 5 years, again, because the driver for this is a federal agency that validated the insights and validated a new process. Next slide.

So in this next slide, this is just an example. The American Association of Kidney Patients is merely one stakeholder on the landscape in kidney care, but as companies understood that this is a formal policy now of bringing patients in and that they, in turn, need to reflect unique patient insights in their data and that there are PROs, in our organization, what we've seen is over 128 companies in the past 24 months coming to us and asking about these types of items and how they can involve patients in study design, trial recruitment efforts, unique patient insights, roundtables, because they're all trying to figure out for their own end in how they fit for product development, how they're going to harvest patient insights from kidney patients. Very optimistic type of thing.

At the same time, we've had over 240 contacts with government officials across the full landscape of the federal government talking about PROs and how patients are now at the table.

So, in terms of a fundamental shift, it's extremely optimistic for patients, it's gone well beyond one agency. And so, inside a stakeholder organization like ours, that has also driven change. Next slide.

So in this next slide what you'll see is for our organization, we had to completely restructure what we were doing. We created brand new centers. In this slide that you're taking a look at, you see the slide for the Center for Patient Education and Research and in that division of our organization now, it is specifically set up so that we have our databases, that we have our national patient ambassador program working in a manner that we can segment our database, target down to the types of patients that a company may need to talk to, and we can alert those patients that their unique insights are now needed, whether it's from industry or from the federal government or respective federal agencies or in

universities and researchers in the new science of PROs who need their insights. But we completely went back to the drawing board for how we work, you can take a look in the next slide. What we did then is we migrated some of the more traditional advocacy activities and engagement activities that we do and made those further refined so that when we go to patients we can clearly tell them look, this is on the research side, this isn't working with government and industry, and some of these other activities that we're doing are more on the traditional advocacy side of legislation or media and that type of stuff, but there's been a very clear delineation now of duties and responsibilities along this line. Next slide.

And this is probably the most optimistic thing, and it's this issue of idealism in what PROs offer to patients and to professionals and to industry and government, I believe, which is if you ask patients that if you could capture their insights and apply their insights, would they participate with government or would they participate in efforts if they knew that those insights that they had would impact and improve the lives of other patients, and you can take a look at the data right there.

We ask this question every year and it's consistently gone up because patients feel like their voice and their life experience and their medical experience matters, it has impact, it means something, not only to those who regulate and who end up making payment decisions, but it will matter to other people, and I think that's probably one of the best things that you could do as a patient is to feel like you've gone through it, you've walked the walk, and your suffering matters because others won't have to.

And again, I'd like to thank the FDA because they have really moved forward and on one last note, I say this to all of the folks at FDA, but if FDA could set up a workshop and train every other federal agency and state agency on how to bring patients to the table in a meaningful and substantive way, I think they could start a side business and do quite well.

Thank you very much, I appreciate the opportunity. I'll throw it now over to Kendra and she'll begin her session. Thank you.

DR. HILEMAN: Thank you, Paul. And I'm here today to talk about the importance of patient-reported outcomes from the industry perspective. Next slide.

So, the objective of clinical research is to evaluate the safety and effectiveness, in this case, of a device. Many safety and effectiveness endpoints can only be evaluated by asking the patient about their experience. Doctors can evaluate the patient to determine the science of health status, but often patients are the only ones who can identify the symptoms they're experiencing.

Patient symptoms can be volunteered by the patient to the health professional, but elicited patient symptoms in the form of carefully worded questions consistently asked of the patient can be even more informative to a product's safety and effectiveness. Next slide, please.

So, my career has been focused on ophthalmology, so I will use ophthalmology as an example regarding the importance of patient-reported outcomes.

Dry eye is a condition where patient-reported outcomes are critical in evaluation of the efficacy of drugs or device effectiveness. A doctor can use standardized scales and measurement devices to evaluate signs like redness, corneal staining, tear production, osmolarity, osmolality. But, the key symptoms of dry eye can really only be evaluated through the patient-reported outcome measures which can obtain patient input on things like redness so the doctor can see if the patient's eyes are red and measure it on a standardized scale, but the patient also knows their redness across a wider time period than just the office visit. The patient is the only one who can know if their eyes are stinging or burning, if they experience eye fatigue throughout the day, or if they experience sensitivity to light. Next slide, please.

In ophthalmology we can find another example that really very clearly illustrates the differences in responses that can be obtained with evaluating the rates of volunteer symptoms versus those evaluated through a patient-reported outcome measurement tool.

We know that when patients receive presbyopia-correcting IOLs, they can experience negative side effects in the form of halos, starbursts around lights or, glare, in addition to many other symptoms that can occur.

These data were taken from a summary of safety and effectiveness document on an extended depth of focus intraocular lens for presbyopia correction. You can see that the responses for these common symptoms of halos, glare, and starburst were from 2 to 20 times higher when asked through a directed patient-reported outcome measurement tool than they were when the patient was asked an open-ended question, "Are you having any difficulties with your eyes or your vision?" This highlights the importance of direct, carefully worded questions in evaluating patient symptoms in the form of a validated patient-reported outcome measurement tool. If you'd go to the next slide, please.

So, we've seen why the use of patient-reported outcome measurements are critical to determining the safety and effectiveness of a product, but the real trick for industry is how to pick the right tool for the job.

First, it's important to understand and review the published literature to determine what tools may already be available. Is the available tool actually fit for purpose? Does it measure the appropriate concept? Are you looking to measure the frequency of an event or the severity of an event, or how much it impacts the patient? Does the validation work for a patient-reported outcome measurement cover the patient population needed for the new study? For example, were the patient demographics and the disease severity similar to what was intended for the study that you wish to conduct? So in the validation work did they cover the right population, the right disease severity that you want to study in your

new trial?

What clinically relevant differences are you trying to detect? This is one of the hardest questions that we answer, we try to answer and address in industry. Is the tool sensitive enough to detect the difference that you're looking to detect?

Are there key concepts in the tool that the tool actually does not cover adequately? Maybe your new device might have a potential new side effect that the other devices for which the tool was developed didn't have. Maybe it has a new potential advantage that the tool can identify that the previous products did not have.

What validation work is available to support the tool? How many studies have been used, has the tool been used with? How refined is the instrument, how many iterations has the instrument gone through? And, is that validation work published? Next slide, please.

So, I also have a few words of advice to offer based on my industry experience in developing patient-reported outcome measurements. And by the way, I also sit on the American Academy of Ophthalmology task force to develop a new patient-reported outcome tool or measurement in ophthalmic devices.

First advice is to engage a professional specializing in the development of patient-reported outcomes. This can be a lengthy, complex, expensive endeavor to develop or even use an existing PRO. And this is a unique area where expertise and understanding of a field in the FDA guidance is critical. Don't try to just do it yourself, engage an expert.

The method of delivery is important, not just the words. If a tool was developed for paper delivery, but you prefer an electronic delivery, then many of the development and validation steps may need to be repeated.

Listen to the patients. Let the patient be your guide. As you have already heard, direct patient input is critical to understanding how they describe symptoms and the impact of their disease on their life.

And be ready to iterate. This is not a one-and-done process. Every time a patient-reported outcome tool is used in a study, it provides really another opportunity to refine that instrument, to evaluate its effectiveness and improve that measurement tool.

Lastly, talk to the FDA throughout the development process to align and obtain feedback. They have experts in this field that can be very helpful in providing guidance and watch-outs.

Now, speaking of FDA experts, Fraser Bocell is up next to talk about the regulatory perspective on the importance of patient-reported outcomes.

Fraser.

DR. BOCELL: Today you have heard about the importance of including patient voice in the evaluation of medical devices from a patient, Paul, and from the medical device industry, Kendra. I'm Dr. Fraser Bocell, a psychometrician, and I'm going to be sharing the regulator's perspective on the importance of patient-reported outcomes. I'll discuss current legislation that encourages the structured collection of patients' perspective. I will also briefly cover FDA policies around developing, modifying, selecting, and using instruments to measure the patient voice in medical product evaluation. At the end, I will leave you with some key takeaways.

The 21st Century Cures Act was signed into law on December 13th, 2016. It is designed to help accelerate medical product development and bring new innovations and advances to patients who need them faster and more efficiently. The law builds on FDA's ongoing work to incorporate the perspectives of patients into the development of medical products and in FDA's decision-making process. Patient experience data includes all information like patient perspectives, priorities, needs, and experiences with their condition or medical product. Cures enhances our ability to modernize clinical trial designs, including the use of clinical outcome assessments, which will speed the development and review of

novel medical products.

Patient experience data includes clinical outcomes assessment of which there are four types. They all provide subjective information about how a patient feels, functions, or survives, and it is important to note that they differ by the reporter.

The 2009 guidance on patient-reported outcomes applies to all the medical product centers. It provides recommendations about the evidence used to support a PRO instrument-based labeling claim. However, it does not directly address other potential uses for PRO instruments within a clinical study, which we will be discussing at today's meeting. It is also limited to one type of clinical outcome assessment, patient-reported outcomes.

To address the 21st Century Cures Act and FDARA 2017, as well as to further the Agency's efforts to include patient experience data, FDA's Patient-Focused Drug Development committed to drafting new guidance documents that clearly spell out the regulatory perspectives on the development and use of clinical outcome assessments. The guidance series is meant to cover how stakeholders can collect patient experience data and intends to facilitate the advancement and use of these types of instruments. This guidance series will eventually replace the final guidance on PROs issued in 2009 and will cover all types of clinical outcome assessments.

The first two guidance documents of the series cover how to collect comprehensive and representative input, as well as the appropriate methods to identify what is important to patients. Guidance 1 was issued as final in June 2020 and Guidance 2 was issued as draft last year. The last two guidances in the series will focus on how to select or modify fit-for-purpose clinical outcome assessments and incorporate it into clinical studies. Guidances 3 and 4 are being drafted, and while we are participating in the development of the guidance documents, the regulations and principles specific to CDRH, such as the least burdensome principle, led us to develop and issue a draft guidance.

The unique challenges to medical device development, along with the different regulations and policy, led to the development and posting of a draft guidance in August 2020. The draft guidance highlights principles to select, develop, modify, or adapt patient-reported outcome instruments for use in medical device evaluations. The comment period is open through October 30th and we would welcome your feedback on this quick read. This guidance is in draft and therefore not current policy. However, I would like to share with you some themes from the draft guidance.

One point that is emphasized in the draft guidance is the importance of using a PRO instrument in a clinical study that is fit for purpose. This fit-for-purpose approach is meant to provide flexibility in generating the evidence used to support a PRO instrument. The concept being measured, the intended use of the PRO instrument, and its role in the protocol and statistical analysis plan, will help determine the level of evidence and therefore, flexibility.

There are a few best practices described in the document that could be implemented to make the process of selecting, or using, or modifying a PRO instrument for a specific use within a clinical study more efficient. I will talk about each consideration.

At CDRH, patients are at the heart of everything we do. While PROs may be included in clinical studies, they do not always reflect concepts that are important to patients. We encourage sponsors to focus on the concepts that are relevant and impactful to patients. The document details that the instrument should not only be patient focused, but also designed to be easily understood by patients and provide response options that make sense. One approach to accomplishing this goal is to work with patients in the development of these instruments. Whether you are selecting or modifying an existing instrument, developing a new instrument, using a PRO instrument in a pre-market study or as post-market surveillance efforts, our draft guidance document recommends that you clearly

define the role of the PRO in your protocol and statistical analysis plan.

As discussed during the tri-center public meeting held in December 2019, the International Council for Harmonization or the ICH guideline E9, "Statistical Principles for Clinical Studies" and the R1 addendum on estimands, could be a useful resource to inform how to define endpoints in clinical studies. It may also be beneficial to leverage existing appropriate instruments and the associated evidence to measure a given concept in a clinical study. We encourage you to consider all the literature, not just the validation papers associated with a particular PRO instrument.

If, after looking for an existing instrument, you discover that you need to create a new PRO instrument, we encourage you to consider efficient development approaches. For example, you may want to use alternative platforms or work with other interested parties during the development process. PRO instruments are increasingly incorporated into clinical practice along with ongoing efforts to develop coordinated registry networks to help generate real-world data. Developers could explore generating validity evidence by collecting the evidence during the conduct of ongoing studies, as well as during the planned development cycles of a device. Additionally, collaborations allow for the pooling of resources, not only financially but also in terms of access to expertise and key stakeholders, such as patients. These collaborative products could lead to a PRO instrument that could benefit many interested stakeholders.

Developers may choose to submit their instruments for review in the Medical Device Development Program. An MDDT is a method, material, or measurement used to assess effectiveness, safety, or performance of a medical device. Each of the different types, including COAs, are scientifically validated and qualified for a use in a specific context of use, not for all uses. The qualification is the FDA's conclusion that, within the context of use, an MDDT has a specific interpretation and application in medical device development

and regulatory review.

The MDDT program helps promote efficient medical device development. It fosters innovation, encourages collaboration in the device ecosystem, and promotes efficiency in regulatory review. We encourage both PRO and medical device developers to engage with the MDDT program.

As I wrap up my talk, I want to ensure that I emphasize a few points. The best practices outlined in the draft guidance are meant to ensure relevant, reliable, and sufficiently robust PRO instruments are developed, modified, or adapted using a least burdensome approach. The use of PRO instruments is voluntary if other means for measuring your concept of interests exists. Lastly, the MDDT program is available to help create efficiencies in medical device development and evaluation, and we encourage you to consider this mechanism.

I'll leave you today with some key principles described in the draft guidance. First, it is important that you clearly define the concept being measured. How is it being interpreted? Make sure it is clear how the PRO or COA instrument is being used in the clinical study. Clearly illustrating how the PRO is used in the clinical study helps to define what conclusions can be drawn from the data. Collect and present evidence that shows the instrument is fit for purpose. And finally, clear, effective, and appropriate communication of the results is critical to better inform healthcare providers' and patients' decision making.

Thank you, and I'll now turn it over to my colleague, Dr. Christina Webber.

DR. WEBBER: Thanks, Fraser. So far you've heard why patient-reported outcomes or PROs are important, as well as how they can be included in the evaluation of medical devices from the patient, industry, and the regulator. I am Dr. Christina Webber, a Staff Fellow with the Partnerships to Advance Innovation and Regulatory Science team at CDRH and I'd like to give you some insights into the trends we are currently seeing in regulatory

submissions.

As Fraser mentioned, CDRH has recently released a draft guidance on PRO use in the evaluation of medical devices, which is currently available for public comment. We encourage the inclusion of fit-for-purpose PRO instruments in medical device evaluations where appropriate.

PRO instruments facilitate the systematic collection of how patients feel, function, and survive as valid scientific evidence to support the regulatory and healthcare decision-making process. By integrating patients' voices throughout the total product life cycle, concepts important to patients can be considered in medical device pre-market evaluation, as well as post-market surveillance.

Let me emphasize that including a PRO in a clinical study is voluntary and should be considered in appropriate applications.

PRO instruments may be used to help define study eligibility or measure study endpoints. These endpoints can be primary or secondary, safety and/or effectiveness endpoints, and can be either standalone or part of a composite endpoint. During the rest of my presentation, I will be looking at how PRO instruments have been used in pre-market submissions and as well in the post-market.

My first analysis focuses on the FDA's publicly accessible premarket approval, also called PMA, database which includes all original and panel-track PMAs. I analyzed all public facing summaries for PMAs approved from October 1st, 2014, which is the beginning of fiscal year 2015, through September 30th, 2019 or the end of fiscal year 2019. I will be abbreviating this time period as FY15 through FY19 during the rest of my presentation.

The PMA database contains the Approval Order and Summary of Safety and Effectiveness Data, also called the SSED, for each PMA. I examined these documents and manually extracted any information pertaining to the use of PRO instruments, including if a

PRO was used, what specific PROs were used, and how each PRO was used, for example, to determine study eligibility and/or the endpoint positioning of that PRO instrument.

CDRH has consistently seen PRO instrument inclusion in approved PMA submissions since FY15 fluctuating between 40 and almost 70%, as shown by the blue bars on this graph. On average, half of all PMA submissions approved in FY15 through FY19 contained at least one PRO instrument. These instruments ranged from universal health-related quality of life measures to disease- and device-specific measures.

Please keep in mind that PRO instruments may not be relevant to every regulatory decision and, therefore, may not be included in all medical device submissions. In fact, many diagnostic devices evaluated by the Office of Health Technology 7 often collect clinical specimens or laboratory samples to evaluate their device rather than conduct clinical studies. Since PRO instruments would not be appropriate in these instances, I excluded medical devices on the pathology, radiology, microbiology, toxicology, immunology, and molecular genetics advisory committees from my analysis. As a result, PRO instruments in PMA submissions increased to range from 50% to almost 70%, as represented by the orange bars on this graph.

Please note that the percentage of approved PMAs containing PRO instruments depends on the types of devices submitted and evaluated in a given fiscal year. Novel and emerging technologies may impact these trends we see in the future.

Looking further into how PRO instrument use varies by medical device type, this graph presents PRO use in approved PMAs by Office of Health Technology, called OHTs, beginning in FY15 and going through FY19. Notably, PRO instruments are included in all approved PMAs from OHT6, our office that evaluates orthopedic devices. Additionally, we also see high PRO instrument usage in submissions from the OHTs 1, 3, and 4.

For some fiscal years, the percentage was zero due to the following reasons: no

PMAs were approved in that year from the OHT, or perhaps no clinical studies were included in the PMA submissions, and/or PROs were not included in the approved PMA submission.

As I mentioned on my previous slide, PRO instruments may not be relevant to every regulatory decision and, therefore, may not be included in all medical device submissions, which partially accounts for the low percentages of PRO inclusion observed in OHT7.

This pie chart presents a breakdown of how PRO instruments have been used in approved PMA submissions FY15 through FY19. Notably, approximately 41% of PRO instruments used in approved submissions were not categorized as a specific type of endpoint. This presents an opportunity to clarify beforehand how the PRO instruments will be used and analyzed in the clinical study. Specifying the endpoint positioning for the PRO instrument, defining the endpoint, and developing a clear analytic plan can help strengthen inferences drawn from the collection of PROs.

To illustrate further how appropriate PRO use depends on device type, I've included some examples of device-specific guidance documents and FDA-recognized consensus standards that describe how PRO instruments can be used in the evaluation of urologic, ophthalmic, neurologic, and orthopedic devices. Standards are documents established by consensus and approved by a recognized body that outline an agreed-upon way of doing something, like the necessary testing of a medical product and how to conduct that testing. For medical devices, the clinical annex of the example standards listed on this slide contain details of clinical study design that mentions the collection of PROs and, in some cases, names a specific PRO instrument. Let me share with you one example in greater detail. The FDA guidance for devices treating benign prostatic hyperplasia, or BPH, specifically calls out that the primary effectiveness endpoint should be one that is clinically meaningful and should fully characterize the effect of treatment. It can be challenging to find an

effectiveness measure that is objective and yet repeatable and also meaningful to patients and relevant to their reasons for seeking treatment.

This is where PRO instruments prove helpful. They can measure concepts that cannot be collected any other way, except directly from the patient. This guidance document recommends that the primary effectiveness endpoint be based upon the improvement in one of two PRO instruments that assess the symptoms associated with BPH, compared to baseline.

Similar to pre-market studies, PRO instruments may be used to complement measures when evaluating the continued safety and effectiveness of an approved device in post-market studies.

Post-approval studies, or PAS, in the first section of the table may be required at the time of approval of a Class III device to continue evaluation and provide periodic reporting on the safety, effectiveness, and reliability of the device for its intended use.

FDA also has the authority to require post-market surveillance studies under Section 522, or PS 522 on the table, of the Federal Food, Drug, and Cosmetic Act. These clinical studies are shown in the second section of this table.

An average of 45% of new enrollment clinical studies ordered between FY15 and FY19 that had an approved protocol or study plan by July of 2020 included at least one PRO instrument. Two of three post-market surveillance 522 studies included a PRO. These trends are similar to what we were observing with the pre-market submissions.

Before we dive into the rest of our day, I'd like to leave you with some take-home messages. First, we have seen consistent use of PRO instruments in about half of approved PMAs since the start of FY15. Despite the fluctuations in devices being submitted, the rate has remained fairly stable over time.

Second, PRO use is voluntary and may not be relevant to every regulatory decision,

as we saw with the varying use rates across OHTs.

Third, when PRO instruments are used in regulatory submissions to inform endpoints, we encourage sponsors to clarify how they will be used and analyzed as a priority.

And lastly, PRO use may be beneficial across the total product life cycle from the pre-market phase of devices through the post-market monitoring of device performance.

And with that, I'd like to introduce Dr. Kimberly Brown Smith, the Acting Assistant Director of the Clinical and Scientific Policy Staff from CDRH's Office of Product Evaluation and Quality, to kick off Session 2 of today's meeting.

DR. BROWN SMITH: Good morning. And thank you for that introduction. So, in Session 2 we will be discussing -- pardon me. In Session 2 we will be focusing on incorporating patient-reported outcome instruments in the healthcare ecosystem. And our first speaker is

Dr. Ileana Piña, who will give a presentation on cardiovascular clinical care.

DR. PIÑA: Thank you, Kimberly, and thank you to the organizers for this very, very important session. I'll take the first slide, please.

So how patients feel has been incredibly important to me. Oftentimes, if they're too ill they may not be able to express how they truly feel. You've got the family member there too, often they are not in accord or often the family member may notice more even than the patient themselves. But in the world of heart failure, which is what I do, I'm a heart failure transplant cardiologist, heart failure has all these ups and downs and that's what we're seeing on this slide, is that you may find the patient is one day doing really, really well and then they have a slump and then they get back up again and they start to feel better. How do we capture those changes? You can see the curve. Almost purposely, it just keeps going down until the point that the patients have really advanced heart failure.

So I have been very interested in PROs for many years, both as a clinical trialist but also as a practicing clinician, hoping that I can capture how the patients are doing about their health status which includes their quality of life, but it also includes symptoms and it also includes function, and so I try to find instruments that will help me do that and something that I can easily use in the office. I have to say this is not commonly done in most cardiology practices and not being commonly done in heart failure practices, but I have found it, probably for the past 10 or 15 years, incredibly, incredibly useful. And let me show you an example of that. Next slide.

You'll see here, this is the NIH/NHLBI heart failure study of exercise, aerobic training on patients with heart failure and reduced ejection fraction. We enrolled, over a period of about two and a half years we enrolled 2,231 patients and randomized them either to an exercise protocol which was started in some kind of a center and then continued at home with a piece of equipment versus excellent medical therapy because we wanted excellent medical therapy in the background and we had the drugs that we knew at that time that worked. And so, the control group was excellent medical therapy with advice about stay active, don't just sit and do nothing, move, and we let the primary care or their cardiologist follow up with them and give them instructions.

We used the Kansas City Cardiomyopathy Questionnaire, we used it early in the trial, and what I have always done in my practice, and we did this in the trial, is these questionnaires are given to the patient by somebody not related to the clinical team. So, for us, it would be a receptionist in the waiting room who would give them a clipboard to fill this out, just like you fill out in a doctor's office you fill out information before you come in, to make sure that there was no bias introduced by the patients knowing us, wanting us to feel better, because patients do want you to feel better about what you're doing because they realize you're trying to do your best and we didn't want that bias interfering. And very

quickly, within the first 3 months, we had some time points, 3 month, 6 month, a year and then 2 years, we found a statistically significant increase in their health status and it only appears here to be two points, but it was maintained.

However, if we start to look at how many patients actually moved at the five point that we considered clinically significant, it was a great percentage of the patients, remember this is a mean, but there were great percentages of patients moving to that five equivalent of improvement.

So, here's a way that we were able to publish and to show this difference in health status with exercise that not only went up very quickly, but actually was maintained throughout the study. Next slide.

So, how have I used this in my own practice? So, this is an example of my Montefiore clinic when I was in New York, we called it the Brown Bag Clinic because it was a clinic that happened at 7 to 10 days after discharge and we know that after discharge is a very, very vulnerable time period where the patients have a high probability of getting readmitted.

We gave the KCCQ, again in the waiting room while they were waiting for us to see them, and you can see there on the slide what the population looked like, these were patients who had obviously been sick because they were in the hospital, their NT-proBNPs, which is one way that we measure severity, was high. So, these were actually sick people and look at the KCCQs, they're in the fifties. So, a hundred is perfect health status. In the fifties, that's pretty significantly low. What does that tell me? It tells me that beyond what I can measure on an echocardiogram or on a blood test, those patients are at high risk because we know that these numbers in the fifties are very predictive of readmissions and they're very predictive of bad outcomes. And so, the lower those numbers, the more I would concentrate on maybe seeing those patients early. So, I'm using the instrument not

only to tell me where patients are, but kind of shake me and alert me that these are patients I need to see more frequently.

So, I hope this is helpful about incorporating it into the practice. Thank you, Kimberly, back to you.

DR. BROWN SMITH: Thank you so much, Dr. Piña.

So, for our next presentation, Dr. Nelson Freimer, Director of the UCLA Depression Grand Challenge, will present on the Assessment of Depression and Anxiety: Moving Toward Continuous Patient Assessment.

DR. FREIMER: And thank you very much, Kimberly, and thank you for -- everybody, for asking me to do this. Now, can I have the next slide, please?

Now, one of the things that really differentiates mental health from probably everything else that we talked about today is, in a sense, our assessments have only been PROs. The history of our field for over a hundred years has been the clinical interview where a doctor, a psychologist, will ask a patient questions and get their report about symptoms. That remains the standard practice, really, throughout the world. And what I'm trying to convey today is that we now are moving for the very first time to having objective measures of mental health that could've been taken for granted in every other area of healthcare. We currently have nothing like a chest X-ray, EKG, or blood test, not to mention any more sophisticated measures.

But as I'm going to try to convey in the next couple of minutes, we're moving towards a process where we're going to be able to continuously assess patients and have more objective measures, but at the same time we're going to see how we cannot lose what has been the history of our field, which has been that we've always centered it on the patient-reported outcomes.

So, in this slide it just really gives a schematic of where we've been, that is with the

clinical interview, which has obviously a high patient burden, can only be done infrequently, usually only gets done when someone comes for a visit, and is completely subjective. At the other end, if you look at the far right, where we're moving to is using phones, watches, and other devices to be able to objectively measure patient behaviors in a continuous way that will again, for the first time, give us some of the kinds of information that have been taken for granted in other areas of healthcare.

But what I really want to draw attention to today are the two boxes in the middle, which is where I see the PROs in our field moving towards, which is, on the one hand, patient self-reported symptoms. Now, this is something that's been available for some time, using questionnaires and so forth, but again, has generally been limited to in-person or very occasional usage and where we're moving to is the ability to use these in a continuous way so that we can really have a good tracking of the trajectory of symptoms as people experience them.

And then even more so, the ecological momentary assessment, or EMA, which is based on the idea that when people are experiencing symptoms in their actual daily lives, is really when we find out how they're doing and so what ecological momentary assessments are getting is, for example, a reminder on your phone or your watch to answer a couple of questions as you're going about your day and give us a much better idea about your actual functioning. So next slide, please.

And so, where we're actually moving, again, current clinical care is still almost entirely reliant on the clinical interview but really, what we see is the integration of all of these tools to get at different kinds of information. So, for example, the clinical interview at the time of intake or when we first try to do an assessment to establish a diagnosis and then on a more infrequent basis than the others, but still more frequent than the clinical interview, you get symptoms self-report as I'll illustrate in a moment, we're increasingly

able to use this in an online way. I'm going to talk about the use of computerized adaptive testing, otherwise known as CAT, that allows us to, on an extremely frequent basis, triage symptoms and institute crisis response as needed. Again, the EMA is something that can be done every day, it only takes a minute or two, and it really gives us an idea about how people's symptoms are actually in the moment when they're going about their lives.

And then finally, this will be integrated with continuous assessment using this passive collection of information on the phone, the watch, sleep monitors and so forth, which will give us the first quantitative and objective measures of symptoms. Can I have the next slide, please?

So just to give you some idea about how we see the use of PROs today, I'm just going to give an illustration with the use of online symptom tracking to guide treatment adaptation and crisis response.

So, I'll give an example for an implementation that we currently have. At UCLA we instituted a couple of years ago a process by which all students at UCLA are offered screening for depression and anxiety using computerized adaptive testing, which they can take at any time if they're enrolled at UCLA. And so a student might, for example, when they're experiencing mild symptoms, decide to enroll in a program of digital cognitive behavioral therapy supported by coaching by peers or other trained coaches, and let's say that during the course of the term acute stress, for example, before exam leads to a mental health crisis and we really wouldn't know this if the student isn't coming in to visit; however, if they are taking this tracking survey using computerized adaptive testing, we'll actually be able to observe when they're experiencing a higher degree of symptoms and that allows us to have an immediate alert and institute a crisis response. And then, as you can see from this graph, let's say the student is then enrolled in a more direct form of therapy and begins to do better, we'll begin to see improvement in the score on

computerized adaptive tests.

And so, you can see how the future, as we see it, in this field is going to be the integration of PROs using connected devices with the tools that we've always had, of interviews and other forms of subjective information gathering, but together with these objective forms of information gathering that are only now beginning. So, thanks very much.

DR. BROWN SMITH: Thank you, Dr. Freimer.

So, for our next presentation, we'll be hearing from Dr. Amy Cizik, a research assistant professor in the Department of Orthopedics at the University of Utah and she will be speaking about Patient-Reported Outcome, EHR Implementation, and Orthopedic Assessments.

DR. CIZIK.: Thank you, Dr. Brown Smith, I appreciate the introduction and thank you for inviting me to be a part of this panel. Next slide, please.

So today I'm going to present a little bit of my background in kind of thinking of holistic implementation in the healthcare system. Not being a clinician myself, but working directly with surgeons, specifically orthopedic surgeons, in understanding both research implementations as well as clinical care and I recently -- well, not recent, but within the last year I joined the University of Utah that had an extensive clinical implementation across their entire health system for patient-reported outcomes but came from an institution where it was more of a research implementation. And so, I just wanted to offer, because I know we have a variety of people in the audience, what does that look like and what are the things that when I approach these implementations and work with clinicians, what do I think about in advising how we do these?

So, for research, we have a little more flexibility in terms of providing longer instruments. We're obviously trying to get at a certain specific aim or endpoint in a

research context and so we want to target that, and we've heard some of the guidance that's been offered earlier in the prior session, but this also can conflict if there's clinical care implementation. So, you have to balance meeting your enrollment requirements and inclusion/exclusion criteria and the time points for a research study, if there's already an existing clinical workflow.

And so, what does that look like? In a clinical care setting we use more generalized measures. We need to meet clinical care needs, we need shorter instruments to improve clinical efficiency. The enrollment, sometimes it's more flexible in how patients fill these out, they come in at various different time points depending on their conditions, but again, when you're integrating both, you have to balance the research needs and the research goals with an existing clinical implementation and respect that clinical workflow.

I have found that engaging the stakeholders also varies between the researchers and the clinical care and the aim of the use of PROs across the system. So, when we think about research implementation, we're involving things like project managers, data managers, recruitment coordinators, the investigators of the study. I'm constantly working and adjusting workflows. Even now, in the COVID era, we're having to think about virtual data collection when before we did a lot of these things in person.

And when we think about the clinical care implementation, we now need to engage clinical staff, we need clinic managers who manage front desk staff and medical assistants who are rooming patients. We think of physician assistants who may be seeing patients instead of the surgeon or running multiple clinics and it also involves residents and fellows. Sometimes the surgeon's running, you know, multiple environments and cannot be in the room to engage either in the data collection or even the feedback to the patient of these PROs.

And then I also think about the platform. So again, we have research platforms like

REDCap, DATSTAT, that help us monitor and get specific time points for PROs. I am a big user of PROMIS, so those are -- that's where I spend a lot of my time. But then if we think more upon the EHR side, we're thinking more of Epic or whatever platform of your healthcare institution and having to incorporate whether there's research and clinical care; again, the duplication of efforts can become burdensome for the patient and thinking about how we do that.

So, in the last part of my talk here, I just want to address some of the things also that we think about when we start to think about disease-specific or pathology or procedure-specific instruments. And so, in orthopedics we think a lot about whether it's an acute episode or a chronic. So I do research in both spine and trauma, and in spine we have the opportunity to really meet patients over a longitudinal period and so we are getting baseline measures, we are getting follow-ups at very consistent time points.

In the trauma population, it's really led to a methodological challenge to think about what do we do when we cannot get the baseline data on patients and how do we monitor them long term when we don't have baseline information. This is where having a system-wide implementation in the healthcare system can make a difference. If patients are accessing care in other parts of the system, we potentially can pull their baseline data from that.

And then the types of measures we use. You know, for us there's primary, and in orthopedics we focus a lot on physical function and also on pain, but in orthopedics there's been a long history of what we call legacy measures or condition specific. So for example, in trauma, currently I'm working on a grant where we're focusing on pelvic and acetabular fractures. Well, that leads to us wanting to collect information on genital urinary conditions as well as sexual function, and so now we're looking at specific domains that relate directly to the pathology of that fracture.

In spine there's a well-known instrument called the Oswestry Disability Index, it's a legacy measure that has been well validated in the literature and people are familiar with it, clinicians understand what the scores mean, and so it allows for clinical interpretation that's familiar.

I was just recently on a call, actually this morning, with one of our providers and it was interesting to hear that even though our system has a PROMIS data collection, he is more familiar with a condition-specific measure and so chooses to use that. So, I think as we move on in thinking about how we implement these, we also need to think about how we provide clinicians' interpretations of these scores. I'll leave it there and look forward to questions at the end.

DR. BROWN SMITH: Thank you so much, Dr. Cizik.

Our next presenter is Dr. Joseph Chin, Deputy Director of the Coverage and Analysis Group at the Centers for Medicare and Medicaid Services, and he will be presenting on patient view -- oh, apologies. Dr. Chin.

DR. CHIN: Thank you, Kimberly. And thank you for the FDA for inviting CMS to participate in this PRO meeting. I think it's been encouraging to see that the FDA is actually interested in this field and also with the guidance document that was in draft. I think we are also -- from CMS's standpoint, we are also, I think, very interested in actually what FDA has said about really incorporating patient-reported outcomes in our considerations.

We also believe the patients' information is also very important, especially when we're talking about treatments where there may be multiple treatments for a number of diseases. In that instance, the patient-reported outcomes are definitely something to consider in really how we approach treatments, not only devices.

So, I think our introduction into patient-reported outcomes has basically started within the last, I think I would say 10 years, and I think fairly sporadically in our coverage

determinations. One of the first really entries, from our standpoint, was based on some of the work that Dr. Piña had mentioned earlier and specifically with the HF-ACTION trial that helped us cover and supervise exercise therapies for certain patients. I think we've also looked at quality of life measures in some of the decisions that we have.

I think we have had some experience. It has been really isolated and selective, perhaps. And we also, another thing to note from our standpoint and much of the discussion that CMS has had was actually presented during a MEDCAC in, I guess in 2018, the summer of 2018. While that Medicare at the development coverage advisory committee meeting was more focused on a cancer therapy and cancer patients, I think there are some broad concepts that we can really highlight and emphasize from that meeting and from -- and I'll also echo what was presented earlier today. So, I think some points that would be helpful from our standpoint, as we have looked at patient-reported outcomes.

And our role is really to use patient-reported outcomes that are developed by the stakeholders and the researchers and other manufacturers, perhaps. We're not necessarily involved in developing that type of specific evidence or products. So, in the way we can interpret the evidence that's actually developed from or based on patient-reported outcomes, I think one of the concepts that we had really discussed was trying to have some standardized definitions, you know, perhaps, or at least some acknowledgement of how to use patient-reported outcomes and actually what they actually mean initially.

There were, I think, some indications of some confusion about what is a patient-reported outcome compared to various specific names. I think we looked at quality of life, for example, in the past and also some pain scores, but there seems to be some confusion as to which terminology gets used, so I think it would be helpful to perhaps have more common definitions as to what we are actually referring to. Are we talking about a global

patient-reported outcome measure or is it various domains or specific measures themselves?

I think the other point that was also mentioned earlier today, I think it's important when we actually have studies on patient-reported outcomes that the studies use validated measures, I think that's very important, and we've seen some variability in that whereas there are some that are -- have been fairly well and well validated such as the PROMIS, NIH PROMIS measure system and some of the heart failure and quality of life measures have been well validated compared to some of the pain ones that we have seen that have been less validated. So, I think that's an important aspect to being able to use the results from patient-reported outcome studies in our decisions, in our considerations.

And I think, really, as we go forward with this, to really have it be more impactful would be to really engage on a broader scale and perhaps thinking of these broader scales and measures in a way that is more uniform, perhaps. I think there are some advantages of having disease-specific approaches, that's sometimes easier perhaps to do. But then, I think, a broader approach, you know, whereas some measures or systems of measures could be applied across conditions such as cancer or heart disease, I think that would be an area that would be helpful to actually get and start moving into more and that's where I think we would like to actually see more for our consideration.

So, I would appreciate continuing. I think we would definitely be interested in participating as we see this field develop more, especially the evidence and devices and how we can actually use that evidence in some of our considerations. Thank you.

DR. BROWN SMITH: Thank you so much, Dr. Chin.

Our next presenter is Mr. Paul Conway, Chair of the Policy and Global Affairs Group at the American Association of Kidney Patients and he will be presenting on Patient View: The Importance of Patient-Reported Outcomes.

MR. CONWAY: Thank you very much. I think the preceding three presentations were quite interesting because they point out the progress that's being made, actually, in PROs and they actually bring up several implications that I think are very important, not just to patients but actually to folks like Dr. Chin at CMS and to medical professionals.

In the first presentation by Dr. Freimer, what you heard quite clearly was the marriage of PROs and wearable medical devices for his field, in the field of psychiatry and psychology. Obviously, the promising thing there is the ability to have emergency intervention, and I think that's critically important when you take a look at today's society and many of the issues that we're dealing with. That's one of the optimistic notes about the application of PROs that I think all patients would embrace.

In the second presentation by Dr. Cizik, what you heard is this issue of not only the knowledge base of medical technicians and records technicians and medical experts in the field of osteopathic medicine, but what I think is very important here is the fact that you have a body of science now, not speculation but science, in patient-reported outcomes is moving forward and what that will mean is that it has to waterfall down across medical education and medical certification so that the promise of PROs is not slowed down by the lack of expertise at any point on the data entry chain in a care setting.

And on the last point here, I think with Dr. Chin, in terms of CMS, this is very important and this is what I was talking about in my first presentation, is what FDA has done is they have actually set forward a very strong force of momentum in that expectation in the patient community, so just think about this. It's going to be very, very difficult to put the magic back in the bottle, so to speak, because if you have patients that are engaged and you have a new science that's engaged of creating patient-reported outcomes and that's moving forward and there's an expectation and an actual participation of patients across the product development life cycle and then that product goes forth for a payment

decision, whether it's at CMS or whether or not it's with an insurer or whether or not it's a piece of data that third-party institutions like the Institute for Clinical Economic Research, or ICER, they don't know what to do with it.

And so, we're transforming the landscape, and with CMS what this means is that CMS is going to have to step up its game, essentially, because for coverage decisions patients are already involved at CMS in technical evaluation panels developing valid measures for quality. Dialysis is one of them. With the dialysis five-star rating system, patients have been at the table for the past 5 years putting forward patient-reported outcome data and patient-qualified measurements as validated in rooms with statisticians who are looking at other types of measures, but the dialysis experience is being captured as a quality measure by patients.

And so, what gets covered and what it means, I think the science is actually getting pretty clear in terms of the language and consistency of science. Well, I think that could be talked about for a very long time, but what you're going to have, clearly, is you're going to have an educated consumer base that looks at what FDA has done and then they're going to ask well, why isn't that same level of intensity and that same level of responsiveness about my medical experience being looked at and adopted by payers, whether they be private sector or the government.

And I think that's one of the things that, looking at this, there's a tremendous amount of optimism and there's going to be a tremendous amount of expectation and drive, especially by the advocacy community, that some of these things that are promising, the data that's been included for device approval or for therapeutic approval is also reflected on the payment side. Thank you.

DR. BROWN SMITH: Thank you so much, Mr. Conway. We will start the question and answer session in just a moment.

(Pause.)

DR. BROWN SMITH: So just as a reminder, if anyone in the audience has a question, please enter your questions using the Q&A feature in the app or using the webcast window.

I'd like to start with a question for Ileana. How have patient-reported outcome measures changed the flow and efficiency of your clinical practice?

DR. PIÑA: Thank you for that question. It really has not changed the flow at all because we obtain the questionnaire while the patient's waiting to come in to see us, so that doesn't even affect my moving from a patient room to a patient room in clinic. And we usually do this in the outpatient clinic and we review it, once we're done with the clinic, then we do the -- we score the test and put that into the patient's chart, very often manually because right now Epic doesn't necessarily have it on hand to put in. So, it really hasn't delayed us or backtracked us. I think it's been tremendously helpful.

DR. BROWN SMITH: Okay. Thank you, Ileana.

We have a question for Dr. Chin from the audience. You mentioned that patient-reported outcome measures are well validated. Does CMS prefer the patient -- I'm sorry, does CMS prefer the PROMIS-10 global measure to the EQ 5D-5L when deciding evidence for new codes?

DR. CHIN: I think it really depends on perhaps the scenario that's being used. I think in our MEDCAC meeting in 2018, I think PROMIS was one that was noted to be validated to a certain extent, so I think having that information whether it's PROMIS or another sort of system having validation and having that available to show would be important. So, I don't know if we have any specific preference in general, it's really about how it's being applied and how often it's being -- how it's been used in that technology, for example. So, I think it's more an individual basis that we would consider the measures at this point.

DR. CIZIK: If I could follow up on that, PROMIS has now issued a PROPr score, which

is a utility score that can be used with the PROMIS. In order to get that score, you need to use seven of the domains, so there's the PROMIS-29 short form plus cognition, which is two additional questions on cognition, and with those you can actually -- there's a formula by Dr. Janel Hanmer out of UPMC and her collaborator, Barry Dewitt, have done amazing work on this. And again, I noted my bias on PROMIS, but I think the NIH has invested a lot of money in it and we're seeing that, just like other measures, there's a lot of utility in using it because you can do a lot of things with it.

And just for those of you that are CAT users, you can actually use the CATs and get the individual domain scores from -- that are also used in the 29 to score the PROPr. So, you don't have to make a tradeoff, necessarily, and I hope I'm not offending any EQ users, but if you do use PROMIS you can do the same thing that you would do in terms of getting a quality of life measure.

DR. BROWN SMITH: Thank you, both of you, for your responses.

So, there's another question from the audience for all of the panelists. Considering the importance of parity of esteem, could you share your thoughts on when and if patient-reported outcomes will achieve parity with biomedical outcomes?

MR. CONWAY: I'll take a first shot. I think that, in terms of parity, I think one of the things to keep in mind is you'll always have tremendous patient desire and want and push for parity. But by and large, I think that patients and their caregivers will always look at authoritative sources, like FDA, to make certain that the weight of the decisions is fair and it's balanced in terms of patient safety and patient outcomes. But I do think that it will not be too far off in the future, at least on a regulatory side, where PROs, if they are not of equal they are of substantial weight at the table throughout the product development life cycle. Again, the biggest thing that I have a concern about is the parity at the payment standpoint and among payers. I actually think government will arrive there first, I'm

optimistic about that. I'm not that optimistic about third-party organizations that only focus on comparative cost effectiveness and don't understand the actual disease burden and what patients go through and how the promise of PROs and the involvement of patients over the past 10 years has actually made a substantial difference in the life of people.

And so, I think the balance is going to come in not necessarily just on biomedical outcomes and patient-reported outcomes, but it will also be on the playing field of how are decisions made about, once they're approved, how are things paid for. I think that's the biggest concern that the many patient organizations we talk to outside the kidney world, and especially in rare diseases, we share that. Thank you.

DR. CIZIK: I would like to follow up on that. I think one thing we need to be cautious, and I was part of a publication where we cautioned a little bit about using PROs for quality assessment, and I think it's a balance because patients can actually have amazing outcomes but -- and on a PRO. So, example, again I spend a lot of time on physical function, patients can actually make MCIDs, minimally important difference, however you want to measure it, a clinical change, and still not be satisfied with their outcome.

And we didn't publish the grid, but we had a grid that showed patients in -- if you think of an XYZ axis where we have patients with pain on one, on the X-axis and physical function on the Y-axis and then the Z-axis we had satisfaction, and we had patients actually in all four quadrants of that, meaning that there were patients who actually had worse pain and worse function after spine surgery but were satisfied with their outcome. And I think, you know, is that a good thing? No, it's not great that their function and pain decreased, but there was something in getting the treatment that they did that made them still think that they had a better outcome than had they not had the intervention and I think that's where -- and again, I'm a huge proponent of PROs, but I think it's not an either/or. I think

it's complementary, that we need to think about that.

And also kind of back to the biomedical outcomes. Surgeons often, and it's a discussion we have often. When we show my clinical colleagues their PROs there's always the caveat of oh, my patient was sicker, my population is sicker, and so we spend a lot of time talking about risk adjustment. And I've actually, personally, in my research tried to demonstrate and show that I think it's actually where a patient starts, and I think this is very important for PROs. So, for patients whose function wasn't actually as debilitating as they thought on a PRO, we actually find those patients don't do well because they weren't worse off.

And so, I think it's a balance, I think we do still need the clinical outcomes, I still think we need the quality measures, and this is just additional information that I think helps us see a bigger picture. But again, I think it's important because it does help patients who aren't satisfied or who don't think their expectations weren't met. If they have their PRO in front of them and you say well, actually you were here, we intervened and you're now here, they pause and say, “oh, maybe I am doing better than I realized.”

I have a child with special needs, I constantly get reminded by an OT, sometimes we forget the positive gains we've made in the past and it's good to be reminded of those and I think PROs do a really good job of that in helping patients and the surgeon see where the patient came from and where they are now.

DR. PIÑA: This is Ileana. If I could tackle that for a moment. We often forget that quality of life takes into consideration the patient's expectations and if their expectations are high, they may be a much worse jury when they get whatever it is that they're going to get. So, in CDRH, and we have been using PROs as sort of a combination of endpoints, we try to get some very objective parameters that will tell us how the patient is doing by the subjective clinical parameters.

When we did the HF-ACTION, Dr. Chin may remember -- and hello, Dr. Chin, good to see you -- we may remember that we did actually exercise testing with cardiopulmonary testing, and we did 6-minute walks, and we obtained a KCCQ, and we actually published the correlations among them so that if you were using the instrument and you were not doing the cardiopulmonary test, small changes may represent something in the cardiopulmonary test. So, we try to publish this both at baseline and within the outcomes because our outcomes were mortality and hospitalization.

So, there is literature published at least with the KCCQ that tries to correlate, and at CDRH we usually use these combined endpoints that include the PRO, but we often get a very objective, for parity's sake, a very objective finding of a clinical measure whether it may be a biomarker or it may be a change in something physiologic. I hope that answers the questioner's question.

DR. CHIN: I'd like to add also that I think it's actually the PROs are actually getting pretty close in some specific examples that we've seen. Chronic pain treatments is one of them, some cancer treatments, also. So, where those situations the new treatments or the treatments are actually performing equally well in terms of -- in outcomes such as mortality, then it becomes increasingly important, the patient-reported outcomes, because that is what the patient and the physician may actually focus on when trying to decide, among various equally effective treatments, you know, which one is best suited for that patient. So, we're seeing more of that and I think in those situations, in those instances, it may be actually be more important of the determinants.

DR. BROWN SMITH: Great conversation. Let's answer another question. Can you share some ideas on how to further engage patients to report outcomes when they are not interested in doing so?

DR. FREIMER: Yeah, so I think there are obviously -- it's obviously a challenging

problem and I think this may be one of the ways in which the use of connected devices to be able to query patients in the course of their life as opposed to when they're in the healthcare setting may really be important.

So, for example, I mentioned the use of what we call ecological momentary assessments where we might have very, very brief reports from patients at various times during a day, and I think by putting together that kind of information over the course of a week or a month we can really get a sort of much richer picture of what they're experiencing and in a way that they're, we think, much more likely to provide that information.

Again, expecting patients to do that when they come to their healthcare visit, you know, where they probably have all sorts of other aspects of the problem that they want to deal with, it may be harder to elicit that information. I think that it's really -- if it's integrated with their use of these devices that really is an opportunity, I think, that we are just beginning to be able to explore.

DR. BROWN SMITH: Did anyone else have any comments?

MR. CONWAY: If I can make one quick comment and I'll make it fast, doctor, too. I think Dr. Freimer is hitting on something very important here, which is there's a lot of stress and tension that goes with going with a clinical visit and especially if you have multiple comorbidities and you're managing multiple chronic disease symptoms. I think making the avenue of communications available in real time to where patients are and harnessing technology is important. I think it's important not only for the patient, but also there's usually a caregiver involved, too, and it kind of demystifies what are we doing here if you make it in real time in settings that are relevant to patients and that fit with their schedules.

There are two other elements to this that I think important. One is nomenclature. I think you need to embrace plain language when you're trying to encourage folks to do

something that they may not want to do and it has to be really clear to answer the question of this, to what end? I think there's heightened sensitivity about your individual patient information now and I think to be able to talk to folks and say, “this is what it will do.”

And along that line, the second point that I would make is this. I think that sometimes in approaching patients, whether it's large patient organizations or the individual patient, things can be just too clinical and, I think, sometimes it's better if you approach folks on the plane of idealism, that it's not simply about you. You have things about you that are unique to you, but they could be extrapolated and they could help people. I strongly encourage people to always appeal to the idealism that one person can help another if they believe that their data is valid and make that then easy for them, through things like technology and through things like plain language, but I think that's probably some of the best ways to engage people.

DR. PIÑA: I can chip in here, as well, because we've always said to patients, when we're using these instruments, and I've been using them clinically for so many years, and I say to them, “I have an opinion of how you're doing and when I see you sequentially, I can tell how you're doing, but I am interested in how you think you're doing,” so -- and some of them get very, very surprised because they've never been asked how they believe that they're doing. And so that kind of stimulates the conversation of wow, you're really interested in how I think; yes, I'm interested in how you think. And these, through the questionnaires, are how they're going to get to that. What do you think about how you feel? I'm interested in social interactions, which some of these questionnaires do have because that becomes part of their life, they walk out of that office and now they're facing the rest of their world and they're having social interactions and in the case of what I do, the heart failure, some of the social interactions get really difficult because it means getting out, walking, getting somewhere and now with the pandemic, may be all virtual, but they

need to understand that I am interested in what they're feeling, not just what I think. I have an opinion and they know I have strong opinions, but I want to know what their strong opinions are, as well.

DR. CHIN: I would like to -- I mean, I think I would like to echo what Paul and Ileana mentioned. I think, from our interactions with patients and patient advocates, you know, for older adults, I think they actually are willing and interested in providing this type of information, so -- which is encouraging, I think, from our standpoint and I think a lot of it, as Dr. Piña mentioned is, is that engagement with their physician and provider. So I think we're encouraged that as we really enter and focus more on patient-reported outcomes in older adults that we will actually get that information and they will be willing to engage in that standpoint.

DR. CIZIK: I would just echo the same thing. When patients know their providers care about this data and this information, they care, and they are much more likely to fill it out and we see that time and time again. The surgeons that I work with who are engaged in this have the highest rate of data collection because their patients know it's meaningful, so I would echo everything everyone said.

DR. BROWN SMITH: Thank you, everyone. We've got another question. In disease states with large unmet needs and limited therapeutic options, how would CMS and payers feel about using patient surveys that incorporate subsections and questions from validated PROs, but not the entire questionnaire?

DR. CHIN: That's a good question. I don't believe I have an answer for that. I think it's a scenario we haven't come across at this point, so I think that we'll need to really think more about that. Validation is important in that aspect to be able to really know what we're getting. So I think there is a balance to that and what can be obtained for certain patients or certain types of treatments and various, I think, severity of illness conditions, so

I think it's to be seen and I would actually rely a lot on the providers that are participating in this to help us with that.

DR. CIZIK: I would say this is a great other plug for PROMIS because the way it was designed in terms of using item response theory allows you to mix and match in select domain specifics. So, if you want to measure anxiety, if you want to measure depression, these items were individually weighted and calculated for response. And so, I think, in those settings, this is where it can be very valuable if you want to measure multiple domains but don't want to burden with enormous amounts of items.

So again, I've stated my bias, but I think it does help us get away from some of these legacy measures and questions that actually even mix domains. Again, I had mentioned the Oswestry, that instrument for spine care is actually a mix of physical function and pain interference and so some of the way the questions are worded, it's very hard to understand if the patient is responding to the physical function deficit or is their pain interfering with their ability to physically function, if we had controlled their pain would their function actually be fine. And so, I think that's one way and why we've gotten away from the classical methods of questionnaire development.

MR. CONWAY: If I could add one quick thing here. I think that what Amy hit on is very important and the other thing that I would just mention again is that, especially in the past 5 years in the rare disease space, among advocacy organizations there has been a very sophisticated change in not only database development and database management, but also the ability for folks to bring forward very substantive and robust responses to patient surveys and the concern, I think, which is a good thing, to up the game for valid instruments for surveying. And I would also like to thank the FDA again because they are very proactive at reaching out to patient organizations for surveys, to also put up against and to use in an informed way with other survey data that's coming in off the medical systems. But I would

strongly hope that -- and I know, because of their past history, that CMS, moving forward, will start to see these types of things, especially in the rare disease space, as a valid input to consider because I do think that the momentum is there, but most importantly, I think the technology and the seriousness of that data has really changed a great deal in the patient community and so I think the capacities are there, as well. Thank you.

DR. PIÑA: I want to comment and maybe put a plug in for the disease-specific questionnaires, which is, in fact, what the KCCQ and the Minnesota Living with Heart Failure are. But as I showed on my first slide, if you remember that trajectory of the patient, as that patient gets worse, a lot of those questions may not be indicated for those patients, they have been so sick, and we have been looking for years for the perfect questionnaire, for example, with an LVAD patient.

So mechanical assistance is something that CDRH also does in my circulatory division and the KCCQ may not be the best for the patients who now have a mechanical device. It's been used, it's been used commonly, but there's a grant out from the NIH, I don't know the status of it, to develop a questionnaire for those sick patients.

And sometimes what we've been using is what we call the EuroQoL, which is a very simple sort of a scale, and making it easy for the patient just to put a line on the scale of how they feel and it's something that you can very quickly put in front of them when they're in the hospital and have them just draw a line across how they're feeling, you know, a hundred percent being the best and zero being the worst, where are they. So, we've always been looking for these easier ways of assessing how the patient is perceiving what we're doing to them and we are doing things to them, how are they perceiving that.

DR. BROWN SMITH: Thank you, everyone. For the next question, could you talk more about the way that PROs are used in your care paradigms on a practical level and what actions or players have been instrumental in making that happen?

DR. FREIMER: So, I'll take a start at that. So, to start with, I'll start with the second part of the question which no one has really talked about yet, but at least in our field, I think the pandemic has actually had an enormous impact which is going to be sustained, which is, you know, as with every other field of healthcare, mental health very rapidly became remote when the pandemic started and, in my view, it's really accelerated these trends that I've talked about.

And so, where providers are not actually seeing patients in person, I think having these sources of information from the PROs on a regular basis is a way that patients have remained connected to care. Again, I'll be interested to see whether that's true in other areas of healthcare, but I think it's pretty clear that in mental health this is something which is not going away as the pandemic comes to an end.

And I think that, again, as I mentioned, these have not been traditional as part of regular flow of healthcare in our field, but I really see that over the past year or two with the advent of technology, as I've mentioned before, it's really accelerated their acceptance in the field. And so, to me, it's the combination of the technology now being available and then the pandemic making it a necessity that has really made use of these kinds of measures really central to our practice.

DR. CIZIK: In my world, there definitely has to be a champion, a physician champion that this is very important to them and I'm fortunate here, I have a chair that's very engaged in this, so it trickles down and if there's engagement at a higher level and institutionally there was someone at the C-level that was very engaged in the system-wide implementation. So, I think it starts with the actual clinical staff being engaged. And I still think we're moving into how -- at least in orthopedic space, maybe not in other spaces, but we are still trying to get that from that research to the clinical use. And I'm going to echo, a comment was made that we should be cautious, though, that group-level estimates are not

appropriate for individual-level decision making. And so, I think that is some of the reason there's been hesitance to move into clinical practice because we don't have good data on that end. And we're still -- lots of other very smart researchers are working on those pieces of what does improvement mean and how does that look at the individual level.

I think, too, at least in the orthopedic space there was a big push for research and there was a lot of, should we say, positive feedback because those were the studies that were getting podiums and presentations and so there was kind of that carrot/stick and I think that we haven't found that yet in the clinical space and I think that's where payors and policymakers can be influential for quality assessments or reimbursements. I know we're seeing that in hip and knee and joints and there's been some talk of it in spine.

So I think, again, (1) we don't have great data to make individual-level decision making yet, but I think (2) it also is going to require, amongst the many things we require of our clinical providers, there's other priorities that they are meeting and if we can fold that in, though, to whether it's quality measures, I think we're starting to see that but that would be helpful in moving this into clinical care.

DR. PIÑA: I think one of the questions being asked is how did we get interested in actually putting this in our practice. And so, I was part of this outcomes research group way over 10 or 15 years ago, and we were discussing about PROs way back then and how could we get at it. So we just randomly selected patients in our own clinics and we did things like the physical exam, we did a 6-minute walk, we actually got a BNP blood test for biomarker and then we got the Kansas City Cardiomyopathy Questionnaire at two different time points, totally clinically, and we predicted, based on our clinical knowledge or our clinical sense, who would get better and who would get worse. And then we looked at the data and saw what predicted that some patients were going to get worse and what predicted that some patients were going to get better and at that point, the KCCQ behaved better

than the 6-minute walk that we had done clinically and these are individual patients and that's when I said, “wow, this is something that maybe I can take to my clinic and figure out how patients really feel about what I'm doing to them and about what their disease is doing to them.”

So, that sort of was the clincher for me, to take it out of just the research area, which I've used it a lot, and actually put it into my practice. I can tell you that the majority of cardiologists are not doing this in their offices. This is not the common practice.

DR. BROWN SMITH: Thank you so much. Well, we are almost out of time. I'd just like to read one comment that we received from the audience. "The PRO research community is actively working to clarify that group-level estimates are not appropriate for individual-level decisions. Use of appropriate individual-level statistical methods should be employed instead to determine if patients have stayed the same, deteriorated, or improved." So very quickly, would any of you like to respond to that?

(Pause.)

DR. BROWN SMITH: Agree, disagree?

DR. CIZIK: I think I touched on that a little bit in my last comment, but, I think, this is where we're looking for opportunities and right now people are doing methods that make it easier for us to make individual-level decisions. I think the group estimates are still very important, especially for population health monitoring, but I know especially if we think about this in the healthcare ecosystem and we trickle down into the individual clinics, providers and clinicians are making individual patient decisions. But for those who are maybe on the call who think more systems based, the group-level estimates are good for population health.

DR. BROWN SMITH: Thank you for reiterating that point. And so, our session has come to a close, I want to thank each of you for your presentations and for a wonderful

discussion, and so we will now leave for a lunch break and the conference will resume at 12:30. Thank you, again, everyone.

(Whereupon, at 12:00 p.m. a lunch recess was taken.)

AFTERNOON SESSION

(12:30 p.m.)

DR. CALDWELL: Good afternoon, welcome back. Our session this afternoon will be Bridging PRO Instruments to Ensure Relevancy Across Demographics. Before we get started, though, I'd like to take a minute to let everyone know that slides and transcription will be available online on our meeting website after the meeting.

To get us started, I'd like to introduce Dr. Bram Zuckerman. Dr. Zuckerman is the Office Director of the Office of Health Technology 2: Cardiovascular Devices.

Bram.

DR. ZUCKERMAN: Thank you. I'm going to be talking for a few minutes on the use of patient-reported outcomes in device development from an FDA Office of Cardiovascular Devices perspective. Next slide, please.

I think there was a marvelous series of lectures and then subsequent discussion this morning where many of the themes that I'm going to talk about were already presented in detail, especially by Dr. Piña. Specifically, PROs and clinical outcomes from a device regulator's perspective are complementary. They are not replacing hard clinical outcomes, but by the same token, as shown in this graphic, they're giving us the complete picture, what we call the totality of evidence, so that we have a better assessment of what it means for a patient to have a particular medical device and consequently, from a regulatory perspective, at the end of the day what it really means for a benefit-risk perspective for this patient to have this particular device, which is critical for making a regulatory approval decision. Next slide.

So consequently, PROs play a critical part in the Office of Cardiovascular Devices right now and one of our cardiologists, Dr. Piña, indicated, for example, the importance of

the KCCQ and this session will focus, to a great extent, on that particular PRO. And I don't think that the questions that a regulator would have are any surprise. It's rather "how can we best use the PRO instrument in a regulatory setting?" And this is particularly important when we recognize that device trials often are unblinded. Also, we need to recognize that clinical trials are often imperfect, they do have missing data, and we'd like to minimize that as much as possible with respect to gaining PRO information and understanding.

So, at the end of the day, we'd like to develop a comprehensive picture of what the PRO is telling us so that we can best communicate that information in our instructions for use and patient labeling. And again, how best to do that is still, in certain ways, being developed, as much of the PRO field is.

So, in summary, PROs are extremely important in device development, there are regulatory questions that should be discussed between regulators and sponsors, but this is the way forward. Thank you.

DR. CALDWELL: Thank you, Bram.

Our next panelist is Dr. John Spertus. Dr. Spertus is a Professor of Medicine at the University of Missouri-Kansas City and is the developer of the Kansas City Cardiomyopathy Questionnaire.

Dr. Spertus.

DR. SPERTUS: Thank you so very much and thank you very much for inviting me to participate today. The next slide just reveals my conflict of interest, which is that I developed the Kansas City Cardiomyopathy Questionnaire and have been working on it for well over 20 years.

I was given only two slides and told to sort of try and address a lot of the broad regulatory issues around the KCCQ, and so my next slide is just a brief overview so we're all on the same page. And the Kansas City Cardiomyopathy Questionnaire is specifically

intended to capture the ways in which the underlying heart failure syndrome manifests itself to patients. And so, you know, patients have an underlying pathophysiologic process whether it's HFrEF or HFpEF or, you know, amyloid or valvular heart disease and because of that they develop symptoms of fatigue, dyspnea, and edema. They develop sort of physical/social/emotional limitations and their quality of life can be impacted.

And so after a lot of extensive interviews with patients and clinicians, we created originally a 23-item version of the Kansas City Cardiomyopathy Questionnaire and subsequently reduced it to 12 to facilitate its use in clinical practice, as Dr. Piña and others talked about in the prior session, and it explicitly measures sort of the symptoms that patients experience, their physical and social limitations and their quality of life, and it could be summarized into an overall summary scale meant to sort of average out the impact of the disease on patients. It's available in over a hundred translations, it can be used throughout the world and in multiple countries, and over the past 20 years we've amassed an enormous amount of data around its validity, its reproducibility, its sensitivity to clinical change and, most importantly, how to interpret changes at the patient level.

And pulling all of that together, we've submitted over 5,000 pages of documentation and data tables to the FDA, and CDRH has been a remarkable partner in providing a very thorough and rapid evaluation and qualification of the 23-item version of the KCCQ as a clinical outcome assessment, and I was very happy this year when CDER also qualified it as a clinical outcome assessment, at least the physical limitation and symptoms scales, as well as the clinical summary score.

The next slide is sort of my four key questions. Now that we have an instrument that we think can capture well the impact of heart failure on patients, what's next? How should we start thinking about using it? The first thing is, is that every clinical trial currently uses the New York Heart as the inclusion and exclusion criteria and yet, you know, patients are

assigned to New York Heart by their doctor. Some doctors do a very good job, some do not, and we have seen, in multiple trials, that being called Class II or Class III had very overlapping KCCQ scores with some patients having scores of a hundred and some patients having a score of zero, and maybe we're at the point now where we should trust the patient and their report of their symptoms and their functional limitations as the foundation for enrolling a more homogenous group of patients with a similar burden of illness.

The second point that I think is a real challenge and opportunity is that there is a need to understand what the scores mean. And so, the KCCQ is on a hundred-point scale and most people don't know what does it mean if a patient has a score of 60, 80 or a hundred or what does it mean if they change by 5, 10, or 20 points.

And we have done a tremendous amount of work to define what's the clinically important difference from patients. We conducted a 14-center 500-patient trial where we looked at the patients' estimation of clinical magnitude of change and positions and we came up with very clear thresholds of 5, 10, and 20 representing "small but important," "moderate to large," and "large to very large" improvements and then have subsequently shown those estimates to be very strongly correlated with survival, with hospitalizations, with costs, with 6-minute walk distance, with mean VO_2.

And so, we do have very clear thresholds of a patient moves by X amount of points, is that a small, moderate, or large change? And yet when we report the results of clinical trials, we only report the mean difference across the population of patients in each treatment arm and that mean difference averages the patients who got a lot better with those who didn't change, with those who got worse. It is not really interpretable and several of the speakers in the last session talked about the need to understand from the patient level for individual decision making how they're likely to do, and because we have developed such clear thresholds for interpreting change, we can now start to report the

average difference between the groups of the p-value, but then to describe the proportion of patients who had moderate or large changes so that we can understand the number I would need to treat with this new therapy for one patient to feel a whole lot better if you're using a 20-point threshold or moderately better to large, you know, much better if you're using a 10-point threshold.

And to me, as the Agency wants to figure out how to use these kinds of scores to create informative labels that can help guide patients and providers in using new therapies, we have to move away from these mean group differences and start looking at the proportion of patients who had clinically large or small changes or got worse or didn't get worse. And so that's my second sort of key opportunity for going forward.

The third one is a mechanical one. You know, right now the 23-item version of the KCCQ has been qualified by both CDRH and the DDT pathway for CDER. And the 12-item version has an exceptionally high correlation with the original 23, it meets all of the same validity, reliability, responsiveness, interpretability thresholds and yet it's half the questions, it's much easier and creates much less burden on patients to collect the 12-item versus the 23-item version and, in the era of coronavirus and increasing movement to telehealth, using a 12-item is just much more practical, it was built to be more feasible and for use in clinical care and I think that it would be fabulous to work towards approving or qualifying the KCCQ-12.

In full disclosure, we had a prep call and I mentioned that I'd given all the data for the 12 at the time we got the 23-item version qualified, but now the process has sort of evolved from the pilot program to an official one, they gave me a very nice opportunity to resubmit all the data for 12 and I just haven't had the time to do it. So hopefully, I can -- that now sits on my shoulders and hopefully, I can overcome that third barrier quickly.

And then finally, the next evolution in supporting shared decision making is I think to

start to individualize the estimate of the outcome benefits of treatment based on the totality of a patient's characteristics such that, you know, I can see a future where a patient is before me and they're of a certain age and gender and a certain disease severity and there's a new treatment and I can say to them, “if we treat you, your probability of having -- you're feeling a whole lot better than you do today is X versus the Y. If you're not treated with this therapy, here's your probability of feeling worse. Do you want this new treatment?”

And, all of the work in modeling the heterogeneic treatment benefit has been done but primarily restricted to survival outcomes or survival and hospitalization. But what's really important to patients is its impact on their symptoms, function, and quality of life and by moving into that phase and starting to create shared decision-making tools around PRO outcomes, I think we can create the evidence to meet the needs of our patients much better than we're doing today.

So, thank you very much for the opportunity to talk, these are sort of my key four thoughts about where we could go forward now that we have a qualified measure in the KCCQ to start looking at heart failure outcomes. And it would apply to all diseases, but I'm a cardiologist, so I can only talk about heart failure.

DR. CALDWELL: Thank you, John.

Our next panelist will be Dr. Theresa Coles. Dr. Coles is an Assistant Professor at the Center for Health Measurement and Population Health Sciences at Duke University.

Theresa.

DR. COLES: Thank you, Brittany. So today we're going to be talking about an ongoing project in which we are exploring how gender may influence how patients respond and interpret patient-reported outcome measures. This project is a collaboration with FDA, Mayo Clinic, and John Spertus, who you just heard from. Next slide, please. Thank you.

So, the purpose of our project was to determine if men and women interpret questions differently on the KCCQ. Why is this important? Well, an inherent requirement of being able to compare scores, PRO scores, across different subgroups is that patients from those different subgroups, for example, gender, interpret the questions the same way.

For us, given that there's different lived experiences for heart failure between men and women, we also note that there's differential impact of heart failure, as women report them from patient-reported outcome measures and there's also been a historical lack of women in heart failure studies; that's changing, of course. But it's possible that the questions and response choices on patient-reported outcome measures for heart failure could be interpreted differently by men and women, and that's precisely what we are trying to evaluate in our study.

Well, what's the consequence if we do find that men and women interpret patient-reported outcome measures differently? Well, it means that we have reduced validity to do between-group comparisons. Next slide, please.

So, this is a kind of schematic of our study, we have three steps. One was to refine our hypotheses. We worked with clinicians and got feedback directly from clinicians on where possible gender differences might lie item-to-item on the KCCQ. With that information we used the HF-ACTION datasets to do a secondary quantitative analysis to evaluate potential differential item function among each of those KCCQ items. So, that's our quantitative study.

And we're taking that information from the quantitative study as well as the hypotheses that we refined in step one to conduct a qualitative study, and in this study we're doing one-on-one cognitive debriefing interviews and concept elicitation interviews with individuals diagnosed with heart failure. We hope at the end of this study we'll have more information on what might be happening with -- well, one, we hope that this will

serve as an example for how to investigate potential gender differences and interpretations for patient-reported outcome measures in heart failure and more widely. And also, we will have more information than we've had before on how patients may or may not interpret the KCCQ differently by gender. Thank you.

DR. CALDWELL: Thank you, Theresa.

Our next panelist that I'd like to introduce is Dr. Courtney Lyles. Dr. Lyles is an Associate Professor at the University of California, San Francisco's Division of General Internal Medicine and Center for Vulnerable Populations at Zuckerberg San Francisco General Hospital, and is a member of the UCSF Department of Epidemiology and Biostatistics.

Dr. Lyles.

DR. LYLES: Thanks so much for having me. As Brittany mentioned, I'm here representing UCSF. I'm also based at the public hospital in San Francisco, San Francisco General Hospital, which was the site of the study that I'm leading for an FDA/CERSI project. So, the goal of our CERSI project was a little bit similar to what Dr. Coles just presented but rather than thinking about the KCCQ by gender, we had thought about it specifically by race, ethnicity, and also for patients who are lower income who are treated in our delivery system. Our system takes almost exclusively Medicaid and uninsured patients, we don't take private insurance at San Francisco General Hospital.

So, I thought I would, on the next slide, just jump right in to sort of what we've been finding. Our approach was a little different in that we started directly with qualitative interviews and we were able to complete, before COVID, about 15 qualitative in-depth interviews of our patients from heart failure clinic at San Francisco General, to show them the KCCQ and talk broadly about their heart failure self-management. And, it’s a lot of information but just to first sit with it for a minute, I think there's three major things that I

wanted to share with you about what we've been working on. The first is that the sample that we collected really did reflect the overall sample of our hospital, which is primarily a non-white sample with representation across multiple racial/ethnic groups.

And then secondly, we've measured self-reported health literacy among all the patients in our sample through a validated one-item screener of health literacy which is really about patients' ability and self-confidence to fill out medical forms on their own, because this has been known in our previous work to really influence how patients interpret questions in patient-reported outcomes more broadly.

The second column here shows, really, that the KCCQ performed pretty well with our patient population. There were only some very minor and concrete suggestions among patients when we showed them the items and talked one by one with them in cognitive interviews for suggestions for improvement or potential comprehension challenges with certain wording, like the word "fatigue" in the item.

But the last two columns really show, I would say, the bulk of what we heard from our patient population, which is really that the medical and social complexity of their lives really interacts with their ability to manage their heart failure. So, for example, many patients in our study had many chronic conditions and one of these clips here shows multiple medication management and multiple episodes of care across their chronic condition.

And so, their symptoms and their way of managing their health really interacts with their ability to understand what their steps are and to prioritize, frankly, across multiple things at once. And then, of course, competing demands or other stressors in life, particularly with COVID now, this idea of mental health demands and social support needs for patients to be able to manage their symptoms and to be able to function at a high level, so those came up a lot. They're sort of ancillary to the items themselves but relate to how

patients interpret their overall self-management behaviors.

And then on the last slide, I thought I would just show, you know, we made some slight adjustments to the KCCQ, mostly based on the literacy level, based on what we heard. So, this is just an example, on the top box of the original item and on the lower box here some small adjustments we've made mostly to lower the reading level and to think about shorter sentences and fewer syllables per word to see how patients respond to these slightly, very slightly, reworded questions. And I'll say that we -- this is very pilot, but just ideas of putting this back in front of the final patients that we interview in our qualitative study to really understand how this type of wording of the question might change their understanding or comprehension in a pilot kind of way.

So that's what we have been working on here in San Francisco General and I'm thrilled to take more questions and go deeper into Q&A.

DR. CALDWELL: Thank you, Courtney.

Our next panelist that I'd like to introduce is Dr. Chris Almond. Dr. Almond is a Professor of Pediatrics and Cardiology at Stanford University.

Dr. Almond.

DR. ALMOND: Hi, there. Thank you very much and thanks very much for the opportunity to participate in this important panel. I think it's really been impressive what the FDA has been doing in terms of trying to expand PROs and the patient voice to the pediatric population, especially Dr. Brittany Caldwell, Fraser Bocell, Michelle Tarver, Vasum Peiris, and Annie Saha. Next slide, please.

I was asked to describe some of the challenges facing the adoption of PROs to children and I think, as many might imagine, heart failure symptoms in children oftentimes differ from adults. There's much less ankle edema for reasons that we don't entirely understand and at the same time, GI symptoms predominate, so it may be that different

questions are actually needed to incorporate the scope of symptoms in PROs.

Another issue that we run into is up to half of children with heart failure cannot report their symptoms reliably. This includes infants and toddlers that make up 30 or 40% of children with heart failure since it's a highly skewed distribution toward kids born with complex congenital heart disease and this creates a problem of missing data by age group or illness severity.

Of those who can report, children with complex congenital heart disease notoriously underreport their symptoms compared to children with cardiomyopathy. This may be for a couple of reasons. One is that they've always had their condition, it's been an issue since birth, so they have very little to compare it to. We noticed this most dramatically around the time of transplant when a patient actually is able to tolerate fully and they could never have imagined what it felt like.

I think another issue is a lot of kids with congenital heart disease, especially single ventricles, have predominantly right heart failure, which tends not to congest. So, symptoms of shortness of breath are less common whereas sensations of fatigue or bloatedness are much more common.

I think another issue is that events, that is adverse events like death and stroke, typically cluster in hospitalized patients and this is a population where many kids are typically sedated or paralyzed, making it difficult to get their voice.

We also know that irritability, especially that depression is a common manifestation of heart failure in adolescents and also in infants, and this can also create a problem in terms of interpreting the scores or whether someone may not feel well enough to want to report their scores. We know that surrogate reporters can differ in their impression from a child, this can happen very innocently. Also, I think developmentally we certainly see times in adolescents' lives when there's almost a tendency to want to be oppositional to what a

parent says and that can create problems.

I think another huge issue is that congestive heart failure in pediatrics is a relatively rare disease, so powering clinical trials is far more difficult. In the Heart Failure ACTION discussion that was discussed, that required 2600 patients to detect two unit difference in the Kansas City questionnaire. We may not see that number of patients for 10 years, which is a real challenge.

And I think the last issue is that because of developmental concerns, use of multiple age-based instruments creates analytical problems because, for example, the Ross and the New York Heart Association are defined slightly differently going from infant to older children and that can create some analytical problems when patients age out from one to the next. Next slide, please.

So, how can PROs be helpful in clinical studies? So, I think it's fair to say that pediatric heart failure is really desperate for novel and more robust endpoints that capture the pediatric voice. This has almost been completely absent and part of that's really been because of a lack of metrics that are available. In the Berlin Heart Trial, one of the PROs that was used was the PedsQL, but so many of the questions weren't relevant, going to school and other things, because they were hospitalized. So, this is a real challenge.

I think PROs are also likely to be more sensitive than survival as an endpoint and this is because many VADs, especially used in cardiomyopathy, may be associated with a 90% survival across centers and you're not really able to differentiate on survival but you could very much in symptoms.

I think it's important that PRO endpoints are more statistically efficient. As a quick example, if a trial is designed with 80% power to detect a 10% difference in mortality, that would require around 3600 subjects, 1800 in each group, whereas a PRO that had a three-point difference in a 12-point scale might require only 32 subjects, 16 in each group,

assuming that the standard deviation of the scores was two-thirds the effect size and obviously, that may change in the ratio of the effect size to the standard deviation, but you get the sense that it's almost an order of magnitude different.

Types of heart disease need to be accounted for in studies and I think this was beautifully said before, we really need to get away from comparing population means and really looking at the change in score for individual patients. I'm reminded that in pediatrics the average duration of pregnancy is 40 weeks, but only 4% of women actually deliver on their due date, suggesting that the average really does not capture the full variability very well.

I think minor modifications to adult instruments may be very promising here. It may be just by adding some GI symptoms and focusing on a few other aspects of right heart failure may actually allow adult instruments to be highly applicable to children. And I think the current work that the FDA is sponsoring through the Stanford/UCSF CERSI project to develop PROs and to validate them with work from Chiu-Yu Chen, John Johnson, and others, I think, are critical to reaching that endpoint.

Ultimately, blended instruments that allow the patient to report scores first, but then kick in a surrogate to impute them reliably in the event that there isn't a voice, may be an ideal way to set up this system for children.

And I think one of the most exciting developments is that with the ACTION registry, different from the Heart Failure ACTION study, which is a multicenter quality improvement registry, there's been enormous amounts of interest from Melissa Casino (ph.) and Lindsey May (ph.) and others to really take whatever we find would be the most promising metric and rapidly implement and distribute that across centers through the ACTION network. I think with that, I'll stop there.

DR. CALDWELL: Thank you, Chris.

Now I'd like to introduce our final panelist, Ms. Heidi Dohse. Heidi is the Founder of Tour de Heart and will give a patient perspective to round out our panelists.

Heidi.

MS. DOHSE: Thank you, Brittany. I would just like to say that as a patient, I very much appreciate the opportunity to participate on this panel. I have actually lived this journey as a patient with heart disease and medical devices for most of my life. I was diagnosed in 1982 at UCSF with a rare heart arrhythmia and then had an experimental procedure in 1983, one of the first AV ablations which left me a hundred percent pacemaker dependent. So, I've been a lifelong patient since then. Next slide.

So, during this journey, and one of the things that I've really noticed in working with my healthcare team in research projects and in the work with the healthcare, my healthcare ecosystem, is that my definition of a successful outcome is different than many other patients' definition of a successful outcome and is certainly different than what my healthcare team had expected.

So this idea of how do we begin to use data and both generate it from implanted medical devices and collect it in the healthcare system and marry that with data that is generated in the context of me living my day doing what's important to me. And I think that as we scale this across many patients and include many patient voices, we'll begin to have a better understanding of how to develop and design therapies that include or provide that custom personalized experience at scale in a cost-effective way.

So for me, if I look at, I have my implanted device that helps me feel safe and a device, the Latitude Communicator, that's collecting information in my home, but the part of me that's an athlete, the part of me that's training for bike races and Iron Man and things like that, it's the opportunity to be in the human performance lab collecting VO_2 max, lactate threshold, and power metrics along with having my pacemaker tech rep in there

with the ability to optimize my device to get the performance that I'm interested in and while I'm at home, I have my Apple Watch that allows me to capture 30-second EKGs when something doesn't feel right. And that becomes information that allows me to be a co-collaborator with my healthcare team on the decision making of what do we do or what needs to be done to allow me to have the outcomes I'm interested in. Next slide.

And this is where it gets -- I think that there are so many opportunities in this new world of PRO data along with the work that's traditionally been done in medical device product life cycle. So, the patient life cycle typically hasn't been a part of that discussion. Products and medical devices are developed in more of a bubble of one-time use, but if we think about the patient life cycle, the journey that I've lived and some of these key phases of initially there were symptoms and a diagnosis and then there was a therapy, surgery, or treatment that then led to a device being implanted and I had to go home and learn how to trust my body, trust the device, and have some sort of window into my body to help me feel safe and then just about the time that happens, I have to, oftentimes, go back in and have another device implanted.

And then there's the unintended outcomes or consequences of multiple devices that were never really thought through how would they work. You know, again, I'm on my seventh device and the issues that I've had that were serious complications such as leads become infected when they had to be extracted, that led to a viral cardiomyopathy and I still suffer and deal with heart failure and then over the years, scar tissue that built up that then led to open heart surgery to go in and rebuild that vascular system.

So there's, you know, thinking through what are opportunities to make the transition from device to device more efficient and less consequential and then, as a patient and a person who is living an amazing life and doing really interesting things, how can my voice be added to the research and product development life cycle for industry. And I think that's

where it gets really exciting to have many voices with many outcomes and patients in different phases of this journey coming together for better products and better outcomes. So, thank you for the opportunity to present my journey.

DR. CALDWELL: Thank you, Heidi, and thank you to all of our panelists for the excellent introduction. I'd now like to shift our discussion over to the question session. Please feel free, from the audience, to submit questions to the web form or the app.

Our first question is for Dr. Bram Zuckerman. Bram, how can PROs be used for products which can be used across different disease states like vascular access devices?

DR. ZUCKERMAN: Okay, so that's an excellent question. The first thing I guess I would venture is if a product is thought to be applicable for a PRO, talk with patients and PRO developers as to how the right questions can be asked. For example, Heidi just gave a really nice talk where she talked about the patient development cycle, a concept that I really am enthusiastic about.

In the case of a vascular hemostasis device, we're talking about issues like decreased time to ambulation, how patients feel and experience that versus the hard clinical endpoints are sometimes an increase in complications. And so, if we go back to the FDA graphic, we're talking about looking at the totality of the data where a regulator would have to look at the patient experience versus any adverse clinical sequelae. And again, I think it is somewhat disease specific and it might be helpful at this point to turn that type of question over to Dr. Spertus or other panelists who are more expert in the actual development of these PROs and can help us validate them. Thank you.

DR. CALDWELL: Dr. Spertus, would you like to respond to that question?

DR. SPERTUS: Well, sure. I mean, I think that Bram has done a very good job, sort of, laying out the challenges. And I think that there's a lot of common sense in what the FDA needs to think through, which is what is an important outcome for this specific

treatment, how is that impacting the patients, and how does it compare with the other outcomes and risks that exist. And when I try and describe to my mom sort of what I've done with my life, she just can't believe that I got paid to just figure out how, you know, patients are feeling and benefiting for different treatments that we offer them and she says, “what have people been doing all along, isn't that what was science is all about and medical research is all about?” And I go, “mom, you know, it hasn't really happened that much and the PROs are just the way to try to reproducibly and accurately and sensitively measure what's important.”

So, for a vascular closure device, it's thinking through clinically what are the implications of that device, how does that manifest itself to patients, what are the things that might lead to a better or a worse recovery from this. And, if there is a PRO that already -- that doesn't exist about it, then you have to decide is this PRO really essential for quantifying what you're trying to improve with your new innovation in vascular closure and if it is, and one of the great advantages or distinguishing features of your treatment is something that's more comfortable or better for patients, then you have to develop a PRO to be able to elicit that information because nobody else can describe what the patient's experiencing.

And so, where it's relevant in understanding a differentiating feature or an improvement or an innovation in your treatment, you got to figure out how to collect that information. And I think it's just really trying to provide the kind of common sense that you can explain to my mom what it is you did and why your new treatment was beneficial and if you can pass the Mrs. Spertus test, well, then, you're well on your way.

DR. CALDWELL: Thank you. You both mentioned the patient experience, so I'd like to now ask Heidi. Heidi, can you explain why the voice of one patient doesn't represent the voice of all patients?

MS. DOHSE: Yes. I would feel bad if all patients were kind of held to the outcomes based on my voice only because not everybody's idea of a successful outcome was crossing the finish line of Iron Man. So I think that having many voices with -- you know, to collect information on where are they in their journey, if it's their first initial experience with being treated they're in a very different place and their concerns and what their expectations of outcome are very different than where I am 37 years later with my treatments.

So, it's important to you to have a variety of voices so that we also don't just focus on the nice neat box of the typical heart patient for a pacemaker. The messaging is all designed around the 65 to 85-year-old with a successful outcome of, you know, able to walk their dogs and things like that. Everything outside of that is then considered an outlier. The outlier population of patients is now much larger than that nice neat box. So, the more that we can include all of the voices, I think we're going to have better therapies, treatments, and outcomes that are meaningful to a broader set of patients.

DR. CALDWELL: Thank you.

Our next question is from the audience for Dr. Courtney Lyles. Courtney, can you talk about the stem of the PRO that you presented was changed from "how limited are you" to "how hard is it." Do you think that these are asking the same thing and do you think patients understand that these are asking about the same concepts?

DR. LYLES: Thanks so much for that question. Yeah, I want to be clear that the version that we showed as a new version or a slightly adapted version has not been validated or tested in any formal way yet. It's our first take at trying to really think from more of a health communication blend rather than potentially a psychometric one yet about how patients might perceive the question and really thinking about the reading level and the literacy level of the question. So, like I mentioned briefly in the talk, from a health communications standpoint, multiple syllables and longer sentences are just harder for

patients to interpret. And so, whenever we can break those up into shorter words or shorter sentences, frankly, it works not just for patients with health literacy challenges that I mentioned in my talk, but actually for all patients that actually tend to be better at wording of things. So that's sort of the broader points that I'm trying to make but it has not been validated or tested, and what we're doing is showing patients both versions, actually, in the last set of interviews that we're doing and trying to understand sort of exactly what the question is getting at, do they mean the same thing in a qualitative sense and how patients perceive that.

DR. CALDWELL: Okay, thank you.

Our next question is for John. John, how do you adapt the scoring or adapt it for external factors that may impact responses to PRO measures? For example, during COVID, activities like shopping or walking may be restricted due to environmental reasons, not how the patient is doing.

DR. SPERTUS: So that's a great question and, you know, we had -- I had the privilege of speaking with CDRH about what is likely to be the impact of COVID on KCCQ responses and frankly, I can hypothesize, we don't really know. You know, my suspicion is that patients are doing less and that the way -- the KCCQ was very much intentionally designed to be disease specific.

So if something external to your health or another co-morbidity, there are patients -- you know, a patient who has heart failure and is an amputee is not going to be climbing stairs or running to catch a bus, and so we explicitly wanted to keep an option that we were limited or did not do this activity for another reason so that we were really trying to, in a fine-tuned way, measure the impact of heart failure on the patient's health status.

And so, my suspicion is that in patients who are really taking COVID very seriously and really locked down and only ordering food, you know, to be delivered and dropped off

at the front door are likely going to be doing a lot less activities and there will be more missing items. I also suspect their symptoms will not be as bad. Now, I could be wrong with that, but usually the more active you are the more often you'll have shortness of breath and fatigue, and we need to really study this and I think there's going to be a tremendous amount of variability. I mean, you just had to look at the way -- the presidential debate last night and how different people view the same situation, right?

I mean, some people in a COVID environment are being extremely conservative and doing very little activity, not stepping outside the door, and others are absolutely not wearing face masks, ignoring the whole thing, it's all a leftist hoax, and they're not paying any attention and limited at all. And so, when we try and understand the impact of an externality, we're going to have to measure how the individual patient responded to that externality and so it's going to require additional data collection, I think, to sort that out.

And, you know, one thing I'll just, because I have the podium right now and because my President taught me I can just start talking as much as I want and ignore all the rules of the engagement, I would say this, that there are tradeoffs in any kind of PRO where there are people who are trying to complete triathlons and at the very high level of functioning there's a lot of nuance needed in understanding how their heart failure is impacting their condition, and there are other people who are waiting for a heart transplant and at a very different end of the spectrum.

And we sought very hard to develop the instrument that was, sort of, gender neutral, SES neutral, race/ethnicity neutrality. I mean, at the time we were developing this, activities used to include golf or things like that that were completely irrelevant to large proportions of our population, and so we worked very hard to do the best we could at the time. But whenever you get to an individual patient, they're going to raise nuances that would be wonderful to measure but may not be applicable to everybody else. You know,

some patients don't have lower extremity edema but they get swelling in their hands or in their abdomen but no lower extremity edema and they say well, the lower extremity edema isn't relevant for me. We have to make tradeoffs if we want a reproducible scale across populations of patients and this is a challenge. And, I do worry, I mean, Dr. Lyles is doing excellent work. If she ends up rewording the questionnaire, you know, 20 years of research determining what a clinically important difference is may have to be redone. I clearly realize that we could've written it shorter, we could have used tired instead of fatigue, but all but one of the patients seemed to understand fatigue and one said I didn't really quite get it. You know, are we going to have to -- we have to move beyond constantly tweaking the instruments to start applying them and they can always be improved, I get that, but then if we have to reproduce 20 years of work before we believe the results, it creates challenges.

And so, I just think we need to realize that these things aren't perfect, but nothing is perfect. I mean, the echo is not a perfect assessment of LV gradients, the angiogram is not a perfect measure of coronary stenoses, you know, we can always get better at our measurement and we can always improve our techniques, but that doesn't mean we should use that as an excuse not to move forward with bringing the patient's voice into an outcome of clinical trials or into regulatory decisions because an approximation that's close is better than ignoring the patient experience altogether, I would say.

MS. DOHSE: And I'd like to just jump in there --

DR. CALDWELL: Go ahead.

MS. DOHSE: -- real quickly because when my heart failure, when I was first diagnosed and it was severe enough where walking up a set of stairs was difficult, I couldn't do the things that I loved, and I did learn to play golf because that's all I could do. And so to the point, like, there are phases of my patient journey where that was all very relevant in its

current state. I chose to do the work to get to where I am today, which is training for triathlons and racing mountain bikes, but it's been hard and it took work and it was made possible because I had tools to allow me, as an athlete, to feel like I was safe enough to take the steps to do the work to complete the journey and reach my goals. But as a patient, you know, it very much was in the ballpark of I couldn't go up stairs without being fatigued and breathless, swelling and things like that. But again, the patient journey and patient life cycle when married with the traditional life cycle, I think we have lots of overlap and also opportunities to improve over time.

DR. CALDWELL: Thank you.

Our next question is for Chris. Chris, can you speak about adapting or modifying a PRO instrument for a younger child, maybe 6 years of age?

DR. ALMOND: Yeah, that's a great question. I think, you know, there's probably two or three different elements to it. One is that if one is kind of motivated to try to keep the language and metric as consistent across age groups to avoid having -- breaking up into kind of infants and toddlers and adolescents, I think one thing is trying to use language that's agnostic to your age. So for example, we might say in an older patient that they're experiencing nausea or vomiting and again, GI symptoms tend to predominate in kids.

In a child where a mom or an infant where a mom is reporting it, there's really no way to infer whether there's nausea that's there, you might just observe feeding intolerance. And it may be that that kind of shift toward language that I think the KCCI does well trying to make it as agnostic as it can to different groups, I think would be one way to do that, so we would talk more about having problems with feeding intolerance rather than necessarily nausea.

I think another issue that has been alluded to is having surrogates who are essentially reporting on behalf of children and I think this is oftentimes not to be a parent

but in many cases, actually, a bedside nurse after several hours of working with the child will start to get a feel for how that patient is doing relative to their baseline. So, I think imputing some of that information can be really helpful, as well.

And at the end of the day, I think, as we start to think about trying to have instruments that are kind of streamlined across different age groups, I think one of the things that we want to consider doing is to have kind of a first choice would be the patient report, a second choice would be a surrogate, and then again to try to avoid missing data there may even be a third, which is how is the patient tolerating their feeds, kind of objectively, so that we end up with something that's a blended instrument across age groups. So, I would say those three strategies are things that may help us to do that.

DR. CALDWELL: Great, thank you.

The next question I have is for Theresa. Theresa, can you discuss the challenges you've encountered when gathering quantitative and qualitative data and how you balance their interpretation when modifying a PRO instrument?

DR. COLES: Absolutely. So, I think going into the study that we designed, we thought very carefully about how best to get feedback from patients and clinicians and thinking about how the KCCQ may be interpreted differently by gender, and one of the ways we did that was going in with a very strong hypothesis that this could potentially be gender related and we worked with clinicians from the get-go to develop hypotheses. The next thing that we did was we did a quantitative study, the very large HF-ACTION study with thousands of patients.

That being said, that's one quantitative study that we're pulling from so we had to take that into account. Based on the steps one and steps two, I don't know if you guys remember my slide, but there are two steps based on the feedback from clinicians as well as the study team and our quantitative data on moving into the qualitative phase in which

we're getting feedback directly from patients on things we found in the quantitative, and the hypotheses that were developed in step one. So one of the challenges we could potentially run into is that there may be mismatching results in the quantitative and qualitative and how do we address that. So one way we think about that is that our qualitative study is developed specifically to look at gender differences, if they exist, and we're pulling from patients who are the different samples from the HF-ACTION study so we're looking at a broader range of patients and that's something to consider as we look at the results.

We also are very careful to look at the magnitude of results from the quantitative study as we move into the qualitative. I think, as John had mentioned earlier, is it a problem that one patient says that they don't understand fatigue or not, well, I think that's an inherent struggle that we have with any kind of qualitative work. There are no guidelines for you to know when is it a problem and so that's something we all have to consider as a study team.

DR. CALDWELL: Great, thank you.

My next question is for Bram. Bram, can you speak on the important differences in how the patient perspective is measured in a drug trial versus a device trial?

DR. ZUCKERMAN: Thank you, that's an excellent question. I think part of the genesis for this question comes from the fact that characteristically, at the Center for Drugs, let's say, in the heart failure arena there's been a strong emphasis on so-called heart hard clinical endpoints, reduction in mortality and heart failure hospitalizations. But I'm happy to say, as Dr. Spertus emphasized, that thinking has changed at both the Center for Drugs and Center for Devices. After all, the KCCQ is an approved MDDT instrument at both centers.

Secondly, the Center for Devices and Center for Drugs has been working very actively

in the heart failure collaboratory and certainly hearing Dr. Stockbridge speak there, Dr. Stockbridge is the director of the cardio-renal group, I think there's an awareness, as you've heard here, of the importance of the patient perspective complementing the clinical endpoints that we can measure.

So, in responding to the question, while it is true that the two centers operate under different regulatory guidelines, I think there's a strong appreciation of the importance of PROs in our ongoing clinical trials and if there is a drug developer in the audience, I would certainly recommend that they interact with the appropriate review division at CDER the same way that we would strongly recommend that anyone interested in incorporation of a PRO in a device trial, just contact the appropriate device division. Thank you.

DR. CALDWELL: Thank you.

For our last question, I'd like to open it up. But I'd like, Heidi, if we can start with you. Can you tell me why anecdotal reports of patient experiences can't stand up robustly in design of PROs?

MS. DOHSE: I think that the reason that individual anecdotal PROs won't stand up is that at that point you're coming from that individual's perspective and there isn't a way to really validate a metric that is measurable consistently across their story versus the next person and the next person because as patients, we're kind of coming from our own -- with our own filters and our own expectations of what we thought was going to happen. And so, measuring that anecdotally doesn't, I think, hold up or stand up, but creating these tools that allow for a broad voice to be captured and measured and made useful, I think, is very beneficial.

DR. CALDWELL: Great. Are there any other additions from our panelists?

DR. ALMOND: I would just add to what Heidi said. You know, I think it's interesting when we think about anecdotal stories, that they still actually can have great power in

conveying understanding. We talked about a teenage girl who came in with heart failure that wasn't diagnosed for 3 weeks and she had her appendix out because she was presenting with abdominal pain and then had another several procedures trying to work up her belly and that story starts to convey understanding that GI symptoms are very important in the pediatric patient with heart failure. But it's true when we go to measure things that that's very difficult to do. However, if we can have a blended approach where those stories actually ring true with both patients and providers because the scales reflect the severity of those GI symptoms, I think that that's probably where we really want to get to. I'm always amazed at the power of an anecdote, but I think it's really when the scales actually can reflect those anecdotes that it has the most power.

MS. DOHSE: Yeah. I just --

DR. CALDWELL: Thank you, I want to --

MS. DOHSE: Oh. I was just -- I was a child that my stories, my anecdotes weren't taken seriously and so I was never officially diagnosed until I was 18 and then they didn't know why I lived as long as I did. So, it's certainly interesting and could be helpful.

DR. CALDWELL: Thank you. I want to thank all of our panelists for the excellent discussion. It's been a really great panel session.

Now I'd like to hand it over to Ms. Kathryn O'Callaghan Capanna for a discussion on Developing PRO Instruments When One Does Not Exist.

MS. O'CALLAGHAN: Thank you, Brittany.

Good afternoon, everyone. Good afternoon to all the panelists for this upcoming session and thank you all, to those of you who are following along with us and participating with us from home or wherever it is that you are right now.

So, this session coming up will extend some of the conversations you've been listening to earlier today. We heard some very interesting discussion about how PROs can

be incorporated throughout the healthcare ecosystem and clinical care and other settings, and some interesting discussion about how to adapt and modify existing instruments to new populations and new uses. This discussion we'll talk about developing PRO instruments when one does not exist and we'll focus on three case areas starting with surgery, moving on to LASIK plus a few others, and novel technologies in the diabetes space. Each area will include the perspective of an instrument developer, as well as FDA's regulatory perspective, and we're very fortunate to have with us today a patient who will share her experience and perspective as a patient representative and collaborator. We also have, as with the other sessions, reserved ample time for audience Q&A, so this is a great opportunity to put your questions to these excellent panelists, so please do jot those down as we make our way through the presentations.

So, with that, let's begin. Our first focus area is surgery. Allow me to introduce Professor Andrea Pusic and Dr. Sung Yoon.

DR. PUSIC: Hello, thank you. I'm Dr. Andrea Pusic, I'm a plastic surgeon, and my clinical area is primarily breast reconstruction for breast cancer patients. So I entered into the world of PRO instrument development largely because previously in plastic surgery we just didn't have instruments that were specifically designed for the needs of our patients and as you can imagine that in plastic surgery, however, so much of what we do is with the view of improving the quality of our patients' lives and optimizing outcomes from their perspective. Next slide.

So, going back about 15 years ago with funding support from the Plastic Surgery Foundation, we set out to develop a series of patient-reported outcome instruments for plastic surgery patients. I think the strengths of this work are the -- our strong emphasis on patient input and rigorous qualitative work. It is just so important to engage with patients early on and to essentially identify what matters the most to them, so we're asking the right

questions about things that matter to them and also using language that resonates with them, that has patient voice. And I think, to me, this is really the essence of content validity.

I think a second big strength of this work has been the use of Rasch measurement theory. We get help in our field test work from thousands of patients and then we apply Rasch measurement theory and Rasch psychometric methods to ensure that we are developing scales that would provide strong psychometric properties with accurate, reliable, meaningful measurement.

The BREAST-Q was the first patient-reported instrument that we developed and I'm happy to say that it's recently been assessed through the MDDT qualification process. The FACE-Q both for facial aesthetics and reconstruction, similarly in that process now. CLEFT-Q, which is instrument -- it's a large international effort to develop a patient-reported instrument for children and adults with cleft lip and palate anomalies and treatment and it's been used widely in clinical care and benchmarking in both developed and developing countries. BODY-Q for bariatric and body contouring procedures.

New instruments that our team is in development, and we're excited about, is the WOUND-Q for chronic wounds, it's just been released and I'm really excited about this measurement because I think we're going to learn about the impact of chronic wounds via patient perspective. HAND-Q for hand surgery, SCAR-Q for patient impact of scars, and both of these have been large international efforts. And finally, GENDER-Q, which is our newest measure, which is currently in its qualitative phase looking at the impact of gender treatment. Next slide.

I'd just like to say that this has been a tremendous team effort and I think that probably the third big strength of our team is our complementary skills, as I say, I'm a clinician. Dr. Anne Klassen is a quality of life researcher at McMaster University in Canada

and Anne is expert in qualitative research methods and Anne really gets sole credit for establishing content validity of our scales and our measurement tools. Dr. Stefan Cano is a psychometrician and expert in Rasch measurement theory, and Stefan has been responsible for ensuring the strong psychometric properties of our scales. Thank you, and I look forward to the comments from the other panelists.

MS. O'CALLAGHAN: Okay, thank you.

Next up, we have Dr. Sung Yoon.

DR. YOON: Hello. Katie, can you hear me?

MS. O'CALLAGHAN: Yes, we can. Are you able to turn up your volume a little bit?

DR. YOON: I'm at the max.

MS. O'CALLAGHAN: Okay, go right ahead.

DR. YOON: Thank you. I will briefly discuss how PROs are used in the regulatory decision making for medical devices. PRO reports the status of a patient's condition that comes directly from the patient, so patient perspective is important, especially for aesthetic devices. Often these are elective procedures in which the patient is deciding, along with their clinician, the best treatment for them. Next slide.

Patients may be weighing several options and therefore an understanding of patients' perspectives on different treatment options can be an important part of patients' decision making.

As you heard in the conference earlier, PRO instruments should be fit for a purpose. What instrument is best depends on what it's going to be measuring and how it is being used in the clinical study. So, we encourage sponsors to engage with FDA early, as we all have the same goal of protecting and promoting patient health.

PROs can also be used to assess for effectiveness. We have seen PRO scales, such as BREAST-Q and FACE-Q, in medical device clinical studies. We really encourage sponsors to

engage with the FDA to determine the applicability of a PRO measure for their clinical study and for the appropriateness of a PRO to address relevant questions, whether the questions are acceptable to patients, easy to administer, or whether the PRO score is interpretable, etc.

They can also be used to collect meaningful safety information like symptoms and functional impact such as pain, treatment tolerability, treatment impact, and quality of life along with the assessment of the treatment on the patient or in comparison to a control of approved devices. Some aesthetic devices, for some aesthetic devices we have seen patient diaries used to collect PRO for short-term common responses to treatment effects.

FDA's decision making is always based on the analysis of benefits and risks of a device or treatment or intervention and understanding how the patient perceives the benefits and risks is an important part of this assessment.

Patient perspective information obtained during the clinical investigation is used in physician or patient labeling -- next slide -- of the cleared or approved product to help inform patients with their decision making. This labeling information provides an effective communication of patient expectations of treatment and results in medical device labeling. Thank you.

MS. O'CALLAGHAN: Thank you, Dr. Pusic and Dr. Yoon.

Our next area is what I'll call LASIK plus. Two of our panelists will focus on LASIK and one will touch on LASIK and a few other areas. We'll begin with Professor Ron Hays, followed by Dr. Malvina Eydelman and Ms. Barbara Berney.

DR. HAYS: Thank you. You can hear me now?

MS. O'CALLAGHAN: Yes.

DR. HAYS: Okay, just wanted to be sure. Okay, so the development of the PRO questionnaire that I'm going to be talking about briefly was motivated by a high volume of

surgery that's performed and reports by patients of dry eye symptoms and burdensome visual symptoms, as well as dissatisfaction with visual outcomes, so that was the motivation. Next slide, please.

So, the project involved developing and evaluating psychometric properties of this patient-reported measure to assess, primarily our focus was on symptoms, double images, glare, halos and starburst, and we also wanted to assess satisfaction with LASIK surgery. So that's what our focus was and this was a collaborative effort between the FDA, including Malvina, which you'll hear from, and the National Eye Institute, EMMES, San Diego Naval Medical Center, UCLA, and RAND. So, in a lot of these kind of projects you do need expertise that varies and a lot of collaborators.

So, when we started the project, in addition to doing a literature search, which you always want to do, and then from there we decided well, we needed input and we got input throughout the process from an expert panel of ophthalmologists, optometrists, and clinical researchers, but in addition we asked patients to identify important concepts to be measured and we also used them to ensure that the wording of the instructions we used in the questionnaire and the questions were understandable. And this is a pretty common practice today, but it's one that we tried to adhere to throughout the project to produce the questionnaire that we can talk about later.

So now, because I wanted to stick to my time limit, I'll go ahead and pass it on to Dr. Malvina Eydelman and she's going to talk about the FDA regulatory perspective on this measure and other projects.

(Pause.)

MS. O'CALLAGHAN: We can't hear you.

DR. EYDELMAN: How about now?

MS. O'CALLAGHAN: Great, thank you.

DR. EYDELMAN: Next slide, please. Ron has highlighted some aspects of PROWL development. The need for development of PROWL originated from FDA's listening to patient experiences. CDRH received complaints from patients regarding symptoms such as dry eye, glare, halos, starbursts, and double vision significantly affecting patients' quality of life following LASIK. None of the questionnaires used at the time quantified the impact symptoms directly had on performing usual activities. FDA, in collaboration with NEI and DoD, produced a web-based questionnaire with new scales that can be used to more thoroughly assess symptoms before surgery and to monitor patients for visual symptoms as well as satisfaction after surgery. The new scales include images and clear definitions for the visual symptoms. This approach was shown to be so effective that we have reproduced it in the PRO development for another technology associated with visual symptoms, specifically premium intraocular lenses.

At the 2014 public workshop held to expedite innovation of these type of lenses, a consensus was reached that a validated PRO tool was needed to assess potential visual compromises associated with the technological advancements offered by this technology. A unique collaborative effort between American Academy of Ophthalmology, industry, and FDA resulted in a new PRO that is currently in a process of completing its field testing. Next slide.

I have had the privilege in leading FDA's efforts in PRO development in a couple of other areas where we believe that incorporating patients' voice is essential for benefit-risk assessment of particular type of devices. These areas include our work on developing PRO for minimally invasive glaucoma surgical devices, which you will hear more about from Dr. Roe of Verana Health later on today. Also, our early efforts on developing PRO to assess patient symptoms in the whole spectrum of temporomandibular disorders. In addition to other government and academic centers, we're very fortunate to collaborate with patient-

led TMJ Association. All of these efforts underscore my belief that it is essential for FDA to listen to patients' perspectives during development, evaluation, and use of medical devices.

Our next speaker, Barbara Berney, has been instrumental in communicating LASIK patients' perspectives and we're delighted to have her here joining us today.

Barbara.

MS. BERNEY: I'm delighted to be here. I'm so happy you included me. I'm an artist and I had LASIK in 2019 -- in 2001 and unfortunately, it changed my life in two ways. It was a curse and a blessing. It irreparably damaged my vision, but it's a blessing because I am now a voice for patients and this is my story.

I lost my clear vision forever. Left with a plethora of complications of varying severity, I could find no medical information that could help me make sense of my suboptimal outcome. As an artist, this should've been catastrophic, but had I accepted that -- eventuality, I refused. I soon discovered the Surgical Eyes Foundation patient bulletin board on line and although I took comfort knowing I was not alone, I realized that most of the contributors did not share my own personal response to their misfortune.

I began working with unhappy patients and in 2003 I assumed the leadership of SE. The following year, my executive director, Dr. David Hartzok, and I dissolved SE and founded the now former nonprofit Vision Surgery Rehab Network. Through my work with Vision Surgery Rehab, the FDA found me following their April 2008 LASIK complications public meeting, which I couldn't attend because I had just had hand surgery, and recruited me to serve as patient representative on the LASIK quality of life, the PROWL study, and this began the blessing of advocating for patients in several health areas and my first experience with PROs.

Once I began working with LASIK patients, I realized that, through my own experiences and everyone else's that I talked to, pretty much the medical and industry

factors did not accept our complications as complications. They called them side effects. Well, for those of us who had life-changing side effects, that didn't float very well and there was very little information about what to do. Mostly because there wasn't really much to do. So, over the years we tried as much we could to publicize this. There are several different groups that are far more vocal than I was. My group was focused entirely on providing help for patients finding rehab options. And during that 2008 meeting, that's when everybody got together and aired their grievances.

We provided a statement because, of course, I wasn't there, and when I was approached to be a part of the PROWL study, I was told by some of these other groups that I was a sacrificial lamb. Well, I don't believe I was, I believe that my input was important, especially on the issue of the images because my images were far worse than anything that I saw there. But that experience led to the FDA hiring me as a patient representative for lots of other representation at advisory committee panels and I probably served on 12 by now over the years. I find that because patients all experience things differently, it is very important to find as many patients as possible to give their impressions and tell their stories.

MS. O'CALLAGHAN: Thank you, Barbara.

For our third session, we will be touching on the use of PRO instruments for assessing novel technologies in the diabetes space. And our developer is Professor Kath Barnard-Kelly and for the FDA perspective, Acting Office Director Dr. Courtney Lias.

Kath.

DR. BARNARD-KELLY: Hello. Thank you so much for inviting me. I'm actually humbled and privileged to follow Barbara's powerful story there because she couldn't be more right in what she says.

We work in the diabetes space. I'm truly privileged to work with some leading

experts in our field, Korey Hood, Jill Weissberg-Benchell, and Lori Laffel, all global experts, and we've all worked in psychosocial aspects of diabetes for many, many years. We work specifically with technologies and the INSPIRE measures that we developed and recently were qualified through the MDDT process. We want to understand the expectations and the important issues, the uptake and ongoing effective use for these systems. It's really important. These technologies are brilliant, but in themselves they are not enough. And it's the way that people are able to engage with them and benefit from them that makes the difference between improving psychosocial functioning and quality of life and not just becoming another burden of disease management. Next slide, please.

So what we wanted to do, we wanted to develop an instrument that would rigorously assess the psychosocial outcomes of automated insulin dosing. Now, these systems do some things subtly different to everything else on the market for diabetes and that is that it will adjust your insulin dosing based on your glycemic level. So, it takes away a lot of the complicated math. However, it also comes with additional problems such as concerns about safety, for example. Sense of identity—if I'm not doing all of these things to manage my diabetes, what does that make me, what does that mean my life will look like, how does that mean my everyday functioning will be altered, and it is altered.

It was very, very important to us that we were informed by good science, by extensive qualitative data. We had focus groups and entities with over a hundred people, focus groups with again, many, many more people. We went through scientific literature, as was said earlier by Ron, and we looked at many, many clinical trials.

We wanted to design our measures to meet the needs of youths with Type 1 diabetes, their parents, of adults with Type 1 diabetes and their partners because diabetes is a family disease. It was very important to us that they were agnostic of social economic status, cultural diversity, and health literacy. Next slide, please.

So, like I say, our measures now are being used by all artificial pancreas, automatic insulin dosing system, clinical trials globally. We're very happy that people have been so engaging and so welcoming. We've had a huge amount of interest in terms of industry and other researchers and clinical teams asking us about the MDDT process, which I think is very promising, and we try very hard to encourage others to follow the MDDT process because it's really, really important that we can demonstrate in our patient-reported outcome measures that we have the same rigor and the same level of excellence that you get in any biomedical measure; it's hugely important to us.

And what we're currently doing is we are adapting the INSPIRE measures for use as a clinical tool so that it will help healthcare professionals when a patient presents to them to understand their own personal facilitators and barriers to these systems and how (a) whether they are appropriate at this time or (b) how we can on-board effectively to really meet the needs of every individual user. It's important that the measures are consistent, they're standardized, and they're sensitive to time, they're useful over time.

So that was our perspective as the developer, and over to Courtney for the FDA perspective.

DR. LIAS: Thank you, Kath. I'm Courtney Lias, I'm the Deputy Director for the Office of In Vitro Diagnostic Devices, and in our group we do regulate diabetes technology devices. And over the years, the development of these AID systems was a really important project for us, and one of the most important aspects really was listening to experts in the community, like Kath, and the healthcare providers who were studying the development of these devices, as well as patients, and the things that we heard from patients ended up being some of the most important things that we could learn about how to get these products to market.

One of the things we learned is they were really excited to get this type of new

technology, the idea of reducing sort of the day-to-day burden of decision making was something that's very attractive to many people with diabetes. We also learned that some people were worried about losing that control, as Kath mentioned.

So with that diversity came a second thing that we really learned from patients which is, not every device is good for every patient. And, where some people may have thought that the new technology would be right for them, we've learned from patients over the last few years that sometimes after trying it they decided it really wasn't for them, while other people were skeptical and found that it really helped them in many ways that they didn't expect. And finally, sometimes they have impacts beyond just the diabetes health that are hard to quantify.

We also learned from investigators, from patients, and from doctors who work in diabetes, that sometimes products are beneficial without necessarily meeting the traditional scientific and clinical endpoints that people want to use. So, in diabetes hemoglobin A1c is often used as an endpoint in clinical trials to show that a device is effective. However, sometimes you may not have a benefit in A1c but you may have benefits in other places. You may have benefits in the amount of sleep that somebody gets, you may have benefits because a parent no longer has to wake up and take care of a child at night as many times and they get better sleep and can care for themselves and their child. You may have benefits, mental health benefits and things like that.

So, the type of instrument that Kath and her group developed and qualified through the MDDT process really provides a tool to enable FDA to quantify the benefits of devices that go beyond just these clinical outcome measures that we're used to using from the serum biomarkers or clinical outcomes that are measured in the trials. And so, in this way we can assess the benefits from the PRO measure in contrast to the risks of the device to make decisions about products that are a little less traditional.

Now I'll close with the other benefit. Not only can we make decisions really considering many more benefits of the device compared to the risks, we can also provide that information to patients. We can put this information in a device label, companies can share this information either on line or in their promotional material, to show patients here are the things that our device does, here's some things you can consider, and as Kath mentioned, here are some things that may enable conversation between healthcare providers and their patients about which device to choose. One of FDA'S goals is to get as many choices of differently designed devices out there to get access for patients who are just as different themselves. So, we're really looking forward not only to greater use of this PRO, but the development of future PROS to enable us to do this better.

MS. O'CALLAGHAN: All right, thank you all for those excellent presentations and remarks.

Audience, this is your turn to have your questions answered, go ahead and initiate those now, if you'd like. And as the questions start to roll in, I'll get us started with a few questions about development.

This first question is for Kath, Andrea, and Malvina. Now, for the three cases that each of you touched on, you had different stakeholder needs that drove the PRO instrument development: patient, healthcare provider, and regulatory. Could each of you touch on how you think this impacted your development work?

DR. BARNARD-KELLY: Yeah, I'm happy to go first with that one. Absolutely, there are basically different needs. I spend a lot of my time lecturing and speaking to people about the burden on healthcare professionals because they simply are not trained in psychosocial outcomes, and that's incredibly difficult for them when, actually, chronic disease management is mostly about psychosocial outcomes and people's ability to self-manage.

So, what we wanted to do with our measure particularly was we needed to understand the burden and the benefit of the AID systems, and they have huge potential and they work very, very well. But we also needed to make sure that healthcare professionals were able to understand very, very quickly each individual user's expectations, anxieties, and to really, as well with the research teams for example, will you be able to assess this and publish that data in the literature alongside the biomedical outcomes because that will help healthcare professionals to really tailor on-boarding and support to each individual user.

And in terms of regulation, very quickly touch on that, our experience has been so positive from the FDA. We have engaged, they could not have been more supportive, more engaging, more welcoming. They asked really good questions in a very constructive and supportive way. So, right from the get-go we involved the FDA literally from day one that we were doing this and I'm so glad that we did because they were amazing, Courtney and her team were amazing, they really are amazing.

MS. O'CALLAGHAN: Thank you.

DR. PUSIC: I mean, I'll jump in to follow off of Kath's comment. I think I would agree with absolutely everything she said. I think that got into a little bit also about healthcare providers not being trained or to interpret PRO data, it's not like -- it's not a vital sign you learn about in medical school, no, it's -- and yet it's so important.

You know, going back to the development of, say, our initial outcome measure rounds of BREAST-Q and FACE-Q, it really was, from a surgeon's perspective, it was an initiative to be able to better understand the patient's perspective so that as clinicians we could help our patients make better decisions about treatment. And so, that was essentially saying the patients -- and I'm going to touch a little bit on Dr. Yoon's slide, as well, saying that idea between risk and benefit, patients don't have procedures with the

goal of just avoiding an adverse event, they also want to receive benefit.

And so to Kath's point, how do we use PRO data to help patients better understand perceived benefits of procedures? And if it's only other patients who have had those procedures -- and I'm a surgeon so I'm using the word "procedure" a lot, but it's different types of treatments -- only other patients can really help. They're the only ones who have that information. And then the challenge is how do we capture that information and rigorously develop measure and bring that back to both clinicians and patients in a way that they can use that information in a meaningful fashion.

I think just the two things that I would say we've seen over time is that with wide use of, say -- I'll take the BREAST-Q example, clinicians start to really actually understand the numbers the same way they think about hemoglobins and blood pressures and urine outputs, it's actually -- it's come into that, you know, and I talk about it because we just use -- it's just become so everywhere and it's part of clinical care in that, so I think that has been helpful.

And then I would say from a patient perspective what has been meaningful is pre- to post-data and long-term data so a patient could see "patients just like me came in with a body image score and sexual wellbeing/social confidence level at this level" and we see it going up to here and that can also help a patient make a decision as to whether they wish to undergo therapy.

And I think, also, the comment that Courtney made about not all devices are right for every patient, not every procedure is right for every patient and that's where I really think is the idea of being able to provide patients with PRO data that they can interpret and make better decisions for themselves in an individualized fashion is kind of the place we need to be going to.

DR. EYDELMAN: I guess I'd like to answer your question in a little bit different

format in that I think, even though it might appear to be a different perspective, what we actually aimed for was the same goal and in that respect it was a very similar perspective. For us, understanding visual symptoms was at the heart of the problem and once we understood that without defining, and I think Barbara was very thorough in explaining what she perceived as the image, you know, it was interesting because after we went back, it seemed like the physicians and the patients, when they were talking, they were talking the same -- they were using the same words, but what the patients meant or what the physicians meant was very different.

So just understanding that as the very foundational principle and realizing that in order for all of us, the patients, physicians, and the regulators to deal with the problem in the same way was -- the first founding principle was to define the visual symptoms by both the pictures and the descriptions and I think that's -- in retrospect, it sounds like a very simplistic concept, but just understanding that, and then Barbara is here shaking her head, you know, once we did that we realized that, for example, what we meant, as physicians, I'm an ophthalmologist, so what starbursts and glare meant to me had no way in any -- you know, had totally different understanding for a patient like Barbara.

But once we understood that and spent a lot of time trying to come up with the pictures and the definitions of the visual symptoms, and actually describing the difference of severity that we then can present to the patients so that at the end of the day the questionnaire can capture their experience and we have a point of reference to understand what it is that they're seeing. That in itself was, I think, a transformational journey for us and became, as I said, now sort of a go-to to all the future PROs that I've been involved in for ophthalmic devices that deal with visual symptoms.

As I said, you know, the premium IOLs, it was so much easier to deal with to start that process because we already knew that is the underlying principle. Once we're all

speaking the same language as patients, regulators, providers, getting to the next level is just so much easier. And at the end of the day, by quantifying problems like starbursts and glare and trying to identify which patients would be likely to experience these difficulties, we at FDA now, for the future technologies which are using this questionnaire after PROWL was finalized, can now provide that information for both patients and providers. And those patients and providers, as a result, have a very well-defined tool to guide medical decisions and future research.

Manufacturers can use a questionnaire to gather valid scientific evidence related to the PRO outcomes that they can now that they have been including in the device submissions. And the PROWL can be used in clinical care to assess patients before surgery as well as to monitor for symptoms after surgery which again, it seems like a very simplistic concept, but wasn't able to be executed prior to this validated questionnaire. And throughout our publications we've encouraged all of the ophthalmic community to investigate the predictors of debilitating symptoms using our questionnaire. So a little bit different take, Katie, on your question.

MS. BERNEY: I'd like to make one comment.

DR. EYDELMAN: Please.

MS. O'CALLAGHAN: Yes, Barbara.

MS. BERNEY: Malvina, before I had LASIK, I had -- I thought I knew what starbursts were, too. I had no frame of reference and that's the difference. I was a minus 10 and a half and with glasses I had starbursts. I didn't have anything like what I got now. So, I can't fault others for not understanding because I didn't understand until that happened to me.

MS. O'CALLAGHAN: Barbara, I'd like to continue with you, if you don't mind.

MS. BERNEY: No.

MS. O'CALLAGHAN: Could you speak a bit about how you think patient advocacy

groups can help in the development of PRO instruments and what should developers learn from your experience?

MS. BERNEY: When I set out to work with patients, I did not think I was going to end up doing what I was doing and it became very clear after my first 2 years trying to find help that there wasn't much available. So, the organization that I started was -- we started it to be able to help patients find that information. And once we opened that up, patients started flooding in and telling us their stories and I was trying to find help for everybody. Well, the same consequences yielded very different experiences for patients.

So, for instance, although my vision is pretty ugly, it's very functional and I'm an artist and I'm still an artist, I'm an editor, I'm still editing, but there were people who had nowhere near the level of aberration that I had who were suffering much more than I. Part of that has to do with attitude. However, getting all of those people to give -- to tell their stories allowed me, when I was on the PROWL study, to add a dimension that I wouldn't have had on my own. So, involving the patient advocacy organizations allows you to collect a much wider range of data than simply talking to a few patients or even giving a questionnaire, for that matter.

MS. O'CALLAGHAN: Thank you, Barbara.

We have a question from the audience regarding the use of instruments which may come at a high licensing cost versus developing and validating new instruments for use. Kath, could I ask you to speak to your approach with your instrument, and I don't know if there are others, if Andrea and Ron, if you would like to add, as well, to address that question.

Kath.

DR. BARNARD-KELLY: Yeah, it's a bit of a bother of mine actually. We ask people to assess patient-reported outcomes and then we make it unaffordable for them to do so,

which is unfortunate. We were funded by Helmsley Charitable Trust to develop our INSPIRE measures and we were all very, very clear from the start that they would be freely available, there would be no costs to anybody to use them, anybody can use them, irrespective of whether they're industry, academia, local peer group, anybody can use them and then all we ask is that they do reach out to Korey and sign a licensing agreement, that means that they agree to use all of the questions as written. They're very short, they're 18 questions, 19 questions, but it's important to us that they're validated for the whole measure, so we ask people to use the whole measure and not to amend them, but they are free to use.

DR. PUSIC: I have a comment. Oh, go ahead, Ron.

DR. HAYS: Oh, sorry. Yeah. Yeah, I have pretty strong opinions about this, I've actually written a commentary for medical care a few years ago with other people from the Resource Center for Minority Aging Research and I agree with what was just said, primarily. Whenever measures can be available I think they should be freely available. Of course, there's always the counterarguments against it, but it's really not fair that, for example, the NEI VFQ visual function questionnaire and all the other NEI-supported questionnaires are freely available but there are others out there who you have to pay a heavy price to use their measure and that really detracts from science.

You know, if the measures aren't available, how are people going to be able to evaluate it unless they can afford it and want to spend the money? You know, one of our recommendations was if that's your only choice, that's your only choice and if you have the money, go ahead, but otherwise look for an alternative and we really think these things need to be out there for scientific purposes and not restricted.

DR. PUSIC: Yeah, I would just agree with Kath and Ron on this. So, our work was all funded by the Plastic Surgery Foundation. Our Q-PROM measures are available free of

charge for clinicians, for research studies, for quality improvement. We do charge industry, so with regulatory decisions, we do charge industry for those studies that they're performing and that allows us to be able to continue to grow the portfolio and be able to extend what we're able to offer for our research community, so essentially we bring that full circle around to be able to continue to develop more instruments as the science and the field changes.

DR. EYDELMAN: If I can just -- okay, I'm not muted. If I can just put the plug in that PROWL is free, it's in the public domain and in addition to that, IRIS, which is American Academy of Ophthalmology's registry, is looking into incorporating it into its platform so it will be easily available to all ophthalmologists and all of the users of that platform.

MS. O'CALLAGHAN: And I believe the question as worded was asking for FDA's advice here, so I'll chime in there, as well. Ultimately, it's a business decision on the part of the company, from FDA's perspective, you know, a company would be free to choose any instrument that could be justified to measure what you are aiming to measure. The MDDT qualified tools do provide some additional degree of certainty on the front end because those have been assessed and the data, validation data, and measurement properties have been assessed by the FDA as part of the qualification. You can be assured that the data that would come out of the use of that instrument in your study would be something that we understand and accept for the context of use for which the tool was qualified.

That being said, if either you are looking to measure something different than the qualified tools that are available can provide, or for other business decisions, cost or otherwise, you would choose to develop a de novo instrument, we would still encourage you to communicate with the FDA early on as you are planning those studies. We provide the same kind of feedback to MDDT tool developers around what makes for good validation studies and what kind of information we would be using to substantiate that tool for the

given use.

DR. EYDELMAN: One more comment on the subject. I know in your next panel you'll be talking about collaborative efforts and I'm a very strong believer on large collaborations for these efforts because, as Ron can attest to it, these are very expensive propositions. So, the more partners can share the cost, I think the more probability that the instrument can be free and in a public domain, so I'm a great, great proponent of large partnerships and free instruments.

MS. O'CALLAGHAN: Thank you.

Another question as we're waiting for this to come in, this is regarding adoption and expansion of tools, a question to Andrea, Kath, and Barbara, although others should feel free to chime in as you continue to do. Could you elaborate on the importance of PROM use in patient care, particularly for identifying and communicating concerns that patients may not bring up on their own?

DR. PUSIC: I can jump in on that one. The ones that come to mind is that in clinical care, what we've seen are some questions -- I think, from a clinical care perspective, I think patients frequently actually don't want to complain to their doctor and don't want to say negative things to their clinical care team. I think PROs in clinical care can actually be a way to communicate something. I think negative things, say pain or changes and decrease in physical function, those are unmet needs that can -- that go unaddressed because a patient may not raise them and they may not be encouraged to raise them in that brief clinical encounter.

In my own area in breast reconstruction concerns about, say, sexuality, women have been put on some chemotherapy and other issues that they have, the PROs can pick up on them and make it easier for us to be able to address those. So, I think just in terms of that, it's -- there are unmet needs that PROS can identify and help us in clinical care from that

perspective.

DR. BARNARD-KELLY: I'm happy to go next. Oh, gosh. So, we actually are doing a lot of work currently in a novel tool around illuminating issues for patients in routine consultations and we use an example, we have two patients that present very, very similarly in terms of age, socioeconomic situation, biomedical outcomes, complications, etc. And then when you actually go through the PRO process, it's really obvious that these two very similar patients have very, very different needs.

It's so hard in an artificial environment, such as a routine consultation, to be able to say what's going on in here when all you can think about is A1c and the fact that maybe my A1c's aren't going to be good, maybe like this happened or maybe it's because of this and you're so focused on the biomedical outcomes that are so disease-specific, it's very, very easy to lose track of all of this stuff, that actually it's everyday life that impacts disease self-management that actually isn't disease self-management. And it's really important to remember the healthcare professionals, unfortunately, interrupt their patients on average 12 seconds after they start to describe the challenges that they face. So, sometimes it's a good idea just to stop talking and listen.

MS. O'CALLAGHAN: So important for you to be here for helping to bridge that communication gap between patients and providers. As you were speaking, I was reminded of a comment earlier in one of the other sessions by Kendra Hileman where she showed the large increase in reporting of symptoms when using a PRO versus an open-ended question to patients and so that's just substantiating the point that you're making here.

It also takes what Chris Almond was speaking about in the panel right before this one about the richness of the anecdote and wrap that around the -- maybe the clinical, the crisp clinical terms that we use to describe these symptoms but that may have very different severity or impact on a patient's life and so it's a way to bridge those and to

integrate those.

We have a question from the audience for Courtney. For devices used in preventive medicine, such as those that your office might review, what are some challenges and considerations for PRO development in those areas, particularly speaking about the differences in preventive medicine where patient cooperation and acceptance of procedures are very important?

DR. LIAS: Right. And actually, we see this sometimes with Type 1 diabetes where continuous glucose sensors may be abandoned because of some of the design features of the product. And so, you know, a PRO might've been able to get at aspects of what things might make a person more likely to continue on with the CGM use, etc.

But I think it becomes -- a PRO becomes even more important than typically in cases where compliance with the procedure or the treatment or the tool is necessary in order to achieve its effect or to make sure it's safe. And so, a PRO can be useful in assessing, even up front prior to the clinical study, what are the barriers that I need to consider in my device design, what are the patient populations that are most appropriate for my device, and then at the end of the day, once you're reviewing your clinical trial, it can assess, you know, how can I articulate the benefits of being compliant, how can I -- once again, how can I, as a healthcare provider, recommend certain devices to certain patients to make sure that I actually get compliance based on the factors that are assessed by these PROs.

So, Type 2 diabetes is a place where we are oftentimes seeing technologies coming through saying that they can enhance a patient's ability to reduce their A1c on their own, for example. However, compliance would be required for all of those things and getting information from a PRO about how annoying the product is to use will give you a lot of information about how effective it might be in the future.

MS. O'CALLAGHAN: Thank you.

Another question from the audience, Kath, I'm going to pitch this one to you. Could you speak about any efforts or tools that are being developed to measure PROs for direct-to-consumer devices?

DR. BARNARD-KELLY: So, we have a different healthcare system in the UK, it's a national health system where all healthcare is supposed to be free, accessible, and available to all. Sadly, it isn't, but attempts are made to do that. It's very difficult when you have a direct-to-consumer device, there's one brought into the UK for diabetes a couple of years ago. Much, much hype, amazing marketing around this system. Social media went wild. And it was, like, a lot of excitement. But it was expensive, you know, so you immediately exclude 80% of the population who might benefit from this system, from being able to access it.

But that in itself is not necessarily, like kind of the PRO point. The PRO point is that you raise an expectation that actually may be unique to a very few people that is not translatable to the broader population. So, the points that kind of we're all making earlier around it's really important when you develop a measure that is for as broad a population as you can possibly reach.

When you have a direct-to-consumer device that actually only reaches a few people, but it's very difficult to know that that PRO instrument that would be developed will reach your target audience. I'm not aware of any direct-to-consumer specific PRO measures. A lot of the measures, for example, are for insulin pump therapy, continuous glucose monitoring, like Courtney said, broader psychosocial functioning measures, like SF-12 for example, and they are systems, they're designed for systems broadly. So, I'm not sure but I think the challenges are very much about who is going to be able to afford and access direct-to-consumer devices, tools, whatever, and how representative will they be of the wider population. In my experience, they're not representative at all of people, the whole

range of people that you're hoping to serve.

MS. O'CALLAGHAN: Thank you.

Let's see. We have a few more minutes. I'm going to pose a question to the developers, to the instrument developers. We heard in the previous session about looking at expanding or bridging the use of instruments into different populations or demographic groups, also interestingly somewhat of the inverse situation, which is taking a tool with a lot of components and stripping it down to something that can be used more efficiently in clinical care. How have each of you either expanded beyond your starting point or are thinking about how to expand the applications for populations for use of your tools?

DR. EYDELMAN: I can take a stab at it. So, the PROWL is specifically for patients who have undergone LASIK surgery, but developers of other refractive surgical devices have been interested in utilizing it. And as I said, it's in the public domain. So, it is probably that one of the manufacturers of another refractive surgery device is actually currently utilizing PROWL and conducting some of the work to try to see how they need to modify it in order to use it as part of the post-market assessment for their device.

So, what I want to stress is while the government agencies, FDA, DoD, and NEI was the three entities that put the PROWL together, by virtue of putting it in the public domain, we allowed anybody to utilize it in order to expand the indication beyond the original scope. So it's currently being done.

DR. PUSIC: I can add just another couple of examples quickly. One of the initially developed FACE-Q for head and neck cancer reconstruction, it's a module, and then subsequently, as face transplant surgery has evolved, we have looked at a way that we can potentially use sentence scales within the FACE-Q head and neck cancer module in a face transplant patient population. I think the key piece of this is to establish content validity, and we've heard this from other speakers as well I think. We can't assume something works

in a different patient population, so that's work that we're doing now is to evaluate, sort of, in these very small patient populations, which is face transplants, what scales are appropriate and resonate with patients and what requires new scale development.

Just a different example of what we're essentially -- I think a PRO measure shouldn't stay static over time, that what you developed in 1990 or 2000 or 2010, reflects the measure, per se. For example, we did with the BREAST-Q, when we first developed the BREAST-Q, we didn't have any way to return sensation after a mastectomy, so we didn't really develop scales around return of sensation after a mastectomy. Now it's a new technique with cadaver nerve grafts and that's more of an investigation. We just recently developed new scales that fit into the BREAST-Q framework and can be used to evaluate return of sensation, so essentially take nerves from -- we can make a breast that looks good to actually something that feels like an actual breast from the patient perspective.

So I think the idea, also, that scales can't be -- they can't be -- you know, the legacy measure stays, that we need to be able to continue to evolve over time. I think John Spertus's comment earlier in the previous session about sort of talking about golf, but maybe it's -- you know, that's not something people are doing so much anymore, so we have to be able to be fluid and changing over time to meet the needs of investigators and patients.

DR. BARNARD-KELLY: I think we use -- often we try to use a bank of questionnaires, so we'll use a psychosocial functioning as well as a quality of life or functional health status measure to make sure that we can capture all of the concepts that we're trying to measure.

In terms of broad audience, what we -- so we have -- all of our measures are translated, but we do a lot of cognitive interviewing and cognitive debriefing to ensure that the meaning is translated, as well as just the words. What we're doing with the tool we're developing at the moment actually is -- we're also doing an audio version so you can listen

on earphones and press the color on the iPad or the screen because often people, you know, health literacy often is poor, language doesn't translate well sometimes and if you're looking at a series of numbers, you ask somebody on a scale of 1 to 10, you know, it might seem obvious if you can read numbers 1 to 10 but you take a 2 and a 5, they're just a mirror image of each other, you know? So, if you can just push a color, we find it's easier. So, we do use a mix of measures, trying to capture all constructs, but we make efforts really to reach as wide an audience as we can and sometimes it's like thinking outside of the box and having pictographs and audio rather than just words.

DR. HAYS: Yeah, so for the PROWL questionnaire, I think it's a lot of the same things with subgroups. So Spanish language, we don't know much about that right now, that could be something that's important, especially in the U.S. And then comparing low education, people with health literacy challenges, does it work there, that kind of thing. Also, we didn't really look very much at nearsighted versus farsighted, those kind of subgroup comparisons are useful. And then finally, I think it's already been useful, as Malvina sort of hinted at, in other projects like the intraocular lens questionnaire development. So, I think that the pictures that were developed for that project are sort of the next step, they're actually better, in my mind, for getting at symptoms, so I think that was a steppingstone.

MS. O'CALLAGHAN: All right, thank you to all of the panelists and to all of you for listening. We've heard discussion about the use in three different case areas of PRO instruments for regulatory decisions, but certainly going far beyond that, extending on the conversations earlier about clinical uses, hearing that physicians and clinicians are getting more comfortable with interpreting PROs alongside other types of measures they may be more familiar with, and some new uses or a growing use as a tool to help patients and clinicians communicate on the same page about symptoms that, although when looking at it from different perspectives, patient, healthcare provider, regulatory, but it's all in service to

the same goal, which is understanding the symptoms and how the patients are feeling and functioning with their conditions and with the treatment options that they have. A lot of opportunities to expand and further adopt use of tools and the importance of multi-stakeholder collaboration.

So, thank you again to all of you for this great discussion and we have a break now, we will reconvene at 2:45 p.m. Eastern.

(Off the record at 2:33 p.m.)

(On the record at 2:45 p.m.)

MS. SAHA: Welcome, good afternoon. We're in the home stretch of today's wonderful workshop and we've had a lot of great discussions. I'm really excited to be moderating this panel this afternoon. I'm Annie Saha, Director of Partnerships to Advance Innovation and Regulatory Science Team, at the Center for Devices, and I'm pleased to bring together this great group of panelists to discuss multi-stakeholder collaborations for instrument development.

And really, this builds on all the conversation we've had throughout the day about developing patient-reported outcomes that really fit the needs of whatever purpose the PRO is going to be used for and really one great way of doing that is going through the collaborative process, and that's something we've already been hearing and you heard touched upon even in the last panel by Dr. Eydelman and some of the other colleagues.

So with that, I'm going to ask each of our panelists to do a brief introduction about themselves, walk through their organization, and then we will open it up for question and answer. And I think each of these panelists are able to really bring a lot of exciting and useful information to the table, and even if they haven't specifically worked in PROs, but how do we collaborate to bring forward tools that are really going to be most useful to patients.

So with that, I will turn it over first to Pamela Goldberg. Pamela is the President and CEO of the Medical Device Innovation Consortium. Pamela, I think you may still be --

MS. GOLDBERG: Good afternoon. And I'm really excited to be here. What a great day full of discussions and such an important topic. For those of you who don't know the Medical Device Innovation Consortium, we're a public-private partnership. We are always centered on what are the patient's needs, and because we're a public-private partnership, we bring together industry and regulators and patient advocacy groups all together to talk about what are the patient needs and what can we do to address those patient needs. We've been around for about 8 years and one of our founding components was really about the science of patient input and how do we capture the voice of the patient and what are the various ways. And maybe we can go back a slide, please. Thank you.

So MDIC is built on four main foundational elements: our Clinical Science, our Data Science, our Health Economics and Patient Value, and our National Evaluation System for Health Technology. And within each of those areas we're very much focused on keeping the voice of the patient front and center, and you can see by this Venn diagram that we bring together all these different community members for a collaborative process. And so, this afternoon's discussion is very relevant to what we do, and I look forward to our discussion and the opportunity to tell you about some of the ways that we've been doing that. Next slide.

And so, with our science of patient input which, as I say, has been very fundamental to where we started from as an organization, and we've grown and expanded that and explored patient preferences and patient-reported outcomes in this collaborative community that I'm happy to talk about more later. So, thank you very much and I'm happy to join today's conversation.

MS. SAHA: Great. Thank you, Pamela.

And next we have Matthew Roe, who is the Chief Medical Officer for Verana Health.

Matt.

DR. ROE: Thank you for the opportunity to participate today, it's really quite a pleasure. Verana Health is a data technology company that works with professional societies to enable their EHR registries and in this case, I'll be talking about the American Academy of Ophthalmology's IRIS registry and how that's been used to stimulate the development and field testing of a new patient-reported outcomes measure. So, thank you for the opportunity to participate today.

MS. SAHA: Great, thank you.

Next we have Jenny Flythe. Jenny is the Director of Dialysis Services at the University of North Carolina and a member of the Kidney Health -- a member of the board of the Kidney Health Initiative.

DR. FLYTHE: So, thank you for inviting me to speak on behalf of the Kidney Health Initiative, or KHI. So KHI is a public-private partnership between the Food and Drug Administration and the American Society of Nephrology. KHI's mission is to catalyze innovation and the development of safe and effective patient-centered therapies for people living with kidney disease. Next slide, please.

It's the largest consortium in kidney disease, we have over a hundred member organizations, 60% of which are industry, many of those are device manufacturers. The consortium is focused on regulatory science and we use multi-stakeholder teams to work in the pre-competitive environment to ensure that the voice of the patient is included in every stage of the product life cycle. KHI has undertaken a number of PROM projects with the long-term goal of promoting patient-centered device development by encouraging the use of PROMs as endpoints in regulatory focused clinical trials.

To do this, KHI works with diverse stakeholders to develop tools, like conceptual

frameworks, to enable the development and validation of PROMs. Importantly, KHI does not seek to develop the instruments themselves, but instead to promote capacity for others to develop these instruments. KHI has conducted three PROM initiatives. One was focused on novel kidney replacement devices, which will be our focus today. There have been others on vascular access and muscle cramping, and all of these are in the space of end-stage kidney disease. Next slide.

IN 2018, KIH, funded by an FDA contract, worked with clinicians, patients, industry partners, and FDA representatives to develop a framework for health-related quality of life that could again be used in regulatory trials for kidney replacement devices. We used stakeholder engagement throughout the project, as exemplified by the diverse team. They included patients as partners and we also sought community input at multiple points during the project.

The project resulted in a conceptual framework, that's displayed on this slide, that showed how transformative kidney replacement devices could impact patient prioritized domains of the ability to be active, fatigue and energy and the intrusion on family and social life as well as symptoms. After we developed the framework and got community feedback, we ultimately published it in a peer-reviewed manuscript. Thank you.

MS. SAHA: Great. Thank you, Jenny.

And our final panelist is Amanda Grandinetti

Amanda.

MS. GRANDINETTI: Hi, everyone. I want to thank you for having me today. My name is Amanda. I want to disclose that I consult for several PRO organizations on the slide. I have been a research methodologist for a bit of time now and I'm currently studying patient-reported outcomes in dialysis patients in my doctoral program. I'm also the vice chair of the Kidney Health Initiative Patient and Family Partnership Council. I was a work

group member in the work Dr. Flythe mentioned, and I'm involved in the other PRO projects that the Kidney Health Initiative has been involved with that are listed on the current slide. I have a unique perspective regarding PROs because I'm also a person living with kidney disease. I was actually diagnosed with FSGS when I was 14. I've been on chemo and peritoneal dialysis, and I currently live with a successful kidney transplant. Next slide.

So, I'm going to talk about some key takeaways for selecting and ensuring success of PROs in device trials that I've discovered in my research and through involvement in many PRO initiatives.

Firstly, the organization or the work group should ensure diversity and inclusivity to reflect the real-world population. For example, kidney disease disproportionately affects people of color and, therefore, patient recruitment and involvement should include representatives to reflect prevalence data. And we should also consider age because not all patients are the typical older kidney disease patient and different age groups have different priorities. Organizations should also consider developing a mission statement to orient themselves to a common goal. This is particularly important because PRO work does not have a golden standard for methodology and it can take a bit of time for the work group to come together and agree how to move forward.

There should be special care towards the patient and ensuring that their voice is heard. Physicians and investigators typically prioritize physiological endpoints, whereas patients prioritize quality of life issues. And there are several missing perspectives currently in the literature and real-world practice. Some quality of life domains have not been accurately defined, materials need to be patient friendly, the work group needs to understand the methodology in order to assess the PROs, and ultimately the patient should be selecting the PRO that matters the most to them. Next slide, please.

And I think the biggest takeaway from the PRO work that I've been involved with is

that patients are extremely eager to participate in this important work. Patients are part of the team. It's important to remember that patients are the expert of what it's like to live with that disease. For example, if you haven't lived it or sat in a dialysis chair, you have no idea what the actual experience is like and it isn't just enough to include patients, there needs to be involvement from conceptualization to finalization and this builds rapport and trust with the patients. The importance of using PROs is simple, patients are the experts in living with the illnesses and using PROs provides patient buy-in to a device immediately and patients won't use a device if they don't think it will increase their quality of life. Thank you.

MS. SAHA: Great. Thank you, Amanda. It's really important to have the patient perspective, so we're really glad to have you as part of this panel, for both your scientific expertise and your patient experience.

We're going to turn it back to Matthew Roe, who is the Chief Medical Officer at Verana Health, to walk through. Go ahead, Matt. I think you're on mute.

DR. ROE: Okay. Sorry about that, my apologies.

MS. SAHA: No problem.

DR. ROE: In this section talking about multi-stakeholder involvement to develop PRO measurements, I think the MIGS PRO project is a great example of that. And so the goal of this project was to develop a survey that measures health-related quality of life measures for patients with mild to moderate glaucoma who are planned to undergo a MIGS procedure and this was a group of collaborators that involved several CERSI groups from UCSF, Stanford, and Johns Hopkins, the American Glaucoma Society, the FDA, the American Academy of Ophthalmology, and my company, Verana Health.

And so, there were several steps, as you can see on this slide, starting with physician- and patient-focused groups to develop the draft questions, doing cognitive

interviews, developing a web-based questionnaire, further refining that. And then, I think most exciting is using the IRIS registry that we help to support and partner with the AAO to assess which sites would be most representative of the U.S. population. So, we looked across thousands of sites that are participating in this registry to understand their volume of glaucoma patients, the demographics, and by doing so we were able to do a targeted site selection mechanism working together with the AGS to select about 20 sites who are participating in the field testing of this instrument, which is ongoing and about to start enrollment in October. Next slide, please.

What's most exciting about this is we'll be using real-world data now, not only to enable the study and set the study up and select the sites, but also during the course of enrollment we'll be using algorithms that we'll be developing to define a patient who's very likely to undergo a MIGS procedure and surface that patient to the enrolling site team so that they may have an easier time to find patients to enroll in the study and test out the applicability and the utility of this approach in a technology enabled platform so that the PROM can be tested efficiently and in enough patients to actually have internal validity.

So, we're excited to be a partner for this program, we're excited that it will be started next month, and I think the five or six different stakeholder groups that are working on this together are exemplary of collaboration that Malvina spoke about during the previous session.

MS. SAHA: Great, thank you.

I think that was a great overview from each of you and just a reminder that we have multiple ways that you can ask questions from those in the audience. One, you can use the live Q&A feature that's in the app. You can also click the bubble icon that's in the webcast window. And I think this discussion will be really great to hear about how we can think about the precompetitive space, and that is one of the qualities we do outline in the draft

patient-reported outcomes guidance that the Center did also put out that you've heard throughout the day and from some discussion.

So, the first question I will ask is, so Matt, following up with your experience with the registry work that you're doing and the PRO development, how is intellectual property being handled? That's certainly an issue that's come up in discussions.

DR. ROE: Sure. Well, the PRO will be publicly available, I think that was discussed in the previous session. It was developed by the CERSI groups, and Ron Hays has been a big contributor and he was a participant in the previous session. So, it will be freely available and used for any purposes for any ophthalmic device that has a potential for regulatory approval or regulatory evaluation. So, our company has no intellectual property in the PROM itself, we're enabling it and happy to support the study and help sponsor it. But my understanding is that it's going to be freely available and there won't be any IP issues that limit its use.

MS. SAHA: Great, thank you.

And maybe, Jenny, you touched on this a little bit with some of the work with KHI that you're really trying to enable rather than create intellectual property. So how do you get the stakeholders to engage in that type of development when there might not be intellectual property or other, sort of, monetary gain?

DR. FLYTHE: Well, I mean, part of the message that we try to give people is that ultimately, we're putting out these conceptual frameworks for these other things that build capacity with the idea that we're helping them. We're kind of giving them a roadmap, too, if you take these next steps, you may be able to use a PROM in the regulatory environment. So, I think in some ways it's just, it's pointing people in the right direction.

What we have found, at least in the kidney space, is that there's tremendous interest in using PROMs in the regulatory space. People are just not exactly sure how to go about it

or they don't understand differences in PROMs that might have been used in the clinical environment compared to PROMs that would be appropriate for use in the regulatory environment. And so, we try to bridge that knowledge gap and, again, the specifics around identifying specific PROMs and then identifying what aspects of those PROMs would need further development or validation to be appropriate for the regulatory context.

MS. SAHA: Great, thank you.

And then, Amanda, I think if you could speak a bit further in terms of the patient involvement and I have one question that had come up earlier in some of the previous discussions and in the chats was about how do you engage patients who may not want to be reached or who may not want to report outcomes. And so, how would you say is the best way to bring patient stakeholders to the table for these sort of multi-stakeholder collaborations?

MS. GRANDINETTI: I think it's important to build trust and rapport with the patients. There can be some mistrust just from the medical care they've received in the past. But I think most importantly, it's just that you need to get the dialogue open and just keep connecting them with opportunities and providing them with a message of hope. I think a lot of people don't want to participate because they feel hopeless and also because they're not really sure what kinds of innovations are currently happening.

Particularly in the kidney space where I work, there's a lot of innovation occurring and patients want to actually feel like they're making real change. So, really getting them eager about the opportunity, involving them from the beginning to endpoint and keeping them just up to date on what's happening, I think, is extremely important.

MS. SAHA: Great, thank you.

Pamela, MDIC brings together a lot of stakeholders, so how does MDIC initiate these collaborations and how have you been able to maintain that over time?

MS. GOLDBERG: Thank you, Annie. And what Amanda said earlier about if you haven't been a patient experiencing something then you don't fully understand and you don't really know. And so that was the premise that we started from with our patient preference work and patient-reported outcome work, that we had some stakeholders in the medical device manufacturing community who are interested in understanding better what Parkinson's patients need and what they see as their major challenges.

And so we worked with the Michael J. Fox Foundation, as well as device manufacturers, as well as some researchers who helped us create some algorithms to better understand the data that we were collecting, and so that was a really valuable opportunity for the FDA to come together with the device manufacturers in the precompetitive space but with a patient panel of experts and hearing that patient voice in such a significant way.

And so what we're in the midst of now is we're doing something similar in the heart failure space and trying to see, with another therapeutic area, if we can recognize that there are certain commonalities in terms of data, in terms of research, in terms of understanding the patient situation from one therapeutic area to another, but with that base group of industry executives and people who are involved in the regulatory science environment for the manufacturing companies in partnership with the FDA.

MS. SAHA: Great, thank you.

And I think this next question I could probably address to both you, Pamela, as well as to Jenny, and Matt, you may also have some experience, and Amanda, you may have experience from the other end. So, from everyone, in terms of how do you interact with patients in terms of as advisors in the studies? So, are there contracts? How do you identify the patients? You know, what are the qualities that you're looking for and then how do you actually engage in that in some ways and you're providing that value that

Amanda discussed?

MS. GOLDBERG: Well, I'll jump in first. I think one of the things that we learned from the Michael J. Fox Foundation is that they call their panel of patients "patient scientists" and I think that it's very important to recognize that the patient is the expert, and to the point Amanda was raising before, that no one understands the needs of the patient better than the patients themselves. And I think that it's taken us a long time to get to the place that we recognize that the experts are not necessarily the scientists or the physicians, but the patients themselves.

And so, getting that voice out, which is why today, overall, in all the panel discussions during the day today are so critical, but certainly, valuing the patient input and being genuine about that is the best way. And certainly, we have made promises to patients that their privacy and secrecy is critical and we will honor that and we're really more interested in the cumulative data that the various parties bring together. So, we do recognize their expertise as well as their privacy.

DR. FLYTHE: So, from the Kidney Health Initiative perspective, so many of our member organizations are actually patient advocacy organizations and so we have kind of deep connections into the patient advocacy community in that regard. But probably even more broadly than that, I mean, at the very heart of the Kidney Health Initiative is the patient, and I think that's exemplified by the fact that we have this Patient and Family Partnership Council that Amanda is Vice Chair of. That council approves every project that the Kidney Health Initiative works at, works on, and in addition to that we have a member of the Patient and Family Partnership Council on every project committee with the idea that we're not doing anything without input from patients. And so, I would say our attempt, and Amanda can speak about whether or not we're successful on this, is to truly treat the patient as a partner.

The other thing that I would say that we do and are maybe getting better at doing are trying to create patient-specific communications, such that if we do a large-scale project that has kind of a professional-facing publication that we also create a patient community-facing publication to make sure that we're communicating about what we're doing in a way that's understandable to a broad group of patients.

DR. ROE: Yeah, I think that's really critically important. I think, you know, if you look at the work that's been done by all these organizations and PCORI and other groups, I think there's a strong attempt now to recognize patients as equal investigators, use language in different communications that are appropriate for patients so it's understandable, but also be completely transparent about everything that's going on with a study.

And, when we think about these patient-reported outcomes measures, they're assessing symptoms, they're assessing patient quality of life and much of medical care that's delivered is designed to reduce the symptoms of a disease, reduce the disease burden, improve quality of life. And so it's so important that physicians, patients, and others who are involved in these discussions are working together towards these common goals, recognizing that whatever treatments that we're trying to develop, whether they're medications or devices or other interventions, they all have the same goal, which is to improve the care that patients receive, improve their functioning, improve their quality of life.

MS. GRANDINETTI: I'd like to just echo that. I think that a lot of organizations are beginning to use patients as co-investigators. Most patients are really used to care happening to them, but not actually being a member of their care team. So, I think that paradigm is shifting or getting better with that and it's been extremely helpful in fostering that message of hope and just building rapport and trust in the community.

And another thing that the KHI Patient and Family Partnership Council has been

working on is being mindful of the language that we use. So, we like to say that we're a person living with kidney disease or a patient with a transplant, rather than patient.

MS. SAHA: I think that's a really great point, thank you for all of that.

So, we do have a question, it looks like, from the audience. So how do you stay ahead of the curve when you're currently assessing evolving technologies over time? And thinking about it from especially a multi-stakeholder perspective when we're really trying to bring people together, how do we bring people together and also stay ahead of the curve, I guess, at the same time?

DR. ROE: I mean, I'll add that I think that there's multiple evolving technologies for capturing data, whether it's through digital devices, web-based interfaces, wearable sensors and other things. And I think, as we see as these mechanisms evolve and they become interoperable, the patient-reported outcomes may not always be just answering a questionnaire; it might be interacting directly through an activity monitor or directly through a smartphone or something of that nature, and it may be an integrated amount of data that describes the whole patient's daily life and then asks some questions to get direct feedback from them.

So, I think we should look at this as an evolving suite of different technologies that are possible and really think hard about how that can be incorporated, in addition to just standard questionnaires, which has been how most PROs have been developed to date.

MS. SAHA: Yeah, absolutely, thanks. And I think this discussion also highlights that in CDRH's draft guidance of patient engagement and clinical investigations we do discuss that there's sort of a dichotomy between patients who are a patient study advisor, who'd be similar to another member of a research team versus, you know, a person participating a clinical investigation would be a study, a research study participant, and thinking about how we look at that.

And sort of dovetailing into that, so another question we have is it seems that patient organizations are important collaborators in these multi-stakeholder collaborations. Does the panel have ideas for how to identify patients and patient groups for these types of efforts?

MS. GRANDINETTI: I can chime in. I think that just looking for patient organizations in the specialty that you're working in, so in the kidney disease space there are tons of different kinds of kidney diseases, so you can take a look at those organizations and kind of create a list of name of contacts and once you contact that organization, they're ready with patients who they think might fill that role.

So, I serve on other organizations, as well, such as the National Kidney Foundation, so when there's something that comes up on patient-reported outcomes, they reach out to me and then I reach out to other patients who might be able to help. So, the organizations are very well connected, and I would just urge people to reach out to them.

DR. ROE: I would add that in addition to that there also are many patients out there who might like to participate in such efforts and either through their clinicians or through other means trying to expand that group of patients who could participate in these efforts, I think, among all these different advocacy groups, would be a good effort going forward.

And in some cases, it might even be through community organizations that we haven't thought of before, and I know that I've been involved in some studies where even churches or community centers have been used as means to contact larger groups of participants in the community to be involved in research and in efforts like these. So, I think expanding that pool would be an important goal for us in the future.

MS. GOLDBERG: And I'll add that in addition to sourcing patient experts through clinical sites, we've also used our partnership with medical device companies themselves to -- and they will often -- people who have been patients who have used their devices are

interested in voicing their view and coming out and sharing their perspective, which is extremely helpful.

MS. SAHA: Great. So, our next questions is, so can the panel discuss the issues of protecting patient privacy and how that's managed when integrating the patient perspective in clinical development? Is consent required for all these aspects, including the protocol, such as protocol design or review of the materials to ensure that they're patient friendly?

DR. ROE: You know, it's interesting, I've been involved in efforts where we've developed protocols together with patient investigators and even in the public domain, and, in that setting, consent is not required because there's no protected health information that's shared from a given individual.

I think once that is the case, so for example, if a patient is in a study and they've given consent and then materials are shared with the patients for study updates or manuscripts and so forth, there has to be some type of acknowledgement that that patient has consented and they're getting that information. But, what's inviolate is that we protect PHI for all patients who have consented to enter into any study. But when patients are contributing to concepts and knowledge generation and protocols, their consent isn't necessarily needed because they voluntarily have agreed to do that and they're not sharing their own personal information.

DR. FLYTHE: I would agree with that. I mean, in the setting that we're talking about when we're interacting with patients as equal collaborators, that's what we consider them, they're collaborators. So, they're authors on the manuscript, they have this much ownership of the product that we do. But I will make a distinction, because oftentimes when we're developing these measures we then need additional patients to do interviews or to take a survey when we're doing the content validity work and that kind of thing, or

that we want to go out to a broader group of patients and gather more information, often in some kind of qualitative form, and then in those settings we do informed consent and we set it up such as, you know, that aspect is a research study. Sometimes in projects we will do an overall kind of Institutional Review Board application just for stakeholder engagement. I tend to do that in a lot of my own personal research because it covers some of these interactions. But in terms of the work that we've done at the Kidney Health Initiative, engaging with patients as partners, that specific aspect is not consented work.

MS. SAHA: The next question we have, and this is actually, I think, from earlier in the day but is most relevant for this panel, is how do we make sure that smaller companies or those with limited resources aren't shut out from being able to develop PROs or license PROs for use? So they may not have the funding in their development pipeline for PRO instrument development.

MS. GOLDBERG: So one of the advantages with the Medical Device Innovation Consortium is we bring together companies of all different sizes and, in fact, I mentioned that we're in the midst of a heart failure study currently, and one of the companies that was in on the ground floor, if you will, when we launched this patient preference study and looking at patient-reported outcomes, there was a small company that was in the midst of their initial clinical trials and they recognized that gathering together with companies of other sizes and doing this as a collaborative effort would be a win for all, including them as a small startup company that was in the midst of filing with FDA and of course, their filing is so much stronger with that patient-reported outcome data.

MS. GRANDINETTI: I think it's always an option for small organizations to develop a patient panel. You don't necessarily need funding to use current or existing PRO tools, so you can put together a panel of patients and other people who work in the space and kind of examine what existing tools are available to measure whatever primary endpoint that

they're looking to examine.

MS. SAHA: Great, thank you.

And maybe just thinking about taking a step back. Maybe each of you could kind of describe your process for how you select the appropriate stakeholders to engage with for a particular project.

DR. FLYTHE: Sure, I can start. You know, we try to think broadly in terms of any stakeholder that would have any interest in the project. And so, for most of the projects we do, this is going to involve a device manufacturer and oftentimes we will try to work with multiple different people from the industry, so we have different perspectives oftentimes, particularly with a group that may have already a developed product versus another one who may be developing a product.

You know, we almost always have a clinician involved in this. We tend to have a methods expert involved in this. As discussed, we always have a patient involved. And then because of the way much of kidney care is reimbursed, we often also require someone on the payment side to be involved. So, in many of our projects we have someone from the Centers for Medicare and Medicaid Services involved because CMS pays for much of dialysis in this country.

So I would say, it ends up being pretty specific to the space that you're working in but you don't want to think about it only kind of narrowly at the moment, you want to look down the road and say is this a product that's going to be reimbursed, if we're talking about that, do we need insurance partners at the table. So again, trying to take a longer view, I would say, is helpful in that regard.

MS. GOLDBERG: Yes, where I sit at MDIC, we have a membership population and so we tend to draw upon our members as a first cut and then expand from there to make sure that all the right voices are at the table. And so, we start out with FDA and the companies,

and then we expand from there and sometimes CMS is at the table and -- but we want to make sure that the patient advocacy groups are at the table and the patients themselves. So, it really is dependent upon the work that we're doing, who's at the table, but all of those groups tend to be represented. It just is how many from each of the different groups that are represented depending upon the study.

DR. ROE: And I'll add that I think that stakeholders are much broader than just, say, the company that's developing the drug or the device, the patient advocacy group, and then, you know, another body. So, for example, in our project, a medical professional society is involved, and we're a technology company that's a data partner for that professional society and we're involved. And so, I think, as I said earlier, there might be in the future digital health companies that offer new means for data collection or companies that have biosensors that you want to integrate data from.

I think the stakeholder group could be much broader and there needs to be forums, such as MDIC and others, where those groups can coalesce and join together in a noncompetitive space to develop these measurements and instruments and test them. And I think that that perspective is broadening quite bit and we're seeing that even from the panel and from the discussion today.

MS. SAHA: Sort of following along with that, if you were -- I guess, if you put yourself in the shoes if you were one of the small companies, how would you go about starting that conversation with your competitors and with other groups to try to figure out how to align under some kind of neutral third party? You know, one concern we hear often is antitrust, so how would you go about actually reaching out and determining that there is some kind of larger effort than maybe what your company would want to do on its own?

DR. ROE: Yeah, I think that's a really interesting question and I think if you're developing a drug or a device in a certain disease state, I think starting with the patient

advocacy groups is a good idea because they likely exist and they would likely have been involved in efforts of that nature through public-private partnerships that we've talked about and those are freely accessible and available, you can do that, as well. And then I think also academic groups because there are several academic groups that are known for developing PROs and have experts at those institutions or organizations and they're a neutral party because they're in academics. And so, I think there are several means that companies could initiate contact or discussions that could help them in the pre-competitive space and also address some of the issues that you were mentioning in your comments, Annie.

MS. GOLDBERG: And for those of us who do work in that pre-competitive space and bring together parties to do that, I think that everybody who comes to the table understands the ground rules of what that means to work in the pre-competitive space, and so that's anyone who wants to come to the table understands that there are certain ground rules and there are certain topics that we don't discuss when we have meetings to address these challenges and opportunities.

MS. SAHA: And actually maybe just taking a second there.

Sorry, Jenny, did you want to add in?

DR. FLYTHE: Well, no, I would agree. I mean, we're also in the pre-competitive space and the only thing that I would add to that is one of the things that we try to do is not focus on a very specific technology, but instead focus on a class of technologies or a class of devices so that, you know, that it would be relevant to a number of companies, you know, we're not focused on a single one. And the negative of that is sometimes it means the work that we do is a little bit non-specific and that actually arose when we worked on the health-related quality of life framework that I talked about, because we were working in the space of novel kidney replacement devices. Well, they're novel because they don't exist yet. Yet

we wanted to develop a framework that could be used in the regulatory environment for them and so it required us to be kind of agnostic around devices, and I think that that just tends to make companies a bit more comfortable when they're clearly not targeting a very specific technology.

MS. SAHA: Maybe actually to that point, following up on that, what is the benefit when maybe something might be too broad that you may not be able to use it specifically for their product? So where is that balance and how would -- you know, how is it with your organizations when you're working with stakeholders to make that balance -- or how do you see them making that balance or deciding whether or not to collaborate and pull together versus going on their own?

DR. FLYTHE: I mean, I think you have to have a little bit of a track record of showing that you even produce a product that will be helpful to a variety of stakeholders. But what we have found, again, being in the pre-competitive space, is that people are really looking for leadership and they're looking for these, you know, these noncompetitive environments where they can talk about these things as a group.

And so I would say that we have not run into just huge issues around this, again, because people are really eager for direction and particularly when you're coming from a consortium with patients so firmly involved, I think, as with the Kidney Health Initiative, it's also a way for some of these companies to interact with patients in ways that they often have trouble doing on their own and they see a lot of value in that. So, you know, ultimately you have to show the value to get their engagement.

MS. GOLDBERG: Well, I know our industry partners wouldn't spend the amount of time and energy that they do if they didn't find value in it, so we have to -- to the point you were raising, Annie, we have to find that right balance of making it valuable and worthwhile and yet sufficiently generalizable to be valuable to people outside of the core working

group and that is a delicate balance, but we have been successful at finding that balance and making it meaningful for those who are at the table.

MS. SAHA: Actually, maybe just to take a quick step back, what does pre-competitive mean to each of you and how would you explain that to somebody if you were to advise them about whether or not to engage in some way?

DR. ROE: Yeah, the way I'm taking the word pre-competitive and how it's used is basically when a company has a promising product and they want to develop it and it's likely in that phase of early engagement where they maybe have not started their pivotal studies yet and they're not competing against others, or if they have a novel therapeutic first in class that also could be considered to be a pre-competitive space, but it's really when you're considering what your development program would look like and what components you would add. To me, that's what I would call the pre-competitive space.

MS. GOLDBERG: I would probably define it slightly differently than Matt did. I think that we're very clear with the people we work with that we don't talk about intellectual property, we don't talk about pricing, that those things, things that aren't available to the general public are not things that we talk about in our meetings and that way we avoid any conflicts of interest and that's what allows us to work in the pre-competitive space.

MS. GRANDINETTI: I agree to both of your points. I think, when I think of pre-competitive, I think of a lot of the work that KHI has been involved in, specifically with patient-reported outcomes in novel renal devices. There are innovations taking place currently and new dialysis therapies, but some of that is not invented yet. So, we're really working behind the premise of bettering patient care and coming from that standpoint and we're kind of using the conceptual framework to even drive more innovation.

MS. SAHA: Thank you.

So, the next question we have is (1) that there's no question that patients as

collaborators is the way to move forward in PRO development. However, much of the literature in this space seems to suggest that it's always a harmonious achievement; however, there surely are conflicts that do occur. How does the panel view this challenge? And I would add that I wouldn't say it's probably just not patient specific.

DR. FLYTHE: Yeah, I would agree with your last comment, Annie. I think that there is conflict with all stakeholder groups at various times and that's just a natural part of trying to be disruptive and innovative and move the field forward. I mean, ultimately, people do have their own interests and sometimes that kind of comes into play. So, I guess I would not specify that to the patients, in particular.

But I do think what I would say that it's really important that there be a group process and when you go into this kind of work to understand that a group process takes much longer than you might think that it should and that these are not -- you know, these conceptual frameworks or the work that comes out of these groups don't happen overnight. I mean, it happens with iterative feedback and being willing to step back and say that's not a perspective that we were considering and it's going to cause us to have to turn a little bit in what we were doing.

And so, I think it requires really inherent flexibility and again, a willingness to change. I mean, you go in with an idea, and what I found working with numerous of these work groups is that the idea on the other side always comes out pretty differently, it's always better and it's always taken a little bit longer than we thought it would and you just need to kind of sit down and enjoy the ride.

DR. ROE: I would add that you need to have good facilitators for these different committees and processes and people who are skilled at helping to represent the different viewpoints and recognizing that the patient viewpoint is very important, but at the end of the day it has to be coalesced with viewpoints of other stakeholders. And so, I think that's

just a skill that each organization needs to have in order to move these discussions forward.

MS. GOLDBERG: Yeah, I will never forget a conversation with a group of Parkinson's patients and the comment was “if you've met one Parkinson's patient, you've met one patient,” that each person's experience is different. So, if we're trying to generalize and create categories, we tried to put together a series of questions in a survey and different patients had different perspectives of how we should prioritize those questions and what were the important questions to ask.

And so, to Jenny's point, you have to just find a path forward and work with the parties that you have and create as much consensus as you can with the parties that are at the table, and you are going to get some differing opinions and that's part of human nature. But I think that the journey makes it valuable because, as Jenny pointed out, you come to better conclusions as a result.

MS. GRANDINETTI: Yeah, I wanted to add that there are certainly challenges when working in a multidisciplinary work group. In developing patient-reported outcomes, I think the literature describes it as being harmonious because the end product is -- it was a harmonious experience and the deliverable’s very rewarding and I think that, kind of, speaks to a point I made earlier with having a goal in mind or a specific mission statement for a work group. So if people started going on tangents or maybe they might bring up good points but might not be relevant to the patient-reported outcome that you're studying, that you can kind of go back to what is the actual goal of this work group and that kind of focuses and keeps people on track.

MS. SAHA: Great. Each of your organizations and your efforts have slightly different governance structures that have been put in place. How do you see how those work to those allay concerns and address any potential, sort of, collaborative concerns and if there are any sort of pros or cons to the structures that you have in place?

DR. ROE: I mean, I'll add from our experience that we're working with multiple different groups and, in some cases, we try to be too collaborative and sometimes it just delays decision making a little bit. So there needs to be, you know, leaders designated within these different efforts to say, “okay, we have some decisions to make and we need to move forward and we can discuss it for a certain period of time but at some point a decision is necessary” and then, you know, who's accountable in that regard. And I think that's just part of good organizational management and depending upon whatever stakeholder groups have been brought together, having leaders and then holding them accountable to actually deliver on what you're hoping to do is usually the best process to use.

DR. FLYTHE: I think the other thing that can be helpful with that is also sometimes being willing to be break out into smaller groups. So not everything requires all 25 stakeholders at the table and a lot of times for efficiency purposes it helps to have smaller, kind of, more nimble working groups that then come back and report to the larger group. I do find that when you've got the really large committees trying to make decisions that it's really difficult to move forward.

Then, I think the other thing that I would say to kind of follow up on something that Amanda said is, the other thing to try to remember is that you have these individuals at the table, but there's also existing information and data that you can rely on. And so we try to do systematic literature searches and rely on data that already exists in the space to build from and that kind of enables us to not have to take an individual opinion or an individual perspective, but route it to what we know from a larger community and if we don't have that data, you know, that is some of the work that the Kidney Health Initiative will try to fill in, is going out to the broader community and getting that data, again, so we're not making decisions or building things on individual perspectives.

MS. SAHA: Great. So, another question that's come in is a lot of PRO tools today are both comprehensive, as well as very purpose driven. For example, specific questionnaires for a certain disease are often repetitive and oriented towards research rather than clinical care. What are the group's thoughts on coming together on intelligent tools that can be more brief and used in ongoing care to create real-world evidence sets?

DR. ROE: So, it sounds like the question is making these instruments fit-for-purpose and, actually, maybe more concise and more value driven rather than having 50 questions, maybe 25 that are more selective would be useful and worthwhile. But I think there was some discussion in the previous session about how results from patient-reported outcomes measures are soon to be incorporated into registries and other measures, and that becomes a source of real-world data and I think that's really important because to date, when we looked at real-world data we considered claims data, EHR data, digital health data, but we haven't really thought too much about PROs and if we can make those concise and very important and high value, then that can be brought into the larger RWD environment and become quite meaningful and have a huge impact.

MS. GOLDBERG: Yeah, I would echo that. I think that having that as a source of real-world data, real-world evidence and having some standards that get applied to that is going to be really critical and making sure that that's quality data is going to be really critical to the future of the use of real-world evidence and real-world data. But EHRs and registries and claims data are not sufficient, that we really need the patient data, as well, and so that creating some expectations and some standards so that we could do it across therapeutic areas and for the total product life cycle is going to be very important.

MS. SAHA: Well, going back a little bit. So, we talked about, Jenny, I think you brought this up, you're trying to fill the gaps sometimes with other evidence and data that's around, but how do you convince people -- and this is to all of you. How do you convince

folks to get involved in some way when there's something that's novel and to take that risk to try out something and to work in that pre-competitive environment?

DR. FLYTHE: Well, I mean, again, I think it's figuring out what's important to different people and I think that one of the initial draws for people -- you know, when the Kidney Health Initiative was in its early years, it was established in 2012 and so now I think it's a bit more of an established organization and people have seen some of the reason or the value to get involved. But I think at the beginning, again, it was access to patients. I mean, even just 8 years ago it was novel to include patients and I think a lot of people in industry were like, "we would like the patient's perspective, but we really have no idea how we can go about getting it." And so, it was an opportunity, again, to bring patients and all of these different stakeholders into the same space. And so, I think, initially, again a lot of the draw was the opportunity to interact with patients directly.

MS. SAHA: Now, so maybe along those lines, and not specifically just to patients, but as you've been working on these pre-competitive efforts, have you seen perspectives missing in that work and then how would you evolve that or shift to that over time?

MS. GRANDINETTI: I think a perspective that's often missing, and this is something we discovered in the novel renal devices work group, was that the area of how treatments interfere with social life and family life, and this is very specific to kidney disease and I'm sure it's pertainable to other illnesses, but on dialysis, that treatment really takes away time from being able to do whatever you'd like to do and I think a lot of tools try to get at that statement and get at that idea, but it hasn't been very well defined. So, I think that's kind of a missing perspective that's not in a lot of tools.

DR. FLYTHE: Yeah, and I would add to that. I mean, again, payers. I mean, we had the Centers for Medicare and Medicaid Services have representatives that come to our meetings and participate in KHI and so they're absolutely partners, but sometimes just due

to burden and workload and a lot of things it's hard to engage with them as much as we might like to early on in some of these things. So, I think that that's an area we could do better. And then to the patient point, though, I do think that we, as an organization, have improved at trying to get better at reaching, kind of, harder-to-reach patients and some of it we do through the patient advocacy organizations but we also, in our case, can partner with some of the large dialysis organization providers, is a way to get the patients who might not know about the advocacy groups or the patient groups to, again, try to get at a little bit more of what someone might say is a representative sample of the larger dialysis population in the United States. It's been hard to do, and I don't think that we have necessarily threaded the needle on that yet, but it's definitely something that we're committed to improving on.

MS. GOLDBERG: And I'll just reiterate how we need to have those shared voices at the table and the right voices at the table, and we certainly have found in some of our work that we're not -- we're missing some pieces and so how do we fill those gaps? And so sometimes, to the points that have been raised, that we ask clinicians or manufacturing companies or patient advocacy groups to help us get different patient voices so that we have a cross-section of perspectives and not just a unified voice. I think that having multiple perspectives is critical before you draw any conclusions.

DR. ROE: Yes, and I would add that the demographics of the patient population whom you're representing, we'd like to try to reasonably represent that on the stakeholder group or the committee or whoever's involved in that regard and sometimes it just takes different approaches to engaging different segments of the community in order to have that degree of representativeness.

MS. SAHA: Great, thank you.

Well, I think we are getting close to time, so maybe what I will do is ask each of you

to maybe just provide a summary of what -- based on this conversation, what would you tell folks to do in terms of how to best collaborate, in 30 seconds. I'll start with Amanda.

MS. GRANDINETTI: I would just urge anyone who's interested in developing or working collaboratively on patient-reported outcomes, that they just reach out to multidisciplinary groups, so for example, like KHI. I would just also urge you to reach out to patient organizations. You'll never know what kind of information they'll provide back and other ways to work with them unless you go ahead and try.

MS. SAHA: Thanks.

Jenny.

DR. FLYTHE: I think I would just echo what Amanda said. I think the public-private partnerships are excellent starting places and it is also just there's no harm and you need to ask. And so, I think there's oftentimes a lot of things going on in this space that people are unaware of just because they haven't kind of reached out and asked. I do think the patient -- to Amanda's point, the patient advocacy groups are good starting places for this because they often know what's going on across some of the industries and so that's good advice.

MS. SAHA: Matt.

DR. ROE: I would just say that I think our stretch goal should be that the data that are collected from patient-reported outcomes not only enable the regulatory environment, but more importantly enable clinical care in the future and that there are ways to collect those data, feed those data back to clinicians in real time or in a continuous fashion and that can enable, I think, better care delivery and improved interactions between clinicians and patients.

MS. SAHA: And finally, Pamela.

MS. GOLDBERG: Yeah, I'll just add that reminding ourselves how critical it is to get the patient voice and make sure that we have that valuable patient information from a

variety of different sources to inform whether it's the creation of a new device, to enhance an existing device, to Matt's point in terms of treatment of patients, that it is really important that we all have those patient-reported outcomes as part of our decision-making tools.

MS. SAHA: Great. Well, thank you, everyone. I think this was a really robust discussion and I hope the folks watching have gotten some great ideas and insights about how to think about working in a pre-competitive environment and have certainly asked something that we do discuss in our draft patient-reported outcomes guidance.

So, with that, I will turn it over to Michelle Tarver for closing remarks.

DR. TARVER: So, we started the day with an ophthalmology reference and you end the day with an ophthalmologist. I'm Michelle Tarver, I direct the Patient Science and Engagement Program here at the Center for Devices and Radiological Health, and I want to thank you so much for joining us today.

I also want to thank the FDA staff who were very committed in putting together a thoughtful program that includes Fraser Bocell, Brittany Caldwell, Christina Webber, and Annie Saha.

We tried to give you a view of what PRO development looks like across the total product life cycle of a medical device because we know that we are not the only users of these measures, they're used throughout the entire healthcare ecosystem. We encourage you to give feedback to us through the survey that is posted on the website and you may receive by mail, because your feedback really helps us to improve on our workshops and public meetings.

I have the pleasure of summarizing just a few points, and I'm not going to keep you for a full 15 minutes, but I want to highlight a few key messages that we've heard throughout the course of the day.

You heard from both patients, the industry, researchers, healthcare providers, and academicians about the importance of measuring the patient's voice and integrating it into our care paradigms, our medical device development programs, and ultimately into payment decisions.

I think what's really important, and a theme that came out, was that patients are not static, they develop and the disease develops and progresses and they undergo treatments and so what we use to measure their experience may need to adapt and evolve. You heard a number of examples from our presenters about ways that we can bridge or modify or adapt PRO measures to meet new needs over time that may be realized by emerging technologies or by different patient groups that are participating more actively in clinical investigations. We want to make sure the tools that are being used are understandable and implementable by patients.

Another thing that I think, I hope, you heard is that we are working to clarify expectations, harmonize on terminology and make it very clear what we expect for fit-for-purpose measures when they're used in a medical device evaluation. We put forward a draft guidance and we welcome your comments on that draft guidance, whether they are saying thumbs up, everything's great, or there are things that we think you could add and improve on in this particular document. That docket is open until October 30th, so please, please give us your comments.

I also want to reinforce the fact that we are one FDA. We do work across many of the other medical product centers to create common guidance documents. You heard about the Patient-Focused Drug Development program, which we affectionately call the medical product development program, because we do work together in creating some of those recommendations. And you'll see that a very clear theme is fit-for-purpose development.

Another comment that I wanted to reinforce, that we heard over the course of the day, is the importance of diversity of patients. Not just diversity in terms of the disease spectrum, but also diversity in terms of ethnic, racial, gender backgrounds, because it's really important to bring all those points to bear, as well as age, to bear in the conversation when we're understanding the experience that patients are having living with their condition or interfacing with a medical device.

We heard that these tools are necessary, that everybody would like to use them, that it helps us better understand how patients are doing, not only in the clinical trial setting, but also in clinical environments where care is being administered. And so, when these tools are publicly available, especially when they are free, and I think that that really does create an avenue for greater integration, more evidence generation and the ability for people to use them more readily, it removes the barrier to inclusion.

The last comments that I would like to bring up is the collaboration theme. I think many of the talks, the sessions, talked about collaboration being very important. It is a critical factor at our center, we have it as one of our strategic priorities for this year, and I will say that collaboration is something that we are embodying in a lot of our different efforts, including in the patient-reported outcome space.

Collaborative communities is an effort that is focused on forming these partnerships, these collaborations with all the relevant stakeholders in the community, to tackle shared challenges and come up with solutions that meet the needs of all the stakeholders, that it's been vetted, that it's been probed, and that they've had the difficult conversations that really does lead to solutions that can be implementable and adoptable.

One of the things that I would like to highlight is that we are encouraging that as we're moving from concept to care in the patient-reported outcome space.

I want to leave you with a quote from Helen Keller, that "Alone we could do so little,

but together we can do so much." And as we continue to move forward in patient science, I am looking forward to seeing the "so much that we can do together."

With that, thank you for joining us today. Good evening and be well.

(Whereupon, at 3:52 p.m., the meeting was adjourned.)

C E R T I F I C A T E

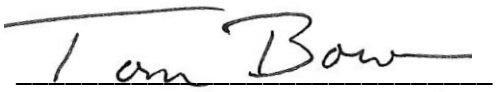
This is to certify that the attached proceedings in the matter of:

MEDICAL DEVICES VIRTUAL PUBLIC MEETING - PATIENT-REPORTED OUTCOMES (PROS) AND MEDICAL DEVICE EVALUATION: FROM CONCEPTION TO IMPLEMENTATION

September 30, 2020

Via Videoconference

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.



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