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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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VIRTUAL ISPOR FDA SUMMIT

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USING PATIENT PREFERENCE INFORMATION IN MEDICAL DEVICE REGULATORY DECISIONS: BENEFIT-RISK AND BEYOND

+ + +

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M E E T I N G

(10:31 a.m.)

DR. PAVLOCK: Hello. I'm Amy Pavlock from ISPOR, and I'm honored to welcome you to the virtual ISPOR-FDA Summit 2020. Thank you all for taking the time to join today's event, entitled, "Using Patient Preference Information in Medical Device Regulatory Decisions: Benefit-Risk and Beyond."

The Summit is brought to you by ISPOR, the Professional Society for Health Economics and Outcomes Research, and the U.S. Food and Drug Administration's Center for Devices and Radiological Health. This summit is being recorded and will be available to all attendees via the ISPOR and FDA CDRH webpages.

Before we start, there are a few logistical items we will go through. First, 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. Next slide.

We encourage all attendees to download the CrowdCompass app to access content from today's Summit, including live Q&A during the sessions, the agenda, speaker bios, and resources for both patient preference information and patient-reported outcomes. For mobile download via iPhone or Android, please search for CrowdCompass Attendee Hub in your corresponding app store. Download the app, and then search for “Patient Input in Medical Device Studies” to download the event. If accessing via your computer, visit the URL on this slide. Follow the login instructions and use the e-mail address used to register for today's Summit. Next slide.

Once you have downloaded the app, click on the profile tab at the bottom of the screen. Enter your first name, last name, and e-mail, followed by tapping "Next." Finally, you will receive a verification code via your e-mail. Enter the code and tap "Verify." Next

slide.

So why log in? We encourage you all to use the app for various reasons. You may join the attendee list, connect and network with fellow attendees with in-app messaging, participate and engage with speakers by posting on the discussion board, or you can simply take notes during the sessions. Access to the privacy settings is available after you have logged in. Next slide.

Finally, a few housekeeping rules. All attendees have entered into the webcast on mute and will remain muted for the duration of the Summit. Throughout each session, attendees will have two options to ask a question or provide comments to the speakers. Please use the "Chat" box via the webcast or utilize the live Q&A feature on the app. If at any time you experience technical issues, please seek assistance from your local technical support. To keep the conversation going, please use hashtag #ISPORSummit for your social media posts. Next slide.

And now it is my great pleasure to introduce Chief Executive Officer and Executive Director of ISPOR, Nancy Berg, to provide welcome comments. Nancy?

MS. BERG: Thanks, Amy.

Good morning, good afternoon, and good evening, depending on where you are in the world right now. I'd like to begin the Summit by welcoming more than 1,950 registrants from 87 countries around the world. This program has drawn significant attention and response because the topic is so important. And I'd like to thank the FDA, and CDRH in particular, for the opportunity to collaborate in producing this Summit. And its development and its production have not been easy.

You may recall that last spring we postponed the Summit due to the impact of COVID-19 on our program and on our country, and on healthcare. And these are certainly challenging times, but I'm encouraged by the fact that 2,000 people from all around the

world are tuned in today. This indicates a strong interest in patient preference research and interest in evolving regulatory practices affecting medical devices and in the science behind regulatory decisions and other topics and trends that ISPOR members think about. Next slide.

I'm pleased to have a few minutes to share some information about ISPOR, as I suspect not everyone viewing this conference is familiar with the extent of our work. ISPOR's mission is improving healthcare decisions and, as we work to accomplish our mission, the Society focuses on the advancement and on the utilization of health economics and outcomes research across healthcare systems.

ISPOR is an individual member society. We have members in as many as 115 countries, and we're a multi-stakeholder organization and our members work throughout healthcare systems. They work in life sciences and companies including med-tech companies, in academia, and our members hold research and decision-making roles within payors and regulatory organizations, and in health technology assessment bodies. Our members include patients and patient-engagement organizations, and healthcare providers, consultants, pharmacists, statisticians, young professionals coming into the field.

And one of the most valued benefits of being an ISPOR member is the opportunity to meet and to interact with such a broad audience of stakeholders and during meetings like this one, many perspectives are shared, discussed, and debated. And we so value our relationship with FDA and other regulators, with EMA, with the European Commission and health ministries and governments all over the world. And it's because of our multi-stakeholder membership that we have a significant commitment to building partnerships and collaborations. And we have a number of alliances with other professional societies and trade associations. Next slide.

This conference is particularly important, as it focuses on the increasing use of

patient preference information and the conference theme resonates very well with ISPOR's multi-stakeholder audience and with our evolving med-tech membership. And it also aligns to our long-term commitment to patient engagement in research. Next slide.

Sorry. I think we have slides that are backed up. The slide that I was going to speak to next describes the high-level work of ISPOR around strengthening the integrity, the advancement, and the understanding of HEOR worldwide. And it's an indicator that the Society's work is steeped in scientific and research excellence and we sponsor many groups of experts who collaborate in the development of good practices for outcomes research reports.

We recently updated our strategic plan, and this directs us to create engagement among identified stakeholder groups, topics, and it speaks specifically to enhancing the involvement of the med-tech community within ISPOR. And it supports the digital transformation of healthcare. We're sponsoring a global real-world evidence initiative because of the explosion of data and technology. And we're also thinking about topics like artificial intelligence and machine learning.

Our strategic plan, it's anchored in science and collaboration, education, and multi-stakeholder member engagement. And ISPOR's global footprint also includes significant investments and activity targeted specifically at lower- and middle-income countries, where needs always exceed resources, and where HE and OR are gaining appreciation and utilization. Next slide, slide 10.

I've mentioned collaboration several times. And no one person, no organization succeeds on their own. And our success as a professional society is the result of a world of experts who are willing to give their knowledge, their experience, and their time to be a part of important discussions, and to contribute to leading practices, and publishing research that leads to better healthcare decisions.

And in addition to programs like this one, ISPOR sponsors a large series of global conferences. We have a myriad of meetings. Tomorrow, for example, we have a multi-stakeholder payor summit taking place. And we sponsor regional patient activities and regional HTA roundtables in Europe, in Asia, and Latin America, in the Middle East and Africa, and of course here in North America. And we're doing our part as an organization to stay connected so that we connect our members to important knowledge and opportunities and evolving issues. Next slide.

We're going to soon announce our future science agenda, which is a topic list and a roadmap for our future investments and our prioritization, and this agenda will be released to the public in the coming months, but I wanted to share some of ISPOR's thinking around priorities like real-world evidence and advancement in economic evaluation, and draw your attention again to patient-centered research, which is on the top of our agenda. Next slide.

So what is HEOR for those who are new to the field? Health economics, the HE, it focuses on measuring and valuing the outcomes of healthcare interventions. And then outcomes research, the OR, is a set of disciplines that evaluate the effect of healthcare interventions on patients. So the HE plus the OR, it's the confluence of two fields that work together to provide powerful data and insights for healthcare workers, healthcare decision-makers, I'm sorry. Next slide.

In this slide, in this slide, we show a graphic of ISPOR's value assessment framework. I hope you're seeing this live. This is slide 13. It's the output of a major global effort that ISPOR led in response to healthcare systems moving toward more value-driven approaches and evaluating therapeutic options based on health outcomes and value to patient and effectiveness compared with other potential treatment options. And the model is also called our "value flower," and it clearly demonstrates that ISPOR is thinking beyond cost effectiveness analysis and qualities. Next slide.

Health decision-makers and health systems are challenged -- next slide. I think you're catching up on slide 14, with the exclamation point. Health decision-makers and health systems are challenged to make decisions during the most complex time in history. And we believe HEOR has never been more relevant or more important.

Medical device companies, particularly larger companies, have rapidly evolved in their use and understanding and utilization of HEOR, as they work to meet these incredible demands from assessors and payors, and do that within very complex and fast-moving product development lifecycles, and clearly, increasing pressure on companies to get products to market faster.

And then I don't need to mention to the new device or app developers that HEOR is more important than ever as you work to demonstrate value and meet expectations of regulators, payors, hospitals, and patients. And I suggest that you really look closely at the ISPOR community. It spans research, med-tech, academia, consulting, payors, regulators, assessors. The entire community is there and has a home within ISPOR. And next slide.

For many years, we've been engaging med-tech through sponsoring a special interest group, through collaborations with FDA, with the World Health Organization. And we've been highlighting medical devices during sessions at our major conferences and in discussions for many years. And as regulations and expectations evolve and change, we're very pleased at ISPOR to be able to provide a platform for med-tech professionals. And last slide.

So ISPOR is connecting a world of healthcare research and healthcare decision-makers, and now you're connected to ISPOR. I'd like to thank again the FDA and CDRH for being a catalyst for this meeting. And thank you to many ISPOR members who are among today's speakers. And thank the expert advisory committee who've done a great job of providing leadership and guidance for this program. And I'd like to recognize two ISPOR

past presidents, Dr. Deborah Marshall and Dr. Shelby Reed, who served on the advisory committee, which again indicates the value that ISPOR places on this relationship and on these topics that will be discussed today.

So I wish everyone a good conference and strongly encourage you to learn more about ISPOR and consider joining our society and becoming a part of the world of science, research, and decision-making that we call ISPOR.

And now it's my pleasure to introduce Suz Schrandt, who is founder, CEO, and Chief Patient Advocate at ExPPect. Suz is also chair of ISPOR's Global Patient Council and a member of FDA's Patient Engagement Advisory Committee.

Suz, over to you.

MS. SCHRANDT: Hear me? We all do these days. Let's see. Let me make sure you're hearing me.

It's great to be with all of you. As Nancy said, I am very closely involved with both the FDA and ISPOR's patient engagement work. I serve on the FDA's Patient Engagement Advisory Committee, and I am the incoming chair of ISPOR's new Global Patient Council after just completing a 3-year term as the Chair of the North American Patient Roundtable. And I know today is going to be a dynamic and productive day, so I'm very happy to be with all of you. And given where I sort of sit across both of these entities, I can say with a lot of certainty that the FDA and ISPOR truly embrace and work to embody the principles of patient engagement. Next slide, please.

This line-up for our time together today serves really almost as a microchasm for the ethos of multi-stakeholder collaboration. When, you know, patients are partnering equally as contributors, as participants to the discussions, hopefully, it goes without saying the immense importance of incorporating PPI into the medical device lifecycle, but it's always good, especially at the beginning of a day, to reorient the purpose of this and keep it front

and center, so it might be worth refocusing on why it is so vital. Unlike this quote from Edison, as a healthcare system, we don't have money, and as patients, we certainly don't have time or patience or the luxury of waiting for 10,000 things that don't work. We need things right as soon as possible and I think there's one key way we can do that. Next slide, please.

We have to do this with patients, of course, and the way to do that really must be twofold. We cannot focus only PPI as data, as data points, as zeroes and ones, because even a, you know, immense collection of data without accompanying context and motivation that supports that data can still leave us lacking. Next slide.

We always have to collect and interpret data in partnership with actual human patient partners. There truly is not a substitute for this. We're going to be hearing about and discussing some phenomenal work today and I hope, and I anticipate that we're going to see this recurring theme of always collecting, analyzing, and using PPI in partnership with those very human patient partners that the data represents. Let's go to the next slide, please.

So I'll do a quick overview of the agenda to get us excited and oriented to what our day will look like. We'll start with sort of starting from the beginning, going through the background, how did we get where we are with PPI today, understanding a little bit of the background. And then we'll move into some case studies for the use of PPI and the medical device decision-making process before we take quick lunch break.

After lunch, we're going to get into some of the tough methodological issues for PPI studies, and where the opportunities are, but also where some of the challenges are methodologically. We'll take another brief break. And then in Session 4, we're going to talk about "the beyond," so there's been so much great work that's come before; where do we go next? Looking at implementation and process of obtaining and using PPI.

And then, finally, we're going to hear closing remarks from Dr. Michelle Tarver before we adjourn at 4:45.

So, with that, I believe I will turn it over to Christina Webber of CDRH to get us started on what I know is going to be a great day. Thanks so much.

DR. WEBBER: Thanks so much, Suz, and thanks so much to Nancy for that great introduction. My name is Dr. Christina Webber. I'm a Staff Fellow on the Partnerships to Advance Innovation and Regulatory Science team at FDA's CDRH, or Center for Devices and Radiological Health. Today's first session, we're going to jump into it in one second. But first, I'd like to introduce our speakers, who will be giving us an introduction to patient preference information, or PPI, as many today will refer to it.

Our first speaker is Dr. Brett Hauber. He is a Senior Economist and Senior Fellow at RTI Health Solutions. Our second speaker will be Annie Saha, Director of the PAIRS team, Partnerships to Advance Innovation and Regulatory Science, at CDRH.

Once Brett and Annie are finished with their presentations, we will be having a discussion with the questions that you, our audience members, will be sending in. Feel free to send in any questions you may have starting right now, actually. Questions are able to be sent in, and we will look at them and get those to our speakers to answer after their presentations. You can do this either using the webcast; there's a little thought bubble link that you can use; or you can use the app if you have that downloaded, as well. There's a live question and answer app feature there.

So with that, I will now turn it over to Brett for his presentation.

DR. HAUBER: Thanks, Christina.

So I guess my job today is to kind of tee this off a little bit. Back in our original schedule, we had a webinar that actually did take place prior to all of the shutdowns related to COVID at the very beginning of March, I believe that was, where we looked at some

background on patient preference methods. And my goal today is to take a very, very top-level view of that and to kind of look at the opportunities for use of different methods, use of different methods in different applications, all hoping to lead up to some of the case studies that you're going to see in the next session. So we go to the next slide, please.

So we might as well start with CDRH's definition of patient preference information, because this is going to be key throughout the day. And this definition has some very specific parts that I think we all need to keep in mind as we go throughout the day, because they will influence how we interpret what patient preference information is, what it is not, and what it can do for us.

So the definition is: Qualitative or quantitative assessments of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions.

So the first thing I want to point out about this definition is that it includes both qualitative and quantitative assessments. Most of what we're going to be talking about today are going to be quantitative assessments, but we don't want to forget that qualitative assessments can also have a role in patient preference information and provide valuable information for decision-making.

A couple other things we want to keep in mind, at least that I think are important to keep in mind, and the first is that when we talk about preferences, we're talking about relative importance, relative preference: “I like this better than I like that”; “this is more important to me than that is.” I can't really evaluate very well how important something is unless I compare it to something else. So this concept of the relative nature of preferences is very important.

The other things I want to point out here are these words "desirability" and "acceptability." Many years ago, when working as an economist, I would use the word

"preferences" for both good things and bad things and people would say, "Well, how can you have preferences for a bad thing?" Because the word "preference" itself lends itself to an interpretation where you prefer good things and don't prefer bad things. So when this definition was developed, the writers of this definition decided to talk about the desirability of the good things and the acceptability of the bad things. Both of these are components of preferences that matter.

And then, finally, we want to focus in on the attributes that differ among the alternatives when we're looking at preferences. You know, if two treatments have exactly the same efficacy, efficacy is not really where the action is, and not necessarily where the decision between two options are going to be made. It's really going to focus on those things that differ between those options. So, with all of this in mind, let's step back a little bit, go to the next slide, please, and put patient preference information into context in terms of the FDA guidance and other forms of patient input.

So CDRH issued guidance that was finalized in 2016, and they have a really nice way, I think, of laying out where patient preferences fit in relative to other forms of patient input. So patient input -- and I'll give the definition of this in just a moment -- is a very broad term, of which patient perspectives is a narrower term that really encompasses both patient preferences and patient-reported outcomes. And before we go to those definitions, I do just want to point out that there is a nice link between this concept of patient perspectives and the concept of patient experience data that is outlined in the 21st Century CURES Act and the subsequent regulations and/or guidances that are coming out of FDA. If we can go to the next slide, please?

As I mentioned, patient input is an umbrella term. It's a pretty broad range of information. Really any information that can be gleaned directly or indirectly based on input from a patient would fall under this concept of patient input. Patient perspectives is

somewhat narrower in that we are looking really at the patient's statements about their experience and about their desires and their preferences. So patient perspectives is a subset of types of patient input. If we can go to the next slide.

Patient preferences, we've already discussed that definition and what we mean by patient preferences, and the guidance makes a distinction between patient preferences and patient-reported outcomes, where patient-reported outcomes are really outcomes -- are realized outcomes stated by the patient. So with that in mind, if we go to the next slide, I'd like to make a few distinctions about what patient preference information is and what it is not.

So patient preference information, again, is this concept of desirability and acceptability. It relates to trade-offs that patients are willing to make. It really comes down to what do patients value, what do patients want. Patient-reported outcomes, in contrast, are really about what patients experience. It is about "what is," as reported by the patients, as opposed to what would be desired or what would be wanted. So they measure two somewhat related but different things, and it's important to keep that distinction in mind as we discuss patient-reported outcomes and patient preference information throughout the day today and in the PRO summit tomorrow. If we go to the next slide, please.

Two other distinctions I want to make: one is between patient preference information and multicriteria decision analysis. And this goes to that what is and what is not patient preference information. Often patient multi-criteria decision analysis is used and described as a patient preference method when, in fact, that's not completely wrong, but the idea is that MCDA is really a methodology. It is a process. And patient preference information can be used in that process to weight the outcomes or the alternatives that are being evaluated in that analysis.

Likewise, if we go to the next slide, often QALYs are referred to as preference-based

measures. And while that is true, preferences have a very specific role in QALYs. Specifically, QALYs themselves are measure of health outcomes, where that time in different health state is weighted by some type of weight that reflects the quality of life in that health state. Often those weights come from the general public, but they could, in theory, come from patients, as well. And if we're talking about patient preference information, the standard gamble on the time trade-off in those methods, if they elicit preferences from patients, are patient preference information, but they are only one component then within this larger concept of a quality. If we can go to the next slide please?

There are many types of stated preference methods that can be used to get patient preference information. And the ones that are listed here in these two different panels are quantitative methods. And I just want to remind everybody that qualitative methods could also be part of this.

But among the quantitative methods, there are two compendia out there, both of which are very informative. The first is the catalog of methods by the Medical Device Innovation Consortium that was published in 2015 that is available on the MDIC website. Then, subsequent to that, IMI-PREFER, which is a public-private partnership in Europe, reviewed methods and created a compendium of methods, a compendium of both qualitative methods, which is not presented here, and quantitative methods, which is presented in the right-hand panel here. And those methods that were identified in this compendium, they're actually more here than in the MDIC compendium of methods, but they're actually quite similar in terms of their content. And that was published in 2019 in *Drug Discovery Today*. We can go on to the next slide, please.

So before we kickoff the rest of today, I'd like to give two very, very different examples of patient preference information and its use by FDA, because I think what, I hope

what this will show, is kind of the range of applications of patient preference information in two very different forms of eliciting patient preference information, both of which were, I think, were extremely useful in their applications. And it shows you kind of the breadth and depth of what we're talking about here when we talk about patient preference information, and then my hope is that the case studies will fill in that story as we go throughout the morning.

So the first is a study that was published in 2015 on obesity devices. This study was sponsored by CDRH to look at the tradeoffs that people with, obese people would be willing to make between the benefits and risks of devices to treat obesity. And that included developing a tool where you could input the characteristics of different devices, the benefits and the risks, and the other characteristics from clinical or observational data, and come up with an assessment of the likelihood that patients would perceive the benefits would outweigh the risks. And that was published in *Surgical Endoscopy* in 2015.

A different example was used, essentially, a crossover trial. There was a new formulation of rituximab for blood cancers that was subcutaneous injection rather than IV infusion. The company had established bioequivalence between the two different formulations, so really the only difference was in the mode of administration. So they conducted a crossover trial in which patients experienced both subcutaneous and IV administration of rituximab to treat blood cancer, one or the other, and then they switched to the opposite so that everybody experienced both. And then they were asked, "Which do you prefer?" So a very different type of approach to assessing patient preferences.

So if we go to the next slide, when we look at the obesity study, FDA actually used the results of this study and presented information to the advisory panel to demonstrate that even though this particular technology did not meet its original endpoint in its pivotal study, the model that was generated by the patient preference study was able to predict

that there was a group of patients who would perceive the benefits of this device to outweigh the risk. And that information was important in the decision to approve this particular obesity device.

If we go to the next slide, when we look at the outcome of this oncology study for rituximab, subcutaneous versus IV in blood cancers, this actually wound up in the product label in the patient experience section of the product label. And I think there are a couple of reasons why this actually got into label, which is often, you know, for a lot of sponsors a very important outcome, almost the holy grail, if you will, is to get something into the label.

And you know, in this case, I think there were some very specific reasons why this may have, in fact, wound up in the label. First, it was interventional. It wasn't hypothetical like the obesity device study. People actually had experience with these particular technologies, and, given that experience, could make a decision based on having experienced both. In this case, also, with the rituximab example, there was a single variable that differed between the two. Remember I had mentioned that the company had already established that the two formulations were bioequivalent, so they could assume reasonably that everything was the same except for the mode of administration.

One of the nice features about this particular study, this rituximab study, was that they administered the survey twice, both toward the end of the study, but they administered the preference questionnaire twice, I should say, and to demonstrate that the preferences were stable, that these weren't just whims that they happened to be catching at a single point in time. And I think that's important, because when people are stating things to us and telling us what they would do, it's important for us to know that these things are stable.

And also in this case, the results were really unambiguous. Such a large proportion of patients preferred the subcutaneous to the intravenous that it was, it was pretty

overwhelming. This was not a close-call by any means. So, in effect, this was a breakthrough just like the obesity study was a breakthrough in that it's the first time, that I'm aware of, that an FDA panel and FDA itself used patient preference information in approving a device, particularly one that did not meet its primary endpoint. This one is really important because it was really the first time that I'm aware of that such patient preference data was cited explicitly in a product label. So if we can go to the next slide, please?

So just to wrap up, this was sort of a whirlwind overview of the types of concepts that we're going to be talking to today. And I encourage everyone if you are interested and did not have a chance to see our webinar from March, to go to the ISPOR website to take a look at that webinar and the content that's in there and do let us and any of the other presenters know if you have any questions.

But the take-home messages from this little presentation here to set up the day are: Keep in mind as we go through the day that there are multiple methods for eliciting patient preference information. And you will see a number of different methods described today. And there are even more beyond the examples that you'll hear of today.

There are multiple potential uses for patient preference information. I described two with the obesity and the oncology example. But I know Annie Saha, who will be speaking next, will be talking about different potential uses for patient preference information. And some of our case studies that you'll see later today will also have very different applications.

And what you will hear about today kind of goes to establish the body of evidence that there are precedents for doing this. Ten years ago, this was somewhat of a dream that we would actually be having a summit like this today, where we would be talking about actual applications in real-life decisions in the use of patient preference information. And

what was, you know, kind of a dream 10 years ago has now become a reality, and all of the examples that we will see today are examples that establish the precedent for using this, for developing this and, for now, looking critically at some of the pros and cons of the different methods in doing this, which is something we'll talk about a bit this afternoon. So I'm really excited about today, and I thank you for the opportunity to sort of share this overview.

And I guess at the moment, do I go back to Annie or to Christina?

MS. SAHA: Thanks, Brett, for that great overview. I'm Annie Saha. I lead our Partnerships to Advanced Innovation and Regulatory Science Team at CDRH, and I'll be following up to really inform how PPI can be used in regulatory decisions.

So patients are really at the heart of what we do at CDRH. Our vision is to ensure that patients have access to high-quality, safe and effective medical devices, first in the world. And the key to that mission is to actually hear from patients. So the benefits from hearing from patients is really that they can help us all throughout the lifecycle to inform product design, clinical trials, identify specific patient populations for benefit-risk for a specific treatment, to communicate treatment preferences, to raise or confirm problems that may exist with specific products, and to bring to light new considerations to inform FDA's thinking on current issues.

Patient input and regulatory efforts include both patient engagement and patient science. And so what do we mean by this? So patient engagement is really what we're thinking about in terms of intentional, meaningful interactions with patients that provide opportunities for mutual learning and effective collaboration across the total product lifecycle.

And as you heard from Brett, patient-reported outcomes are really the report of a status on a patient's health condition that comes directly from a patient without

interpretation of that response by a clinician or anyone else. And that patient preference is that qualitative or quantitative assessment of the relative desirability or acceptability of attributes that differ among alternative diagnostic or therapeutic strategies.

And really see that patient input is useful across the total produce lifecycle for devices starting at patient-informed needs for discovery and ideation, inventing and ensuring devices are using human factors, informing clinical investigations by using patient-informed designs as well as patient-reported outcomes that we can leverage patient preferences and the benefit-risk assessments, and then, ultimately, we want to be able to communicate those benefits and risks to patients. And then in the post-market, we can use patient-reported outcomes to better assess how devices are performing.

So CDRH has issued a number of guidance documents that emphasize the importance of including patient preference studies as one component of scientific evidence that informs a benefit-risk assessment, whether it's in the pre- or post-market, or in looking at how uncertainty impacts regulatory decisions. Patient preference is mentioned as an important factor for consideration. I will briefly highlight this in the next few slides, and you'll hear much more about this at the next session today.

We first put in our pre-market benefit-risk guidance, that was originally published in 2012. That stated that one factor to consider is patient perspective on risk and perspective on benefit. And we recognize that risk tolerance will vary among patients, and that we may find that there are reasonable patients who are willing to tolerate a very high level of risk to achieve a probable benefit.

In our uncertainty guidance, we recognize that to meet FDA's mission to promote public health, in light of inherent uncertainties involved in the provision of medical care, it is important to acknowledge and appropriately address uncertainty and benefit-risk determinations that support FDA pre-market decisions. And the FDA, of course, considers

the totality of evidence to the extent of both the probable benefits and the extent of probable risks of devices. And with that we also consider the appropriateness of risk mitigations and the collection of post-market data to address uncertainty. There can be uncertainty around the type, the magnitude, duration, frequency or other aspects of a device's benefit or risk to patients.

Now, how does PPI fit into looking at uncertainty? We can consider a patient's perspective on appropriate uncertainty about probable benefits and risks about a device or the probable benefits of earlier patient access to that device if that information is available to us. And that consideration should be, of course, consistent with all of our statutory and regulatory requirements and authorities.

As you've heard multiple times both from Brett and me, we define PPI as the qualitative or quantitative assessments of that desirability or acceptability among different diagnostic or therapeutic strategies. And with that, we also consider the relevant perspectives of caregivers or other healthcare professionals, depending on the situation.

PPI can inform medical product development across the lifecycle to really identify unmet needs, what matters most to patients. It can help in clinical investigations to really inform endpoint selection, performance goals, or effect size. When you're thinking about it from a benefit-risk assessment, we can look at the analysis of the condition, treatment options, perspectives of trade-offs, and subgroups. And in the post-market, it can inform our interpretation of new data, new or expanded populations, and also how to communicate those benefits and risks to patients.

We can say that PPI can provide value about which benefits and risks are most important to affected patients, the trade-offs that they're willing to accept, and how they think about these trade-offs to really identify potentially clinically meaningful and relevant subgroups.

As I discussed, there are many potential uses to inform PPI and study design, labeling, and availability. And also beyond the regulatory concept, PPI could be included in shared decision-making or other types of reimbursement decisions, and you'll be hearing more about that discussion in our Session 4 later this afternoon.

And in our guidance on patient preferences, we really focus on four objectives. One is to encourage the submission of PPI, if available, by sponsors or other stakeholders to aid in mutual, in FDA decision-making; to outline recommended qualities of PPI studies that could result in valid scientific evidence; to provide recommendations for collecting and submitting PPI to the FDA; and to discuss the inclusion of PPI in decision summaries, as well as providing recommendations for inclusion in labeling.

And we want to be clear that PPI is voluntary. PPI may not be relevant for all or appropriate for all device types. PPI could be useful when we're trying to, when those uses or decisions by patients or healthcare professional are preference-sensitive. Some examples of preference-sensitive include where there might be a direct patient interface, where the device could directly affect health-related quality of life, for certain lifesaving high-risk devices, or maybe in an area with a new technology.

Well-designed and conducted preference studies can provide valid scientific evidence regarding patient risk tolerance and perspective on benefit that could inform our evaluation of a benefit-risk of a PMA, HDE, or De Novo review processes. And so what do we mean by well-designed study? We highlight in the guidance the recommended qualities of PPI studies and that they really need to be in three pieces: all about the patients, have good study design, and good study conduct and analysis.

So when we're talking about the qualities about all about the patients, were looking at four different pieces. That is, when you're looking at the study, it needs to be patient-centered, that patients are really at the focus of the study and are they well-informed as

part of the study. And we want to make sure that these studies ensure comprehension by the patients to ensure that they understand the harms, benefits, risks, and uncertainty, and any medical information that may be provided in the PPI study. We want to ensure the PPI study is representative of the population of which the device is intended for and sized to be generally, reasonably generalized to the patient population of interest. And these studies should also aim to capture the heterogeneity of the patient population.

When looking at good study design, we want to see that studies follow good research practices, such as those that have been put out by ISPOR, and studies should ensure effective communication of information to ensure, to try to reduce uncertainty that's caused by health numeracy. Studies should try to ensure that they're minimizing cognitive biases, such as framing or ordering effects. And ultimately, the study needs to be relevant. As you hear more in the case studies in the later sessions, you'll really hear more about what these mean, especially in terms of that relevance of a PPI study so that it can be useful in a regulatory decision.

The third set of qualities for a PPI study is study conduct and analysis. Just like any other type of data that FDA is reviewing, we want to ensure that the PPI study conduct is compliant for both researchers and study participants. PPI study should also be conducted in a way that they're logically sound and include tests for logic and consistency. And we want to sure that of course that the analysis of the results are robust as, just as any other data or statistical analysis plan we would see.

Should a PPI study have those qualities, I highlighted, we may consider it as valid scientific evidence, along with other information from the clinical and non-testing when we're making our benefit-risk determinations. And of course our patient preference guidance does not change any of our review standards for safety or effectiveness.

Now that I've walked through the guidance at a high level, I'd like to further discuss

where PPI could be most valuable. This figure, as part of the MDIC PCBR project that Brett highlighted, highlights where and how PPI could be used based on the benefits and risks of devices. So for a device that's in that top green corner, if it's high benefit and low risk, PPIs may not add a whole lot of additional information when we're making a benefit-risk assessment. When you're looking at low benefit, high risk devices, PPI could inform whether the benefit is important enough for a subset of patients. And probably really when you're thinking about PPI the most is those yellow and orange boxes, where you're talking about high benefit and high risk or low benefit and low risk, where PPI can inform whether there's a subset of patients who are willing to accept those tradeoffs and provide valuable information in us understanding that.

So as I discussed earlier, we can see PPI can be most useful in areas that are preference-sensitive. So what do we mean by that? We put out a list of areas we consider to be patient preference-sensitive, and we plan to periodically update that list. And those areas include where we would like to better understand patient values in terms of diagnosis or treatment, understanding relevant clinical endpoints, such as which patient-reported outcomes are most important to patients, understanding benefit-risk tradeoffs, and then also the impact of uncertainty across different medical specialty areas.

So now that I've walked through where PPI and how it can be used, I want to highlight how to ensure the study is relevant for FDA. We strongly encourage that you come in with a pre-submission and use that as an opportunity to discuss the regulatory relevance, the research question, the survey participants, survey design, and analysis approach. And one pro tip is please make sure to include the CDRH PPI team to be a part of that pre-submission meeting to ensure that we're able to answer all of the relevant questions. And MDIC has also put out useful resources about what the different types of questions you might want to think about in a pre-submission.

We're continuing to see the regulatory impact of patient preferences. Brett highlighted the obesity study example, and we've also expanded the labeling for home hemodialysis, which, as well as approved devices for ear tubes for children. PPI was used in different -- some of the different areas that I highlighted earlier. You'll actually hear a lot more about this in the next session on a case study, so stay tuned for further details. And we also see a jump in industry sponsor studies. And we now are at 23 studies that have either been completed or are now in the pipeline.

So to close out, here are some final considerations. FDA is invested in the importance of patient preference information and regulatory decision-making. Our partnerships through ISPOR and other professional societies and patient organizations can help advance the science of patient input by addressing existing scientific questions about how to ensure that their PPI studies are robust and reliable through capacity-building and methodology research. Sessions later this afternoon will talk a lot more about this.

And ultimately, we're all working together to do more research so that we can strengthen approaches for greater quality, trust, cost efficiency, and respect for patient views and times. We have a number of resources available both from the FDA as well as external collaborators. Since these slides will all be available, I'm not going to read through all of them, but I will highlight the last bullet. So when in doubt, just e-mail us at CDRH-PPI@fda.hhs.gov.

So with that, thank you for your time, and Brett and I are now available for questions, so I will turn it over to Christina Webber to moderate the Q and A.

DR. WEBBER: Thank you, Annie, and thank you to Brett, as well, for giving a really good introduction on patient preference information and getting everyone set up for the rest of the day.

I do want to remind people, as Annie mentioned, the slides will be available after.

ISPOR's website and our meeting website, the FDA's website, will have the slides posted after the meeting, as well as a transcript and the video recording.

So now our session is open for questions. You can either ask your questions via the webcast. There's the little thought bubble that you can enter questions in there. Or you can also do that for the app that we have, the CrowdCompass app. If you have that already downloaded, all you need to do is tap on the session, and you will be able to see a little live Q and A. You tap that, and then you can submit your question there.

If you would prefer to use a web browser for this, you can also do that. Please visit https://crowd.cc/ptinputmeddev2020. So that's crowd.cc/ptinputmeddev2020. So with that, I will start a question for Brett.

So when do you think would be the best time to -- PPI whether it be in device development, early feasibility studies, maybe post-market? Annie touched upon the total product lifecycle, but is there really a best time to have a PPI study?

DR. HAUBER: In one sense, that's an easy question, because the answer is always "earlier than you think." But it's a little bit hard too, because sometimes the need or the realization of the need for PPI doesn't crop up until a little bit later. So one of the things I think that has changed is that the recognition of the uses of PPI and the possibilities of using PPI have allowed people to begin to think about it early.

But I'd still say, you know, these studies can take a lot of time. And if we're going to use them as valid scientific evidence, as Annie outlined, there's a lot of thought that has to go into these. We've got to make sure that they are good, reliable, valid, trustworthy studies, and that all takes time. So I think that original answer that I gave as "earlier than you think," it still applies.

But when specifically? You know, I think as you're developing the concept for a technology, you can begin to see whether, in fact, it might be preference-sensitive or

whether there will be these types of concerns based on the type of technology that it is. And at that point is when you should start thinking about where would patient input and patient preferences in particular be able to help us understand the appropriate design, appropriate use, appropriate labeling, for technology such as this.

So really almost at the ideation stage or soon thereafter is when you have the possibility to think about patient preferences. And again, if you're thinking about patient preferences, don't waste any time, because you don't want to be too late, and you probably should have started 6 months before. So --

MS. SAHA: Yeah, and I think I'll add on to Brett's comment, too, is that depending on where you're thinking about, and certainly, the earlier, you may not need a full patient preference study. It might be more that a qualitative PPI study to understand what patients are willing to accept or what they care about when you're at the discovery or ideation phase may be enough information for that particular purpose. So, you know, there's also that fit-for-purpose and context of use of what do you want to get out of the preference study.

DR. WEBBER: Okay. Great. So another question that we've had coming in -- also, I just want to let everyone know. We only have 5 minutes left in our session, but we will be keeping note of all of the questions that are coming in. So maybe they could be added into some of the other sessions during the day.

But before we have to close out this first session, Brett, you had spoken on some PRO versus PPI. How do you decide whether to use one or the other, which would be best? And then maybe, Annie, you can follow up with that.

DR. HAUBER: Okay. Thanks. And thanks for that question. I don't think it's an either/or. They provide two different types of information, you know? If there are effects of a product on a patient that we can only get by talking to patients, you know, that's a

PRO. That is an outcomes assessment. That is dependent upon getting information from the patient. And I think, you know, we are seeing -- and I am not an expert in PRO so take this as only my opinion -- but I feel like we're seeing more and more patient-reported outcomes being used as primary and secondary outcomes in clinical studies because it's important to know the impact, if you will, on a patient. So I think those are almost becoming pretty common or more common.

Then the question becomes for a patient preference study is: Do you have these decisions about tradeoffs? Are you talking about trading off benefits and risks or are you talking about trading off among different options? And, you know, is the decision kind of going to be based on those types of tradeoffs from the patient's perspective. That's when a preference study comes in. And so I think we're really talking apples and oranges here, and both are useful. So I wouldn't say that it's an either/or proposition in any case.

MS. SAHA: Yeah, I would echo that, that it's certainly not an either/or. One can certainly inform the other. So we could see that patient preferences could help with understanding or prioritizing what outcomes are most important to patients, which could include which PROs are most important. And as far as hearing more about the usage of PRO instruments, we do have a workshop tomorrow, so we hope people tune into that, and you'll be hearing a lot more about the use of PROs in medical device submissions.

DR. WEBBER: Great. And so, Annie, you had mentioned about you want to make sure that you capture the heterogeneity of the patient population that you are interested in for your preference study. Are there any methods or suggestions on how to make sure that you capture all that data and make sure that your data that you gather is representative of your patient population?

MS. SAHA: Well, I think, you know, there are sort of two pieces with that. One is there is still a lot of research, I think, effort that needs to be done about how do we better

ensure heterogeneity and what is the appropriate sample size that's going to get to that generalizability. So that's really where it's so critical to come in and talk to us, to have those discussions, because at least as far as I'm aware of -- and Brett, feel free to correct me -- there's no hard-and-fast rules about any of that, so it's really going to probably be context-specific to the specific patient preference study. And so that's where we really encourage, again, coming in and talking to FDA in a pre-submission.

DR. HAUBER: Yeah. And there are no hard-and-fast rules. And I'd like to add that, you know, there are kind of two types of heterogeneity we want to keep in mind. One is sort of the traditional heterogeneity of the patients, where we can segment patient groups by, you know, disease severity or other characteristics that we typically collect or observe. But we also want to capture preference heterogeneity, because you and I could look exactly the same on paper and have very different preferences.

So one of the ways that we capture preference heterogeneity is to allow the data to tell us, you know, how different the preferences are among the sample, and then to the extent that we can, we try to relate to individual characteristics. But you know, they're not necessarily lockstep. So we could have preference heterogeneity in the sample that's really important, but not know who's in what group. And that doesn't mean that information isn't valuable. It just means that people aren't segmenting based on the criteria that we might normally think of when we talk about for heterogeneity and patient groups.

MS. SAHA: Yeah, and I think that will also be further discussed in the methodology session later today. So that's good to whet everyone's appetite.

DR. HAUBER: Yes.

DR. WEBBER: Well, great. It is time for our session to wrap up. Thank you both for being a great introduction to our day. We have three more sessions to go into specifics of patient preference information and how it's used, and where we're seeing that.

I would now like to turn it over to Michelle Tarver. Dr. Michelle Tarver is the Director of the Patient Science and Engagement Program at FDA's CDRH. She will be our moderator for Session 2 on some case studies on how PPI has been used so far. So with that, I'll turn it over to you, Michelle.

DR. TARVER: So welcome to Session 2. I'm Michelle Tarver, and I direct the Patient Science and Engagement Program at CDRH.

I'm going to share with you and open up the session, where we're going to talk about case studies in patient preference information that has been submitted to FDA for its medical decision-making, as well as potentially submitted to HTAs in their decision-making. Can I have the next slide, please?

In our session, you'll hear from four cases, and one of them will be from Dan Harfe, who is the Vice President of Regulatory Quality and Strategy at Smith and Nephew; Christine Poulos, who's a Senior Research Economist at Research Triangle Institute Health Solutions; Todd Snell, who is a Senior Vice President of Quality Assurance, Regulatory and Clinical Affairs, at NxStage Medical of Fresenius Medical Care North America; Barry Liden, who is the Vice President of Patient Engagement at Edwards Lifesciences. And Kimberly Brown Smith -- excuse me -- will be weighing in on how benefit-risk decisions take this into account. May I have the next slide, please? And the next slide?

So today I have the opportunity to share with you a little bit about how patient -- excuse me -- patient preference information can be used in decisional frameworks, how it can be put in the context of healthcare providers' and regulators' perspectives to help understand how patients look at this same benefit-risk decision-making when determining their choice for care, as well as how they're living and experiencing their conditions. It also informs their priorities and a list of many different outcomes particularly when you're designing a clinical trial. It may also illuminate their tolerance for adverse events or risks, in

exchange for quality of life benefits, earlier access to potentially effective treatments, and convenience. Next slide.

Patient preference information also can be used at various points along the device development pathway. It can be used when they are developing the device itself to identify an unmet medical need, help design a clinical trial so that it can inform the endpoint, as you heard earlier today, inform the performance goals, and help inform uncertainty, which is the error that patients may be willing to tolerate for earlier access to a medical product.

It also can be weighed in with a benefit-risk assessment, clarifying what matters most to patients about their disease and their treatment, illuminate the tradeoffs they're willing to make, and identify subgroups that are willing to make different choices. It also can be informative in the post-market arena, helping to understand the benefit-risk decision-making for compliance, as well as informing studies for new and expanded-use populations.

So without further ado, I'm going to turn it over to Todd Snell -- excuse me -- Dan Harfe, who will be talking to us about a case study and patient preference information.

Dan?

MR. HARFE: Thank you, Dr. Tarver. Thanks to ISPOR and FDA for inviting me to present this case study. I'm Dan Harfe from Smith and Nephew via an acquisition earlier this year with Tusker Medical, which was a small startup based in Northern California. So I'm going to be presenting a case study using preference testing very early on in the regulatory process, when designing a protocol for pivotal studies for a combination product PMA. So next slide, please.

You can see my disclosures on this slide. I am an employee of Smith and Nephew. Next slide. Next slide, please.

Thank you. So, here's the disease we'll be talking about. I want to briefly go over

this so you understand the preference tradeoff that we are understanding here. So, the disease is otitis media, inflammation in the ear. And if you have young children, you're probably, unfortunately, very familiar with this disease. It comes in two forms, recurrent acute, which is the ear infections that typically young children get over and over and over again, up all night with a crying child, fevers, very irritable, very common in young children.

Another flavor of otitis media is otitis media with effusion, commonly known as "glue ear," which is not infected, but it causes hearing issues, so very concerning, again, for young children, who are trying to learn a new language, who can't hear very well. We have fluid in the ear that becomes very problematic. It's very common. You can see on the slide by age 2 in the U.S., greater than 60% of children will experience at least one episode. And again, if you have children, you probably unfortunately are quite familiar with this disease. Next slide, please.

So when conservative therapy fails, which is typically antibiotics and multiple rounds of antibiotics, a procedure called a tympanostomy is performed. On the right side of the slide, you can see the procedure. It's very straightforward. What's known as a tympanostomy tube, which is that white cylinder, is placed across the ear drum. And what that does is it ventilates the middle ear space, resolving the inflammation. Very successful. Very common surgery in the U.S.

Unfortunately, it has to be done under general anesthesia, as shown on the left. The ear drum is extremely sensitive, and there are no -- there were no techniques or local anesthetics that can be used. And so you have to put the child under general. This of course comes -- while considered to be extremely safe, it comes with risks.

We've got the societal risk, anxiety, the stress on the parent, on the child. This is likely the first time a parent is handing their baby over to a physician to take under general. I can tell you from personal experience, it's very stressful. Then there's the

medical risks of general anesthesia -- spasm, arrhythmias, et cetera; the postoperative concerns of nausea and vomiting; and then there's long-term neuro-developmental risk, which is an area of ongoing research and controversy. But I think most people would agree if there's a way to avoid general anesthesia, particularly in young babies, we should try to do so. Next slide, please.

So Tusker Medical, which is a startup, we believe there has to be a better way to do this. So we developed a combination product device-drug system, which provides a local anesthetic that is kid-friendly, so no needles. This can be done in an office setting under local anesthesia. So this enabled -- it opened up the possibility now for performing this very prominent surgery now under local anesthesia in a physician's office. There's a tube delivery system, as well, as part of the procedure. You can see one of our clinical study subjects on the bottom right actually undergoing the procedure, as you see with -- sitting in dad's lap there. Lots of advantages. No exposure to general anesthesia, no parent/child separation, no sedation, et cetera. But with this transition of extremely popular procedure from the OR under general to the office under local comes some very difficult regulatory questions. Next slide, please.

And here's the source of our challenge. That is a picture, on the right, of our typical patient. You can see the plot on the left. Most of these kids are 1 to 2, 3 years old. And you know, toddlers typically don't like you to do things to them. And so not every procedure in the office is going to be successful. This is known for any pediatric procedure. Think pediatric dentistry, pediatric MRI or CT, where you try to do it, and if you can't, you have to go to general. Or even a haircut, right? If you've got a toddler and you're trying to get their first haircut, how often is that successful.

So, in contrast, the procedure in the operating room under general is virtually 100% successful. When I say successful, I mean in getting the tubes into all the targeted ears. So

you can see already the tradeoffs are developed. We've got this OR procedure, which is virtually 100% successful or this office procedure, which gives you the advantages of avoiding general anesthesia, all the stresses/anxieties, but will not be 100% successful. Next slide, please.

So this is a first-of-its-kind medical technology. There was no prior ability to do this in the office. So we would all like to have an RCT for this, particularly for a combination product PMA being performed primarily in pediatrics.

So what do we randomize against? The first, and most obvious option, is general anesthesia, but we already know that the in-office procedure, which is known as TULA, will have a lower success rate. So there's no reason to compare the procedural success. We already know the outcome going in. And comparing adverse events is apples to oranges. You've got a general anesthetic complications versus local anesthetics. And so, not really useful control arm. Next slide.

So why don't we randomize, then, to another alternative in the office? Well, for a first-of-its-kind technology, there are no alternatives. And so that's not possible either. Next slide, please.

So we agreed with FDA to run a single-arm study with a performance goal of technical success, so how often can you insert tympanostomy tubes in all of the ears we intended. For most cases, some background, it's bilateral: 85, 90% of these children need tubes in both ears.

So let's assume that all the failures for the in-office procedure are safe. There's no safety issues, and all future surgical and medical options are preserved. What success rate in the office is acceptable? So if you're parents and this physician says, "Hey, your kid needs to get tubes. I can do it in the OR under general and I will get the tubes in, or we can try it in the office. We avoid general anesthetics. You can stay with your child. Your child

can go right back to school after the procedure. But, there is a chance it's not going to work." What percentage is needed for this to be a viable technology? As a parent, would we take a 50/50 shot in the office first? A 70% chance? 90% chance? This is the preference decision that needs to be made. Next slide, please.

So, of course, this set up a pretty challenging negotiation with the Agency. So from our perspective, from the industry perspective, the benefits of avoiding general anesthesia are quite meaningful and parents are likely to prefer this option. So technical success significantly lower than 100% should be acceptable. The FDA, of course, is approaching it from a different perspective, which is the current standard of care is 100% successful. So what's the rationale for accepting something meaningfully lower than that? We were really approaching the question from completely opposite perspectives. Next slide, please.

So it became clear that we needed additional data to resolve what was turned into a negotiation impasse. Next slide.

And that additional data was patient preference testing. So rather than have Tusker Medical or FDA determine what the acceptable success rate is, let's just ask parents. So this sets up some very interesting features here, because now we're talking about a patient preference study for a pediatric procedure, where we're asking parents what their preferences are because they're the decision-makers. And, at the time, this was, I believe, the only example of using preference testing to set a performance goal in a pivotal study. I suspect and hope there are other examples like this, in general, but when we did this back in 2016, this was quite early in the preference testing paradigm. Next slide, please.

So here's the fundamentals of our preference test. I'm not going to go into the study details or the study outcomes, but I do want to point out the main features. So it was a stated preference threshold design with a fixed reference of the operating room, the standard of care, where we told responders that assume that more than 99% of these will

be successful versus the alternative, the target, which is the office, where there is some variable failure rates, and we vary that in the study, and we ask parents, after describing both of these types of procedures, both of these alternatives, which would they prefer.

So, as Brett and others have already mentioned, we did first qualitative interviews, and then we ran our preference study. We had a sample size of 400, screening questions, of course, consent, background, and we did comprehension testing, et cetera. You know, one of the -- this was certainly my first preference test, as I suspect your next preference test, if you're not RTI, will be your first. It's really, really important to take your time in the study design phase. Every single word here is critical to avoid bias, or if not bias, the perception that your study might be biased for or against a certain preference option.

So we did the study. We got the results. We were super excited about it. We submitted it to the FDA. And next slide.

Their initial response was "using survey respondents to set a performance goal is not adequate." So this was not what we were hoping for in our response from FDA. They clearly were not impressed with our study.

So remember this was 2016, so it was really early on in FDA's encouragement of preference testing. And our review was particularly complex, because we're pediatric device-drug combination products. All our filings went primarily to CDRH, but with a collaborative review from CDER. CDRH and CDER, of course, are known sometimes to have different perspectives on data, and that's I think particularly true with patient preference data, and they're varied in enthusiasm for the technique.

So, the first -- and we of course just -- we had no idea who the experts were within FDA when we sent this in, so we just sent it in to our review branch. So, you know, lesson number one is make sure when you send something like this into FDA, it gets to the right people at FDA who are the experts in this area. I suspect submissions these days with this

type of data would be received quite differently. Next slide, please.

So then we kind of worked through, "this is kind of a real technique, and we're following FDA's guidance on how to perform it, and please, let's consider this to be a study and not a marketing survey and consider it as serious data." Once we got through that initial problem, then we got the standard questions that I think everyone should expect to receive and be prepared for, which is: Is your sample adequate? Does it represent the broad or narrow population? Did you do the right pre-testing?

And treat this study like you would your pivotal clinical study. Collect the data in a study database. Make sure your statistical programs are replicable by FDA statisticians, just like you would expect for a pivotal clinical study, because they will do similar things to the study data. Next slide.

So lessons learned. As I mentioned, treat your preference study as you would any complex clinical study. Most of us in regulatory, at least, don't have prior experience with health economic research. So, make sure your budget and timeline are appropriate. The proper study design is critical. Can't emphasize enough this is not a marketing survey. You can't do this yourself with SurveyMonkey. Be sure your preference study makes it to the experts within FDA. Next slide.

If you don't have the internal expertise within your company, which we did not, work with the right partners. We chose RTI. We actually worked with Brett, who you already heard from. And quite frankly, we chose RTI primarily because FDA had chosen RTI for the obesity study that was already discussed. And again, we're talking 4 or 5 years ago, fairly early on in this. We wanted to make sure we chose experts who FDA had confidence in. So we chose RTI. And of course, there are likely others you can select as well, or internal organizations that now have this expertise.

And I think the most controversial -- next slide, please -- points that I'm going to

present, you know, do you work with FDA? The obvious answer is of course you work with FDA. Why wouldn't you? You know, if you get this in front of them, make sure that your study is designed properly and is going to answer the regulatory question that you want to answer.

In the real world, this is not always so straightforward, particularly if you're a startup and you're burning cash. So, you know, we are a combination product, pediatric device, which is a pretty complicated development environment, in northern California, a pretty expensive place. So we had around 30 employees at the time we submitted this.

For all the CEOs, CFOs out there, northern California, we're probably talking $25,000 a month in employees. So, can you wait 4 months? Can you burn 3 to 4 million in dollars of venture capital, you know, negotiating this with FDA, or do you take the risk, run the study with the right partner, and then submit the results?

We decided just do the thing and submit the results. And you can see it didn't go great for us. We submitted this in July of 2016, and FDA was aligned with the results a year later, with really no change from our proposed endpoint. So it took a year to get alignment on the results, and I suspect that would have gone a lot quicker and smoother if we had engaged with the agency ahead of time. Next slide.

So, in conclusion, this was a success story. The preference study was absolutely instrumental in the design of our pivotal study. Without it, quite frankly, I'm not sure how we would have come to our performance goal endpoint. It resulted in the approval of our PMA in November.

And just as a side note, as I was listening to the PPO versus PRO discussion, we had both. We had a patient-reported outcome, which was pain reported by the 5 to 12-year-old children in our study. And if you go search up that P number, and you can see on our summary of safety and effectiveness data, you'll see both the PPO information that I

presented here, but also the PRO information on the tolerability of the procedure. So very distinctive, different purposes over these both in the context of this study. Next slide, please.

So that's the end of this presentation. I think at the end of this session, I'll be available for questions, and with that, I'll turn it over to Christy also from RTI. If you're sensing a theme here, they are the experts, so I think Christy also has a very interesting case study of preference study -- preference data used during the PMA process.

Christy?

DR. POULOS: Thanks, Dan.

Yeah, the case study I'll be talking about is a little bit different than Dan's example in that this was a PPI study that was conducted to support benefit-risk assessment, so it was conducted a bit later in the process. And it was designed to support a PMA submission. But, there are some similar themes you'll see as we go through. Next slide.

I have no financial disclosures to report. Next slide, please.

So this is a little bit about the therapeutic area. The device I'll talk about is a treatment for severe emphysema, which is a type of chronic obstructive pulmonary disease in which the walls of the alveoli in the lungs are damaged and destroyed. So this leads to trapping of air inside the lungs, which makes it harder to move oxygen in and carbon dioxide out, and it can lead to the lungs becoming hyperinflated, which causes breathlessness and significant morbidity and decreased quality of life in patients.

The way it works is that it becomes difficult or impossible for patients to perform their daily activities without feeling breathlessness and the fear and stress that comes with that feeling of breathlessness. So they reduce activities, which leads to weakened muscles, which increases breathlessness, which leads to less activity and more breathlessness, and so on. So there's this downward spiral.

PneumRx and BTG developed endobronchial coils to treat individuals with severe emphysema. These coils are placed inside the lung using a bronchoscopic delivery system that straightens out the coils and places them in the lung. And then after they're placed, they are restored to their coil shape, and it reduces the volume of the lung tissue. Next slide, please.

They were developed to address unmet need. Despite available medical and surgical treatments, optimal medical therapy for patients with severe emphysema is represented by this red circle, and it offers modest benefit shown on the *x*-axis and relatively low risk, which is shown on the *y*-axis. By the time we did the patient preference study -- next slide -- the only realistic alternative was lung volume reduction surgery -- next slide, please -- which may provide substantial benefit, but also has substantial risks, and LVRS is really appropriate for a very small subset of patients. Next slide.

The endobronchial coils may offer a benefit relative to the optimal medical therapy -- next slide -- but they also do pose some additional risks. So the coils lie somewhere between optimal medical therapy and LVRS on this graph, where none of the treatments is superior to another. So we conducted a patient preference study to try to understand how patients would evaluate the benefits and risks of these treatments. Next slide.

So, as I said, it was designed with the intent to support the benefit-risk assessment in a PMA submission, risk assessment of -- a benefit-risk assessment of coils relative to optimal medical therapy. The study began in late 2015, and we completed it in early 2017.

At the time the study began, the pivotal trial was still ongoing, so the final clinical trial results were not available in the early days of the study development, which had some implications I'll describe in a few minutes. It was also when the study began, the CDRH guidelines were still in draft form, the guidelines on PPI, so like the study that Dan

described, this was one of the first studies completed after the draft guidance was issued, and this was the first PPI study that was presented to an advisory panel, which met in June 2018.

So when we did this study, the teams at RTI and at PneumRx and BTG, had experience with preference assessment on the one hand and the PMA process on the other. But the combination of PPI and PMA was new and really unfamiliar to all parties at that point in time. And one of the issues the team grappled with was the extent to which we engaged with the FDA team -- when we should do it, how often we should go back -- and there was no precedent at the time. The sponsor was balancing the time required for engagement with their PMA timeline.

So as it ended up, the research protocol was submitted to the FDA as a formal pre-submission before the survey pre-test was completed, and then there was an in-person meeting to discuss FDA's comments on that pre-submission. And then there was no additional engagement until the study was completed and the results were submitted with the PMA application in 2017. And after that, there was a period of interactive review before the panel meeting. Next slide, please.

So a little bit about this study. The key endpoint was the proportion of patients with severe emphysema who would consider the benefit of the coils to outweigh the risks, based on the results of the pivotal trial. The sample included patients who were not part of the trial, but they did meet enrollment criteria similar to those used in the trial, and they were recruited through eight clinical sites across the U.S. Next slide.

So we used a discrete-choice experiment in this study. This was a method in which treatments are broken down into their component parts to -- that differentiate among the different treatment options. And in this case, the component parts were -- next slide -- the type of treatment, and the treatment benefit, and then the next slide adds the increases

and the risks of the most frequently reported serious adverse events, which were COPD exacerbations, pneumothorax, pneumonia, and the risk of death.

So we chose these attributes to align with the trial endpoints and results and to use in the benefit-risk assessment, and in-person pretests and in-survey checks were used to check that respondents understood the attribute descriptions in the survey. We assigned levels to each of these components and used an experimental design to develop hypothetical treatment profiles. And then the next slide shows that we asked patients to choose between two different hypothetical options in each of a series of questions. I think there's one more build here. So next slide.

The next analysis quantified the tradeoffs that patients were willing to make between the benefits and risks, and then we applied the results to clinical data to estimate patient preferences for treatment profiles that were similar to coils and optimal medical therapy. Next slide, please.

So, the treatment benefit in this study presented some challenges. As Annie described, the attributes in a PPI study, to align with the qualities in the CDRH guidelines, should be clinically relevant and aligned with the endpoints in the trial to facilitate that benefit-risk assessment, and they should be patient-centered, meaningful to patients. And these qualities were at odds. The primary and secondary endpoints in the pivotal trial were the change in the 6-minute walk test and the change in forced expiratory volume in 1 second, or FEV-1.

But, patients do not readily understand changes in these endpoints. There was a measure of patient's quality of life as a secondary endpoint, where the quality of life was measured as the change in the total score for the St. George's Respiratory Questionnaire, or the SGRQ. This is an instrument with 16 questions over three domains: symptoms, activity, and impacts.

Given the breadth of this instrument, patients also do not readily understand what the change in the total score means. So, we set out to develop a treatment benefit attribute that aligned with these endpoints but was also understood by and meaningful to patients. And to do that, we used these endpoints along with expert and patient input and some early clinical trial data, as I'll describe in the next few slides. Next slide, please.

So, we had clinical experts advising the study team and input from them and patients participating in qualitative interviews indicated that reducing breathlessness with activity was the primary goal of emphysema treatment. And this slide shows quotes from patients who participated in the qualitative interviews that demonstrate what this endpoint meant to those patients. Next slide.

So to balance these perspectives from the experts and the patients, with the relevance of the clinical endpoints, we focused on Question 11 in the SGRQ, which is shown to the left on this slide. This question captures a patient's self-reported breathlessness with activity. And then we adapted this item to create a scale, which is shown on the right, to describe an improvement in breathlessness as the treatment benefit in the study.

So to do this, we imposed a relationship on the responses in Question 11 such that the ability to do any particular activity without breathlessness would require the ability to do less strenuous activities in that scale without breathlessness also. And while this was broadly consistent with the data from the trial once we are able to look at that, and patients found it credible and easy to understand, it does depart from the interpretation and the scoring of the SGRQ. Next slide, please.

We also found that this one-step improvement was highly correlated with the SGRQ responder rate in the trial once we were able to look at that data.

And so that was a brief overview of how we use patient and expert input to develop a patient-centered treatment benefit that was related to the trial outcomes. Next slide.

When we did get FDA comments on the study results that were submitted with the PMA application, the benefit attribute was a primary point of disagreement, one of their main concerns. So, the reviewers were concerned that that benefit attribute was not sufficiently aligned with the endpoint, especially in terms of how the SGRQ total score was used, and how it related to the other endpoints like FEV-1. Some of the other comments we received related to the range of risk levels that were used for the pneumonia attribute.

So here the risk range was defined before the analysis of the trial data, and so it didn't include the final estimate of the pneumonia rates. This was a problem due in part to the timing of the PPI study relative to the trial and some study design decisions. Other comments related to whether and how data from patients that were recruited from different clinical sites should be pooled and whether respondents sufficiently understood the attribute descriptions. Next slide, please.

So, a quick summary of the results and what the outcomes were. So, we found that 32% of patients with severe emphysema would likely perceive the benefit of the coils to outweigh the risks when compared with the benefits and risks of optimal medical therapy, and that result is shown on the left. The pie chart on the right shows that that proportion increases to 51% when we look at those patients with greater hyperinflation.

So these preference studies -- sorry -- study results were presented to the advisory panel in June 2018 along with information on the coil development program, the clinical trial design, the effectiveness and safety of the coils, and post-marketing plans. The advisory panel had fundamental concerns about the effectiveness of the coils and ultimately voted to reject the PMA on that basis. Next slide.

So, there are two lessons that I'd like to highlight here, although there were many lessons we learned in conducting this study. The first is, as Dan pointed out, that the challenge in striking a balance between the level of engagement with FDA during the study

development and the time it adds to the study timeline. So this is a balance that each study team must attempt to achieve. Looking at those comments that I summarized from FDA, it's possible that those comments could have been identified and resolved before data collection had there been more engagement, especially the concerns related to the survey design and analysis.

But, FDA's fundamental concerns about the benefit attribute are an area where there's not a lot of resolution at this time, and there's some ongoing research. There were at that time and there still are no guidelines in the literature or regulatory guidance for how to adapt a patient-reported outcome measure like the SGRQ for use in a PPI study. In our case, we tried to do it in a systematic way using evidence from patients and the trial, and we considered alternative approaches to that adaptation. Each had pros and cons, but none exactly aligned with the use of the total SGRQ score as it was used in the trial as a secondary endpoint.

So these challenges with adapting the PRO instruments for use in PPI have been increasingly recognized, and, in fact, there were two issue panels presented at the ISPOR workshop in the spring focused on this issue, and RTI is actually conducting a pilot study with CBER in which we're testing the impact of different ways to adapt PRO instruments in a new study.

So that's my presentation. I want to thank you for your attention and thank ISPOR and FDA, and then I'm going to hand it over to Todd Snell from NxStage Medical to present the next case study.

MR. SNELL: Thank you, Christine.

And good afternoon, I'm Todd Snell, as Christine said, from NxStage Medical of Fresenius Medical Care. Next slide, please.

What I was hoping to accomplish over the next few minutes is give a brief

background of our experience with our patient preference pathway for expanding an indication for home hemodialysis. I'm going to briefly get into why we went the patient preference pathway and how it worked for us as an organization, as well as get into the study design and results, and then last, but not least, some lessons learned about what we recommend other manufacturers consider embarking on this pathway. Next slide. And one more.

So real briefly, to provide some context as to how we arrived at a patient preference pathway, first off, you know, before we were acquired by Fresenius Medical Care, we were a mid-sized company founded in 1998, two primary businesses, a home hemodialysis for chronic kidney care, as well as critical care for acute renal failure in ICUs. Prior to our FMC merger, we represented about 90% of all home hemodialysis treatments in the U.S. Despite that large number, we found that home hemodialysis was very under-utilized at the time, accounting for about 1.7% of all dialysis treatments in the United States. And then last, but not least, we were purchased by Fresenius Medical Care in February of 2019. Next slide.

To set some additional context for the indication expansion, the system that we're discussing, that followed the patient preference pathway, is called the NxStage System One. At the point of this slide being prepared, we have a history of over 19 million home hemodialysis treatments. So, we've had a good understanding of the market of what was working and what's not working.

With the NxStage System One, if you look at the screen, it's a very small dialysis machine. Basically, it's a home-use life-sustaining device compared to if you were in an in-center dialysis you would be hooked up to a machine the size roughly of a refrigerator. The value proposition of the NxStage System One is to be able to have a simple-to-use, extremely portable and flexible, and safe machine in your home that allows you to treat and cleanse your kidneys and refresh electrolytes as you see fit throughout the week. As

opposed to in-center dialysis, which is really a three-day-a-week treatment, where there's quite a bit of fluid overload and patient effect of not being able to, sort of, clean their kidneys every day. So with the NxStage System One, a lot of our treatments are five and six days a week, so it allows a patient to really try to mimic that kidney over the course of a week. Next slide.

In our history, when we first had NxStage System One cleared for, you know, cleared through a 510(k) pathway for use, we did conduct some clinical studies, multiple studies over time to advance our indication. One of the things that stayed in the indication in discussions with the FDA Renal Branch at the time was, if you can see on the slide at the very bottom, "all treatments must be administered under a physician's prescription. It must be observed by a trained and qualified person considered to be competent by the prescribing physician."

That became a real barrier for patients, primarily because our patients are treating sometimes 20 to 25 hours a week. Requiring an observer to be there to watch the treatment was extremely burdensome on the observer, and in a lot of cases, our patients may not have a ready, willing, able, competent observer to stay with that treatment throughout the patient's life. So that was really something for us we wanted to try to advance, but we weren't sure how to do it technologically speaking. Next slide.

So the original idea or the original feedback we had to start considering, this idea of solo home hemodialysis, where a patient is treating without an observer, originally came from a workshop sponsored by the Kidney Health Initiative along with the FDA Renal Branch and industry to really, really hear patients' feedback as to things that are making home hemodialysis, among other therapies, limiting for patients to, you know, utilize.

And we started to think at that point at NxStage, you know, why solo hemodialysis? And we always felt that home hemodialysis brought significant clinical and quality-of-life

benefits and had, you know, multiple studies, multiple post-market studies documenting those benefits. So we believed in home hemodialysis versus in-center. We also realized, like I mentioned before, we still had a pretty low penetration rate of home hemodialysis, and partly our reason was partner burnout or patients just not being able to find a partner. We felt that the idea of having a trained observer was a pretty high bar to hit, especially compared to other therapies like peritoneal dialysis. In one study that was done, you know, 30% of patients with peritoneal dialysis had indicated that they would not be able to secure a partner or they lived alone. So, we felt that that was, you know, a significant burden if there was a partner requirement put on a peritoneal dialysis patient.

And then last, but not least, we had a number of active groups, one of them being Home Dialyzers United, that were really vocal about patients being able to make their own decision in whether to choose to treat solo or going in, let's say, in this case, in-center for dialysis treatment. At the patient preference workshop that Kidney Health Initiative had sponsored, one of the things was really interesting is, at a spouse event, a naval aviator came to us and said, "Every time my husband deploys, I have to go back in center to treat. And, you know, this observer requirement is really burdensome, because I really want to treat at home." So that became sort of a push for us to really start to think how we do this. Next slide.

So we said why the patient preference pathway, you know, why would we go down this path? Next slide, please. We really, at the time with solo home hemodialysis, we knew that the practice was ongoing, but we didn't have it really quantified as to how patients were experiencing that type of treatment, what the risks were, and had very little post-market data to tell us how safe the treatment was. We also didn't really know what was the current use and what percentage of patients even tried to do solo on home hemodialysis.

So really, for us, we felt, and this was really in great partnership with the Renal Branch, we had to figure out at the time how do we really look at benefit-risk of solo HHD and what are, sort of, those thresholds that we would feel comfortable recommending this treatment and those thresholds where patients would be comfortable treating, as well. So that became, sort of, the nucleus for us of why, why go down this patient preference, sort of, pathway at the time, which was still -- when this came up in 2017, there was a patient preference guidance that was issued by FDA. However, that was primarily for PMAs and De Novos and HDEs. So, we weren't really sure if we could apply this to a 510(k) device. So, we really had -- we really started the engagement early with the Renal Branch as to how we move forward. Next slide. And one more slide.

So, regarding the study design and the results, how do we start this pathway, and what were some of the key engagements? First off, we knew that the care partner requirement when we talked with FDA and also Kidney Health Initiative, that the care partner requirement was exclusive to certain patients that would not be able to enjoy the benefits of home hemodialysis.

I mentioned before about the patient preference workshop that was conducted. And then as a follow-on of that workshop, we started some active interactions with FDA's Renal Branch looking at how do we get at this both qualitatively and quantitatively. And then what it turned out to be was for us a patient preference survey. We ended up having 142 respondents that were able to tell us, one, what's their general attitude of the risk of solo HHD, as well as what were their risk thresholds for certain types of events that could happen with the treatment. Next slide.

So, our pathway evolution, you know, at the top of the slide, really started with exploratory discussions with FDA. And I think at the time, because this was a Class II life-sustaining device and not a PMA or a De Novo, we were really trying to figure out how to

make the patient preference pathway work. We started out with qualitative surveys, realized that those were not rigorous enough to really establish risk thresholds. We talked about this idea of do we put an informed consent tool in, and how do you do that from a guidance perspective. And we ended up landing on a discrete-choice model, which really was an effective tool for us to quantify risk.

In addition, you know, we did look in our internal risk file and said is there a way to mitigate all risks related to solo HHD. And from a technological state of the art, we didn't feel we were able to do that, that some of this was going to rely on the physician and the patient to evaluate the risk and decide if the risk was worth it. We also, at this point, had an initial plan to submit a 510(k) for an indication expansion with additional labeling. We originally started it as an informed consent tool but migrated the language with FDA to more of a supplemental labeling or sort of a training aid to help people assess the risk. Next slide.

So our study objectives: Identify risk tolerance thresholds for experienced home patients who'd be willing to perform solo HHD and also to determine if experienced patients would perform after considering the benefits and risks. Next slide.

In our survey, we ended up surveying a little over 1,000 current HHD patients in 129 dialysis clinics around the country. We did utilize a third party to conduct this. We realized that we didn't have the skills. And one of the previous speakers has mentioned this is not just a simple Survey Monkey, go out there and ask people what they think. We really had to design this one pretty smart, and we also relied quite a bit on FDA for also the input of how we approach patients.

We wanted patients to have -- we wanted clinics that we approached to have a significant number of patients, not just one, they had some experiences as well. And then we ended up with a 13.5% response rate. Next slide.

The techniques we were using, we really got into the beginning more qualitatively. Their experience, how often did they perform solo without a partner, what they felt the role of the care partner was, and the frequency of adverse events that they were experiencing during the treatments. We asked our patients to consider different scenarios, primarily mortality on treatment, as well as needle dislodgement as areas of risk that we could focus on and say, "Where would you be comfortable with the level of those events happening as compared to in-center treatment?" And at the very end, we asked to state the preference, if they prefer solo HHD over going back in-center because they didn't have a partner to perform the normally prescribed HHD. Next slide.

So, qualitatively, we really came out with -- and this is not necessarily for patient preference, but this gave us an understanding of where the patients land on this type of treatment in the first place. We came out with 61% of our respondents would choose solo HHD as a means of treatment as opposed to going in-center. That pleasantly surprised us. I didn't think we realized -- we didn't realize it was going to be that high. But nonetheless, it gave us some confidence to really try to establish the risk thresholds. Next slide.

So I mentioned before about the different types of events that could happen on solo HHD, one of them being just an overall death on treatment. And when we look at this slide, this is part of our discrete-choice model results, we were able to ask patients different levels of death-on-treatment as opposed to death on in-center treatment, and basically try to understand their comfort level.

So one of the things we understood was if the risk of death is equal, about 95% of patients prefer doing solo HHD over in-center treatment without a partner. If you go down to the third set of columns, and you look at if you had a death rate of 50% higher for solo HHD versus in-center, we still had 2 in 3 patients preferring solo HHD. So that was really compelling to us that this was still pretty overwhelming. And it's also a call to action for us

to continue to monitor this in the post-market space, in making sure that we don't get to a rate that maybe goes outside what these patients originally told us from a comfort level they were willing to accept. Next slide.

Same thing. A similar analysis as compared to mortality. We also did needle dislodgements. This is where the needle would actually exit the vasculature during treatment, could cause significant injury. We found that if the risk of needle dislodgement was equal again, we were in the high 80%, patients would feel more comfortable doing solo HHD as opposed to in-center. And then also, one of the key things we learned, even if a risk of needle dislodgement were 1,000 times higher, 3 in 4 patients still preferred solo HHD. So that was also a surprise to us. And again, another place for us to monitor in the post-market surveillance world, that if we're seeing needle dislodgements with these patients that are much higher or not. Next slide.

So key observations for us: Patients, you know, surprisingly to us, actually perceived numerous benefits from HHD, but there were still concerns about the risks. Things like needle dislodgment, intradialytic hypotension leading to mortality were concerns. But despite those risks, we were pleasantly surprised that current HHD patients would prefer solo over in-center, and, you know, given the certain level of risk that we articulated in the discrete-choice model. Next slide.

Overall, the NxStage proposed pathway, we did come to FDA not with a brand-new device, this was an indication expansion. And we did come at the time of 14 million treatments. We had done multiple clinical studies for our initial indications, as well as treating at night, and we had a pretty solid complaint handling reporting history since 2005. With that, we brought patient preference survey results to the Renal Branch, a shared decision tool, like a supplemental user guide, to be used with the patient and a physician, as well as some additional ancillary devices and training that could help, you know, secure the

treatment to be more safe. With that, that's where our -- really our pathway for clearance. Next slide, please.

And then you can see the updated indications for use. If you go to the second paragraph, "The system is indicated for home hemodialysis, including home nocturnal and solo home hemodialysis during waking hours." We did negotiate with the Renal Branch that the waking hours are more safe and we weren't ready yet to go to a nocturnal setup for this treatment yet. And next slide.

So last two slides, really a summary of lessons learned. If we can go on the next slide, please? So, what are the challenges throughout this process? I think first off for us, we debated heavily as an organization for years about assuming that we had to solve something from a technology perspective, and not thinking about patients are willing to accept some risk for possibly better benefits. And so, we were really hung up on what's the state of the art, how would you do this, and I think not having that post-market experience really put us in a spot where, until the patient preference pathway came along, we were really stuck with how will we ever move this therapy forward.

I think the second lesson learned for us was how complex to make that patient preference study for clearance. We start with a limited qualitative assessment but realized that that wasn't going to be rigorous enough to really set risk thresholds. The discrete-choice model became really, really effective for us. And I think for manufacturers, knowing that ahead of time and getting in there quicker with the discrete-choice model for this type of a scenario, would save a lot of time. I think we, along with the Renal Branch, learned this together as we went through the process.

Definitely pilot the study. We started out with a pretty small pilot. We learned quite a bit. Some of the feedback we got was we were not making this easy enough to understand to a lay user that's not well-versed in statistics. Likewise, we have a very, very

large range of socioeconomic demographics across our patient population. A number of folks came back and said, "We don't understand what you're asking for with risk thresholds." One of the things that we did, we had significant help from FDA on how to articulate risk threshold in a sort of graphical, visual manner to allow patients possibly with lower education to understand it. Next slide.

And my last slide is really what would be advice for the medical device companies in this journey. I mentioned before plan on discrete-choice model for a patient preference survey. And make sure, as mentioned before in the previous speakers, secure the statistical and market research expertise. I think we had the statistical expertise in the company, but we weren't really solid on market research, and so having an outside firm that knows market research really helped us approach our patients more effectively.

Know your audience. The patient preference survey, make sure it's understandable to the patient if you're going to survey the patient, not just physicians. That was a lesson learned in our pilot and really helped us go through and make the adjustments we needed before we went broader.

Make sure you understand your device risk. Are there existing technologies that can address the risk, or are you at the state of the art, and really now you're basing this on patient risk? I mean, one of the key things learned here is that, in any event, our risk files for solo HHD, we don't have every risk mitigated, that there are risks, i.e. mortality, hypotension on treatment, as well as needle dislodgements, that, given the scenario right now we don't have a way to mitigate, so we are basing it on patient preference and patient acceptance and physician and risk.

And I mentioned the pilot before. Seek feedback prior to the survey. Make sure you get it right before you launch.

And then the last thing, we had a lot of help from the FDA branch, as well as the

Quantitative Innovation Office up front, especially on how to communicate with patients in visual ways and trying to really move that discrete-choice model. So, I'd highly recommend start at FDA early and leveraging some of the tools they have to be able to really communicate with patients.

That's all I have until we get to the question and answer session. I will be followed by Barry Liden from Edwards Lifesciences.

Barry, it's all yours.

MR. LIDEN: Thanks a lot, Todd.

Hi, I'm Barry Liden, Vice President of Patient Engagement for Edwards Lifesciences, and I'm really thrilled to be here to share some of the lessons that we learned in executing one of the first patient preference studies in the field of cardiology and a unique use of patient preferences at a latter stage of medical device product development. So far, what we've heard from the other speakers is how patient preferences have been used at different stages. And if you're following, we're working down a timeline. And in this case, this is really probably the last stop of when patient preferences can potentially be used. And that's actually in the value assessment process. If you can go to the next slide, please?

We did a patient preference study around severe aortic stenosis. This is a disease that affects roughly 100- to 200,000 patients a year in the United States. It's got fairly significant health implications. Clinical studies have shown that after the onset of symptoms, the likelihood of survival after 2 years is only 50%, and at 5 years, 20%. The other problem with this disease is that if it's not taken care of early, it can be very difficult to treat, for reasons I'll go into in a second.

And it's kind of a stealthy disease. It's essentially the blockage or the failure for the aortic valve to properly allow for the flow of blood to your vital organs, oxygenated blood, which can affect your main organs, particularly your brain. And as such, the symptoms

actually look a lot like just getting older. It's a progressive disease. It tends to affect the aging. So as a result, frequently, people who have aortic stenosis just think they're getting older. And that causes a lot of problems in terms of when to treat, particularly given the treatment options that are available. Next slide, please.

Those treatment options are really four. They are watchful waiting and medical management, surgical replacement of the aortic valve, balloon valvuloplasty, and transcatheter valve replacement. Surgical replacement involves open-heart surgery, which is very invasive treatment. You have to stop the heart, put the patient on a cardiopulmonary bypass, open the heart. A surgeon then excises, or cuts out, the existing diseased valve and sews into place a prosthetic artificial valve.

Edwards Life Sciences has been in the business of developing those prosthetic valves for over 60 years. We had a lot of experience with what kind of challenges that kind of treatment can have for patients. It's actually a fairly successful procedure if the patient is relatively healthy. However, a lot of patients are fearful of going through that procedure, and there are some significant, potentially negative, health outcomes if the procedure is not executed very well, or if the patient has other comorbidities.

As a result, we invented one of the first commercially available transcatheter approaches to replacing the valve, and that is done through the valve is actually crimped onto a small catheter that is then woven up through the vasculature and implanted into place on the heart. It's a relatively minor procedure compared to open-heart surgery, although it is not a simple procedure. It's complex, but its actual impact to the patient is significantly lower in terms of burden immediately following the procedure. Those patients are discharged from the hospital, depending upon their general health, in a day or three, as opposed to open-heart surgery, where they can sometimes be in the hospital for as long as a week. And their immediate recovery is much faster than open-heart surgery. Next slide,

please.

We decided to do a patient preference study, the decision was made in 2018, partially as a reason to really quantify the stories that we had been hearing from patients about this conflict that they had faced when they are looking at alternative therapies. Transcatheter valve replacement had actually been out on the market for over a decade in Europe, and in the United States, it's been on the market for about 6 years. So, we had a lot of clinical experience with the various therapies. And we were still hearing a lot of concern that patients had with the traditional open-heart surgery option and were really seeing a lot of preference towards the transcatheter option.

However, a lot of third-party payors like CMS, Medicare, or other payors like governments around the world, were looking at this relatively new therapy through the lens of clinical outcomes and measures that have been developed back over a decade ago. And those were really fairly harsh endpoints. Most of them really centered around all-cause mortality at 12 months.

And if you look at those two procedures, actually, from a clinical perspective, at the time that this study was conducted, the clinical outcomes were relatively the same at 12 months between the two procedures. So, through the eyes of a payor, those two procedures looked somewhat equivalent, even though from a patient's perspective, transcatheter valve replacement was vastly superior on a number of measures.

So, we decided to enlist another consulting firm aside from RTI, Evidera, and they helped us design a study in partnership with Heart Valve Voice, a patient group that helped us find patients. And we designed a study, really, to help inform reimbursement. At the time, there was a national coverage decision open on that, on transcatheter valves, and we had hoped that we could bring to the table data, qualitative data, that could help inform their decision-making process.

In addition, what we were really trying to measure in this study was what were the patient -- what were the outcomes that mattered most to the patients and what were the weights that patients gave to each of those outcomes. We were also in the process, at that time, of looking at a shared decision-making tool that had been developed through a study funded by the Patient-Centered Outcomes Research Institute, or PCORI, and we felt at the time that the attributes, or the outcomes, that were being used in that shared decision-making tool might not have been the right ones given the feedback that we had received from patients. Next slide, please.

Again, we worked in partnership with patient groups, not just Heart Valve Voice, but also the American Heart Association, and Mended Hearts, who helped us find patients. Next slide.

To figure out which attributes we wanted to study, remember part of the reason for this was to compare the attributes that had been identified by PCORI, we looked at other patient preference studies that had been conducted, sought extra consultation with patients and clinicians, and did a clinical literature review. Next slide.

We identified 12 different attributes, some of them fairly similar. As you can see in this slide, they are grouped by different kinds of types, and you can see also on this slide that five of them were the PCORI model attributes, and seven were other attributes that had been identified through our attributes identification process. Next slide.

We also used a different technique. We've heard a lot about discrete-choice experiments, but we had a lot of attributes to study. And to study that many attributes, you really -- it's hard to use a discrete-choice experiment. If anybody has tried to participate in a discrete-choice experiment, it can be cognitively challenging to juggle all of the different attributes, even if it's four or five, at a time when compared therapy A versus therapy B.

So instead Evidera recommended an alternative approach to adapt a swing weighted approach, which essentially just allowed the respondents to compare just two attributes at a time. And each time, they would choose which attribute they would like to see improvements in. And then -- next slide -- they would repeat that process about 300 times. Now, really, it was actually a very iterative process. The swing part of it is that if they chose one attribute over the other, then the levels would be adjusted, and then we asked the question over and over again until they got down to a point where you actually got a very specific level of what is the tradeoff that that patient would be willing to make in exchange for the other attribute. Next slide.

So here are the results. Next slide. First of all, we were successful in recruiting 219 patients. Most of them had been treated, and out of the treatment cohort, most of them had received transcatheter aortic valve replacement. About a third had not been treated. We had more women than men, which is a little unusual for this patient population. And all of the respondents were fairly educated, with at least a high school education. Next slide.

The outcomes that we got out of this were startling. In fact, we guessed that there would probably be some favorable perspectives from patients towards TAVI, or TAVR, transcatheter aortic valve replacement in the United States; it's called TAVI outside the U.S. And we were actually blown away at how big those numbers really were.

You'll note on the slide here that patients who are over 60 years old or even -- actually, all patients looked at the risk of disabling, non-fatal stroke as something that was significant, but that they would be willing to tolerate a 20% increase in the risk of stroke. If you look at the far right-hand corner, the actual performance of TAVR as compared to surgery at the time that this study was conducted and the survey was implemented in late 2018, actual performance was under 1%. So, patients were willing to tolerate almost 20 times more risk than what the product was actually performing on that one measure.

We also identified a number of other areas where we identified the different cohorts, where older patients, it looks like, were willing to tolerate more risk. And I highlighted in here four different attributes where there's a statistically significant increased amount of risk that older patients were willing to tolerate versus their younger counterparts. Next slide.

The other thing that we learned was the priorities. What was the most important to patients? And we'll go into a lot of detail here, but the big one was that independence, the ability to get out of the hospital fast and be discharged to their home, and not be dependent upon other caretakers was incredibly important to patients. In fact -- next slide -- patients who were over 60 years old actually showed that they were about four times, putting more -- about four times more weight on independence than the risk of a disabling stroke. And you can see here that mortality is fairly important.

So when we're talking about patient preferences, it's not just what do patients want and we're not taking into consideration clinical outcomes. Clinical outcomes are very important to patients. But in this case, what we show is that when you stack them all up together, TAVI tends to be more preferred. Next slide.

We also learned there's a lot of heterogeneity. The distribution of preferences in this study were actually on a bimodal distribution at either end of the spectrum. Basically, you can categorize it as you're either very risk-tolerant or not very risk-tolerant. In general, it swayed more towards risk-tolerant in the tradeoffs that patients are willing to make. We also saw that the risk tolerance tended to be that older patients were willing to tolerate more risk. Next slide.

And lastly, how big does the patient preference study have to be in order to be statistically significant. We actually did this study in two cohorts. We did an initial phase, where we recruited about 93 patients. And we decided to do another cohort, another

wave, and recruited an additional number of patients -- 219. And part of the reason we did that was because even though Evidera was telling us that the results were statistically significant, our concern was that the general community would have a hard time accepting that a 93-person sample was reflective of the patient population. In doing an analysis between the two cohorts, we saw that almost all of the attributes were similar between the two other cohorts. Next slide.

We also identified one other lesson, and that is when you're developing your decision-making tool, which is something that we believe is really important if you're going to have that kind of heterogeneity in a patient population, that you need to pick preferences -- you need to pick attributes to talk about with a patient that are preference-sensitive.

It was mentioned earlier in this discussion, but in this case, you can see visually that patients put a relative weight on each of the attributes, but when the two options are performing virtually identical on most of those attributes, then it's not really a decision, it's not really a choice. The one attribute that was different in terms of performance was the independence or the location of discharge in this case, and TAVR performs a lot better. So, generally speaking, if this is your decision-making tool, it would probably end up resulting in people being pushed more to TAVR than SAVR. Next slide, please.

We took this data to CMS and talked about it with them, and they appreciated the information. They really thought it was very helpful. But they really struggled with how to apply it to a coverage decision. I think that's our first mistake. In fact, I would say we didn't fail. It's like kind of how Thomas Edison would say, "I didn't fail, but I succeeded in discovering a way that won't work."

And one of those ways was not -- well, actually, a better way of putting it would be talk to the people that you're going to be using the data with before you start the study.

Not that that might have made a difference with CMS, but certainly, they were -- they didn't really understand how the data had been collected. They didn't understand the process. And we really didn't have time in a national coverage decision process to go through that with them in a detailed process. So they did not, we believe, incorporate that into their ultimate decision. Next slide, please.

However, we did get this data published, and through a literature review, this information was picked up by a health technology assessor in Canada. Ontario Health reviewed this as a part of their overall HTA, and along with the clinical evidence and the economic evidence, made a recommendation to cover this therapy under an expanded indication to our low-risk patients based, in part, by this patient preference data. Next slide, please.

So, there's the lessons learned. One is, is it's really important to ask patients what matters to them, and just looking at the clinical evidence isn't really enough. And while we've heard a lot about needing to align the clinical outcomes with the patient preference study, I think we need to be careful not to have that be the only spectrum that we look at when we're asking patients what matters to them. Remember, a lot of clinical studies are designed by doctors, not by patients. Hopefully, that's going to change over time, but for now, we need to also be open to including other attributes that might be important to patients.

We also learned recruiting patients can be very difficult. That's why it's an important to partner with a patient advocacy group who has access to a patient community. And then, as I mentioned before, it's important to work with decision-makers and ensure that you understand, you know, what their interests are and they understand what the process is as you go through that process.

With that, I'll go ahead and turn it back over to Michelle.

DR. TARVER: Thank you very much. And thank you to all of the speakers that spoke today and shared their case examples.

I want to highlight a few points, a few take-home points that I think will be important for us to remember as we think of the series that was just shared. One is that these patient preference studies are often done separate from the pivotal study. And they are used in some cases instead of a clinical study, where it's not pragmatic or practical to observe the concerns or risks in the clinical trial format.

I also want to clarify a couple of points. One is that we are focused largely on medical devices. We did hear an example of a combination product, but the regulations between the Center for Devices and the Centers for Drug Evaluation and Research and the Center for Biologic Evaluation and Research are different. And so, some of the nuances you may be hearing us talk about today are reflecting our particular Center's regulations.

I also want to highlight there's opportunities to talk to us through the pre-submission process. And you heard a number of speakers talk about the importance of talking to FDA early and often. So, I'm going to first talk about some things you might want to consider talking about with us, as you can see on this slide.

The first is that it's important that you use language that is patient-friendly and that patients understand. We are really working to make sure that patients are given information in a neutral manner that is unbiased, so that they can truly weigh the benefit-risk and make an informed choice. The exercise itself often has a comprehension component involved, and I encourage you to visit the webinar that Brett Hauber talked about during the first session.

The other thing I would also like to highlight or caution as you are thinking about doing a patient preference study is think about the regulatory question you really want to ask, and think about that upfront and early, and clarify that's a question that's impactful to

the regulator's decision-making.

Another concept that you heard come out in a number of the talks is the importance of mapping the attributes in the patient preference study to what is going to be collected and studied in the clinical trial, because the benefit-risk decision is based on what we see in a clinical trial, and how we weigh that benefit-risk is going to be informed by the patient preference study.

Now, last question that I'd like to highlight is, tell us everything. Sharing all the information that allows us to see the qualities of the patient preference study can help us make an informed decision about the quality and whether or not it rises to the level of valid scientific evidence. Next slide, please.

So the lessons that we heard I think that was an overarching theme on all of the talks first starts with making sure you do solid qualitative work. That includes including patients in the process, whether they be advisors or co-advisors as part of the study design or focus groups to help inform the attribute development. Whatever methods you use in totality, it should really lead to a tool that patients can understand and that we can believe is truly representing their preferences.

The other thing that I would say is consult us early. I think that was a recurrent theme. We have a pre-submission process, and we encourage you all to use that and specify specifically the Patient Science and Engagement Program. We have expertise in health economics and other measures of patient science that could be very useful to provide input as we're looking at these submissions.

We also encourage you to be very clear about the regulatory question. As you saw in the very beginning, patient preference information can be used at multiple nodes along the total product lifecycle. So state up front how you'd like to use it. The other lesson that I think we heard in a number of the studies was the importance of planning your

recruitment for patients. This is not a simple study to do and not a simple survey to do. So garnering the important expertise you need up front, making sure that it's aligned with the regulatory question at hand, and that there are frequent touchbacks to make sure that the tool that's being developed meets the needs of the regulators as well as the medical device developers, or the HTAs, as Barry just alluded to.

And then determine how you're going to find the patients. Are they going to need to be clinically validated patients, meaning that there is a clinician that can attest to the diagnosis that they have? Or is it a condition that patients are very good at self-reporting on, and therefore, other, more efficient means could be used to identify those patients.

Regardless of what the approaches that you use to get patients, I think it's really important that for the studies to inform more benefit-risk decision, they have to match what we're seeing in the pivotal clinical studies. And so considering that at the outset and throughout the design and conduct of the patient preference study will make it more impactful downstream. Next slide.

So with that being said, we have a number of resources on our website. We encourage you to visit them. We also have mailboxes if you have questions that you'd like to ask us. Please reach out. We welcome questions and will answer them.

And so without further ado, we'll start with our panel discussion. And we've received a number of different comments in the chat. So, I'm going to start first with one for Dr. Kimberly Brown Smith, who is the Associate Director of -- excuse me, forgive me just a minute. Let me pull up the question slide. I apologize. She is the Associate Director of -- Associate Acting Director, excuse me, of Clinical and Scientific Policy Team at CDRH.

Dr. Brown Smith, could you please speak to how the FDA weighs various benefit-risk factors in its decision-making process, and how does patient preference information fit into all of this? And in your comments, could you touch a little bit about when there's a lot of

uncertainty in the results, how can this information be used by FDA?

DR. BROWN SMITH: So thank you, Michelle, for that introduction. And you know, I'm just going to kind of make some statements that are supportive of what you've just said in your remarks about benefit-risk. But, generally speaking, benefit-risk assessments are qualitative in nature rather than quantitative. And each assessment is unique. CDRH has several benefit-risk guidances, which explain the ways in which benefit-risk principles are used in medical device regulatory process, as well as how patients are impacted by those principles. And, as has been mentioned, FDA's benefit-risk framework encourages the use of patient preference information, patient-centric assessments, and patient-reported outcomes, when such information is available.

And a lot more information is available in CDRH's PMA Benefit-Risk Guidance, 510(k) Benefit-Risk Guidance, and its Compliance and Enforcement Benefit-Risk Guidance. Those are abbreviated titles of those guidances. There is always some degree of uncertainty surrounding the benefit-risk data that FDA receives about medical devices.

Broadly speaking, when there is a high degree of uncertainty in the provided data, FDA may first consider the relative magnitudes of the benefits and risks associated with a device. The availability of effective alternative treatments is also a significant consideration, and then also patient preference information, when available, is important to consider when there is a high degree of uncertainty in the data. And FDA has a guidance on uncertainty and benefit-risk considerations, which provides additional useful information on that subject.

So, one scenario that is touched on the uncertainty benefit-risk guidance is a situation where we're looking at a device that is intended for small populations. In that guidance, FDA has acknowledged the fact that small clinical trials may have a greater degree of uncertainty, in particular, small trials for devices intended for small populations.

And that guidance provides a potential path forward for such devices. And this is another example of a scenario where patient preference information may really play a significant role in determining the overall benefit-risk profile of the device.

The other thing I'd like to highlight or mention, if it hasn't been mentioned previously, is that FDA has a Web page that provides additional details about patient preference information and benefit-risk considerations. And so, some of the ways that patient preference information help CDRH in its decision-making is that patient preference information helps us to identify, for example, most important benefits and risks of a technology from the patient's perspective. It helps us to assess the importance of clinical study outcomes to patients. It helps us to better understand meaningful changes and study outcomes. And there are a number of other advantages.

So, I think that kind of wraps up the highlights in terms of patient preference information and benefit-risk, and so thank you, Michelle, for the opportunity to comment on this issue.

DR. TARVER: Absolutely. Thank you. And then I'd like to actually ask Christine if she could address one question that we saw on the chat. Could you talk a little bit about the difference between a patient preference study and a human factors study, and how they could be used in the regulatory context?

DR. POULOS: Sure. So, I think both, both are obviously very important studies about medical devices, but they address different types of questions. So, I think of a human factors study as looking at usability and how the usability may affect the efficacy, the treatment efficacy, with a device and user satisfaction, how users are interacting with devices and how it might affect those outcomes, and it can be done across many different situations.

Whereas the question in a patient preference study is typically, but not always, as

we saw in these case studies, focused on how the patients view the benefits and the risks associated with devices and how they would trade them off, the weights that they place on those different features. And so, they can provide some systematic, whether it's qualitative or quantitative, information on the tolerance of the patients for those different outcomes the benefits and risks. And they tend to be focused on more limited situations or indications.

DR. TARVER: Thank you.

Todd, could you speak a little bit about how important it was to work with the patient groups as you were formulating your patient preference study and what that experience was like, and what advice you would give to others that are considering doing a patient preference study in terms of --

MR. SNELL: Yeah, we were very fortunate to have the relationship with the Kidney Health Initiative and in having some of these forums where we could bring patients in and have them really push our thinking on therapy. I think we were locked in, as I mentioned in the presentation, to sort of state of the art technology to solve a problem, in this case, requiring a partner in treatment. And it took the discussions with the patients to really reset our thinking and having them tell us, "It's our risk to take here, too, so help us, you know, make that decision, as opposed to you making it for us."

So I would recommend any type of patient engagement through some of the different industry groups is just really, really helpful giving a new perspective.

DR. TARVER: Dan, there was a comment that came into the chat I'd like for you to address if you could. There's a lot of different factors that come into play when people are making choices about a particular intervention. Could you speak a little bit about your construction of the attributes that you put in your patient preference survey? And specifically, talk about the cumulative risk of anesthesia with multiple reoperations and how

you frame that for the parents of these children to respond?

MR. HARFE: Yeah. That was a good question. It's probably -- it was the most challenging part of -- in designing our study, quite frankly, was the attribute description of the two alternatives. You want to provide enough information so that your respondent can make an informed decision, but you don't want to overwhelm them with kind of pages of descriptions of the two alternatives. They'll lose interest in your survey. So it's a very fine balance.

I do agree completely with the spirit of the question, which is the preference study has to adequately convey the risks or else your results will, in the end, be invalid to the regulatory situation that you're trying to answer.

In our particular case, it was fortunately pretty straightforward for that specific attribute, which is our local anesthetic is applied topically to the external ear. It's a low-risk, well-known lidocaine-epinephrine solution that is temporary-acting and not systemically available. So we, in our attribute description, told patients that if the procedure was not successful in the office, they would have to schedule a procedure in the OR for standard of care. So, the parents were aware that if it was not successful in the office, they should assume a second procedure in the OR. But our pre-clinical, bench, and earlier clinical studies indicated that there was no latent risk from a failed office procedure, so that was in our favor in the attribute description.

DR. TARVER: Thank you for that.

So, Barry, I've got a question for you. You started talking a little bit about conducting a patient preference study, submitting it to multiple payors. Can you speak a little bit to your experience, outside of this particular submission, your experience with payors, and is their appetite whet for this particular type of study type to inform their coverage decisions?

MR. LIDEN: I think it depends upon the payor and the health tech assessment agency. There was a publication that ISPOR just put out two weeks ago that did an assessment of all of the different HTAs or many of the HTAs in Europe, looking at which HTAs are looking at what kind of patient evidence, and really I think the bottom line is there's a lot of variety. Some of them are very suspect of the data because they probably really don't understand what it is now that all the viewers on this webinar probably know now. And also, they don't have a process or a technique for including the data. It's kind of like how we experience with CMS.

However, there are several HTAs that are very eager to include the patient in their decision-making process, and they've got a lot of different techniques that they've already started to use; CADTH in Canada, NICE in the U.K. are great examples. Actually, the German HTA is also very progressive about using patient preference -- or patients and patient input in their process, including qualitative information, and also just patient participation. And so, coming to the table with preferential data, quantitative data, is even more robust and helpful to their decision-making process. And we have seen some decisions in various HTAs to start to use that kind of data.

We ourselves at Edwards have not yet been successful other than this HTA example in Ontario, but that was actually little bit of luck. I mean it was a patient preference study that got published. They picked it up. While we do reference it in our value assessment, or dossier, when we applied for the expanded coverage, it was really through their own individual research that they discovered the data. So, I think that that's another little lesson learned is that we really need to make this information available for everyone and make sure that this data gets published so that patients around the world can potentially benefit from them. And when an HTA or a healthcare decision-maker is interested, they can have easy access to it.

DR. TARVER: Fantastic. Thank you.

So I saw one question in the chat that I wanted to make sure that I address. One of them was asking can we give a specific regulatory question that a patient preference study could answer. And often these studies have addressed the question of "what's the maximum acceptable risk that a patient be willing to accept for a given benefit?" And so that's the question that we often will see asked. But there's also "what is the minimum benefit that a patient may be willing to accept?" So there are options for how a patient preference study could be used.

We also have seen and have had discussions about "there's a lot of different outcomes I could assess in my clinical trial. I'm trying to minimize the burden on the patients. How do I prioritize which patient-reported outcome measures maybe that I would ask those patients?" A patient preference study may be a way to do that. And bringing that evidence to FDA as part of our consideration and the design phase of the pivotal study may also be useful.

I know we are at the top of the hour. We are two minutes over. I want to thank all of the panelists for a fantastic discussion, and I hope you all join us after lunch, which will start now. We will resume at 1:30. And this afternoon, we're going to talk a lot about the payor models as well as the healthcare setting and methodologies involved in patient preference studies.

So enjoy lunch, and we'll see you at 12 -- at 1:30, excuse me, Eastern Standard Time. Thank you.

(Whereupon, a luncheon recess was taken at 1:03 p.m.)

A F T E R N O O N S E S S I O N

(1:33 p.m.)

DR. REED: Welcome back, everyone. We are going to start this session on Methods. I've really enjoyed the beginning of this summit this morning. I appreciate everyone on my panel who is willing to provide their presentations on different methodological considerations in conducting patient preference studies.

So, first, we have David Gebben from Calvin University; also, former employee of the FDA CDRH.

So David, I'd like to turn it over to you.

DR. GEBBEN: All right. Thank you for that.

So the next slide, please. All right. By way of disclaimer, I have -- I'm employed by Calvin University, and I am actually currently employed only by Calvin University, and I have no conflicts of interest to declare. And all the opinions and comments that I will be providing are my own and are not reflective of the views or policies of the FDA. Next slide, please.

What I'd like to cover today is considerations when thinking about choosing which PPI method to go forward with. The selection method should inform and support the objective of the study. This includes things like endpoint selection, as well as possible benefit-risk decisions, and this can be applicable in both the pre- and post-market scenarios.

It's also important we want to keep in mind -- and I think we've heard throughout other speakers today as well as during the case studies, we want to keep in mind what the phase is within the total product lifecycle of where the study would begin or end, or where the most applicable part on that would be, because that could also then have an impact on which method would be best. And then, finally, we also want to be mindful that the

statistical analysis -- we would expect and want that we would have robust analysis of the results. Next slide, please.

As we think about the research process, MDIC has put out a nice document that summarizes some of the qualitative steps we want to think about in a survey, preference survey development. Step one is perhaps a bit obvious, but I think it's one that we often maybe glide over a little too quickly, which is identifying the relevant research question. We want to ensure that the research question is going to address the problem or the quality that the reviewer would be interested in. And also, we want to be mindful that a strong research question can help prevent scope creep and can also help prevent things that are extraneous to the actual question from being included.

The second part would be defining the study results of interest. If we need to understand the maximum acceptable risk, we want to make sure that the research questions can provide that. And that would be a potential meeting spot for pre-submission with the FDA. As we've heard from Dr. Tarver and Ms. Saha, they are encouraging practitioners of patient preference information to engage early and often with the FDA to ensure that alignment. So, I'd say let's try to take them at their word.

From there, we want to think about defining the preference elicitation method and the study design. And this is where we want to make sure that things are tractable and doable.

And then step four would be identifying the attributes and attribute levels that would be included. And again, this would be another area where touching base with the FDA would be advisable, in my opinion, because at the end of the day, really it is the FDA review team that would be the audience for the study and ensuring that the attributes are covering what they think are important.

Then of course developing the survey, the survey tool, and then, again, pretesting

that instrument, which is another potential meeting point with the FDA. Next slide, please.

As we think about the research question, we want to be mindful that a good research question is going to be well-defined. It's going to clearly lay out what the problem is and how we can tackle it. It's going to be narrow to prevent scope creep, because as we've all seen and done projects, it's easy for little things to kind of creep in, and by the end when the surveys begin to be implemented and the study is going, it's hard to know what the research question is anymore.

We want to make sure that the research question is aligned with the study's objective. So, if we are looking at a pre-market situation, we don't want to create a research question that's going to be more applicable for a post-market scenario. And then, also, I think in the submission, again, thinking about who the audience would be, we would want to make sure that the research question is clearly defined within that submission. Next slide, please.

Again, MDIC has provided a nice overview of different elicitation methods. As we move from left to right, we kind of move up in complexity. And I'll spend a little bit more time on the next few slides discussing these in greater detail. Next slide, please.

So, currently, with the discrete-choice experiments, the DCE is probably the most familiar, and the one that's probably the most commonly used, I would suspect. This allows for the evaluation of multiple attributes at once. It can inform endpoint selection prior to clinical trials and can also inform benefit-risk analysis. However, with all that flexibility, there is the cost that is referred from various people already. It is cognitively more burdensome because we're asking respondents to evaluate multiple things at a time. Next slide, please.

The threshold technique is another familiar method, and as we've heard from various case studies, the threshold technique has been used. And it can inform endpoint

selection in a clinical trial. It can also allow for a benefit-risk analysis, much the way the DCE can. However, it can only evaluate one attribute at a time. However, with that, it is potentially less burdensome for the respondent than a DCE, which may be appropriate for certain populations and may be, in fact, a desirable characteristic. Again, if the research question is only examining one attribute, including multiple attributes and trading them off at a time may not be advantageous. Again, if all we need is a threshold technique to answer the question at hand, why go to the next step of having the complexity from a discrete-choice experiment and with a threshold technique in place? Next slide, please.

The best-worst scaling could be used to inform the prioritization of the endpoint selection. This could be useful in situations where earlier in the total product lifecycle we're not sure exactly which endpoints are the priority. So by using it as just a nice ranking mechanism like best-worst scaling, we can inform that and say, okay, these are the things that should be prioritized. Next slide, please.

Other potential methods include things like swing weighting, which could be used with rare or hard-to-reach populations. To my knowledge, I don't know if this has been submitted to the FDA for use, but it is a potential method that would be out there, as well as focus groups could be used in situations where, again, the population may be small or hard to reach, or rare, or could be rare. Or, it could be where, as Ms. Saha pointed out, when quantitative research would suffice -- excuse me -- when qualitative research would suffice, we may not need to include the quantitative research based on the total product cycle. Next slide, please.

As we think about attributes and the considerations for those, we want to keep in mind framing effects of the attributes and the framing effect of the survey design. Again, if you want to think about it, "which would you choose" is not equal to "which is better." So how we frame those questions is going to be important.

Time to decision. If the decision proximity is going to be impactful on prevention versus promotion focus, that would have an -- that could shift how people would state what their preference is. If it's a decision I have to make in 10 years versus a decision I have to make in one month, I'm going to have very different opinions and attitudes about that.

Also, we want to keep in mind the number of attributes that are included. We want to ensure that the number of attributes included is relevant to the question at hand. And this is an area where, again, taking the FDA at their word, we would be advised to go and ask them, "have we included all of the relative and important attributes included?" We do want to be mindful of the design space. We can't include every possible question, so we probably want to distinguish between what are the need-to-know attributes versus what are the nice-to-know attributes. And again, we want to be careful that if we include too many choices, that creates more opportunities for respondents to defer the decision.

And then, finally, the number and spacing of the levels. We want to ensure that the clinical range is reflected within the attribute levels. This is to ensure that the clinical question can be answered. We also want to make sure there is space so that patients don't inadvertently recode those levels. For example, if we had a level that was numeric that was 0, 5, and 10, we might be wondering, well, are they just really counting that as 0, 5, and 10 or are they recoding it at low, medium, and high?

Also, we would want to think about are the levels going to end up being statistically overlapped? If we had a level that was 0, 1, and 10, is the respondent going to truly make a distinction between 0 and 1 or are they just going to just lump that together as a single level? Again, just things to keep -- be mindful of and things that are probably going to be addressed in the pretesting. Next slide, please.

Robust analysis of results. On the next few slides, we're going to be talking about a determinant, how we can think about -- how we determine sources of uncertainty as well as

think about some sensitivity analysis, and as well as heterogeneity considerations. Next slide, please.

So when we think about robust analysis, it's worth remembering that the FDA PPI guidance does not identify a specific analysis method. So, the method that's chosen, again, should be driven by what is the research question at hand. We want to be aware that sound and robust analyses should answer some questions: Did the analysis identify the sources of uncertainty? Did the research consider subpopulations that could be accounting for increased variability? Is the analysis robust using different modeling assumptions? All of these things are pieces that can be considered early on and are probably better off done prior to analysis and prior to data collection. And then, again, presentation of the analysis should be clearly identified and explained within the submission to the FDA, I think. Next slide, please.

If we think about heterogeneity, it is something that is just always going to be a part of things that have to be thought about and considered. It's always going to be a challenge, but it is not something that's insurmountable.

Better analysis of considerations for heterogeneity are: Can we think about some of these pieces early on? For example, if we have a suspicion or a hypothesis that the time of condition is going to impact the respondents' preferences, probably we'd want to include that as something that could be tested. The same with severity. If we suspect a more severe condition would have a different benefit-risk profile, then we might want to try and capture that within the study. Again, as we talked about, proximity to choice, and sociodemographic factors. Again, we may not be completely able to address heterogeneity, but we should acknowledge it and try to do the best we can. Next slide, please.

Again, we want to make sure we don't skip that first step in the research, which is stating the research question. That's when we can get an opportunity to get feedback from

the FDA and access their clinical and regulatory expertise. And as they said, talk to them early. So let's take them at their word.

We have more tools in that toolkit than just the DCE. So, we want to make sure that we're not thinking of every problem or every question as a nail that requires the DCE. And whatever the analysis that's chosen, we want to be mindful that it should be robust and it should address the research question, and it should be relative to the relevant medical decision, regulatory decision.

And with that, I would like to turn it over to Ryan, who will be discussing with us.

MR. FISCHER: Great. Thank you so much, David.

I want to thank ISPOR and FDA for this opportunity today to present. I'll be speaking of PPMD's experience with using different methodologies and preference research through our BRAVE initiative. The goal of this program has been to better quantify and understand how patients and caregivers think and feel about emerging therapies and living with Duchenne so we can ultimately better communicate to regulators and other stakeholders in our drug development ecosystem the preferences of our patients and caregivers. Next slide.

And we've done this through a very multi-pronged approach, first recommending and supporting legislative provisions around patient-focused drug development, conducting our own research, and disseminating the results, and our efforts actually led to engagement with FDA on the development of the first patient-community-led draft guidance, and benefit-risk was the cornerstone of that guidance. And FDA did produce their own version, and it was finalized in 2018.

The other result of this work really has been to create models for other rare disease communities to utilize in their own efforts. Next slide.

And with that in mind, we have published our patient-centered approach to

preference research for developing these studies. Patients are involved from the start to the finish developing the instruments, the research questions, attributes, helping to interpret the results, which is really important. We often speak to other advocacy groups on doing these studies and the importance of doing these studies as a part of their overall traditional research portfolio in order to advance really the science of patient input. Next slide.

And we've been able to test several different methodologies, which has been spoken about during this meeting over time. This has really been capacity-building in some sense for our community on demonstrating how these methods could be used within a rare disease context. We're extremely grateful of Dr. John Bridges and colleagues, and Holly Peay, who worked with us early on to help planning with this work. And we've received incredible support from pharmaceutical partners who've been willing to do this in the pre-competitive space. Next slide.

So just a quick primer on Duchenne so you can understand better what our community is weighing their preferences on within these studies. Duchenne is a genetic disorder caused by the absence of a key muscle protein. It's a fatal genetic disease. It's a very predictable course, with a progressive loss of function over time. Patients lose their ability to walk in the early teenage years, and sadly, lose their lives by their mid-20s. We have some approved therapies aimed at slowing the disease progression to some degree. But there's no cure. And it really does impact all systems of the body. Next slide.

So, to start, with our first study, we had been engaging the FDA for some time as first therapies were heading toward the clinic, and we were expressing to regulators the willingness of our patients and caregivers to take on risk and uncertainty in exchange for even modest benefit. And the FDA was certainly interested in this and were wondering if we had data to support what we were communicating. We had seen the obesity study that

was done and was mentioned earlier, and we wanted to see if we could attempt using patient preference research in Duchenne so that we had more tools in our arsenal to talk about our community to regulators and drug developers. And this ultimately led to our first study with Drs. John Bridges and Holly Peay on caregiver preferences using best-worst scaling. Next slide.

So just to look at the first experiment within the study was a prioritization of caregiver worries. We chose a very understandable set of methods using best-worst scaling. The attributes were developed with the caregiver advisory board. We were looking to understand disease impact on caregivers. And then we also sought to look was there a difference between ambulatory patients and non-ambulatory patients of caregivers.

And on the left, you see the domains and the attributes we've developed together with our advisory board and through focus groups. Domains covered medical concerns, impact on child emotionally, family stress, parent well-being. And then you see the experimental design with object case, where caregivers needed to choose what they worried about least and most in the past 7 days. And I'll talk about the results in a minute.

But the next slide, this feeds into how we had a second part of the study, which is developing a set of hypothetical treatment scenarios using best-worst scaling, too. The attributes were based on input from caregivers, clinicians, researchers, drug developers, all in one using our approach. We developed relevant attributes, including effect on muscle function, with various levels, lifespan, how much knowledge and data existed on the drug. On the risk side, we chose risks of nausea at various levels and risks of bleeds, and the most serious risk of heart arrythmia, including up to potential risk for death. And below you see the experimental design there, where patients choose what was best and worst amongst the attributes in the treatment scenario and, importantly, whether or not they would actually take the drug presented. Next slide.

So here's the learnings. In terms of the worries experiment, we see the highest rate of worries were about a child getting weaker over time and getting the right care was second-highest worry. We saw ambulation status did predict -- did not predict, rather, the highest-ranked items, but some of the lower-ranked items, there were some differences to the extent based on ambulation, which can be found in the publication that we put out.

The treatment scenarios we see that, overall, caregivers prioritized the protection of muscle function over all other attributes, including mysterious risks we presented, and even longer lifespans. So, in a sense in this study, caregivers were choosing quality of life over quantity based on their preferences. And we shared these results with the FDA to give them more insight about our caregiver preferences, and as the FDA was reviewing their first set of Duchenne-related therapies. Next slide.

In our second study -- well, first, with PPMD's draft guidance, we put out recommendations within our guidance for industry to collaborate with advocacy groups on these preference studies. And Santhera Pharmaceuticals was actually the first company to approach PPMD. They currently have therapy in development at improving lung function in more advanced patients. And together we were interested in exploring what really constituted meaningful benefit when it came to pulmonary treatments. And here, we had the opportunity to elicit both -- preferences from both caregivers and the patients themselves, which was something we hadn't done yet. Next slide.

So the first experiment, we wanted to understand preference for treating symptoms, and not related to skeletal muscle, using best-worst scaling. And patients and caregivers were engaged, developed this list of symptoms. We also included questions about their experience with those symptoms to see if that factored into some of these preferences or predicted some of these preferences. And there you see the experimental design, where they had to choose most important to treat, least important to treat. Next slide.

And here are the results for the symptom prioritizations, and these are in aggregate. There is a strong agreement between patients and caregivers on which symptoms to treat that were most important, and those lifespan targets related to lung and heart were ranked the highest, something that we thought would happen, but we could quantify. These were followed by related quality-of-life symptoms, like weight and depression. Finally, the less-quality-of-life symptoms from their perspective of headache, constipation, poor attention. And the final poor attention was really not valued by either group.

Notably, there was some heterogeneity within the symptom choices, and we did see two latent classes emerge based on experience with symptoms. And that can be found in the publication. Next slide.

So, the second experiment in this study was a hypothetical treatment scenario using best-worst scaling, too. We based the attributes, actually, on Santhera's therapy in the trial aimed at pulmonary function. We really wanted to see if a treatment like the one they were developing represented something families would be willing to take on given the treatment profiles. And attributes were developed with the same approach we always use in order to understand those attributes were meaningful and understandable.

So, for instance, you know, when trials are measuring lung function using something like forced vital capacity, that score doesn't really tell these families much. But knowing a therapy could impact something like cough strength and number of lung infections, that does resonate with family. So, this is where we landed with the experimental design. And here, we're doing attributes and levels within the actual task choice. Next slide.

And the results here. Here you see represent treatment scenarios on the right with the symptoms. We see agreement that patients and caregivers are willing to accept the highest levels presented in the experiment for risk and burden in order to achieve pulmonary benefit. So, in theory, they had preferences for a drug similar to Santhera's drug

in trial. And we at no point in the study named Santhera's drug within the actual study.

The results demonstrated maintaining cough strength and having less lung infections certainly represented meaningful benefits to both patients and caregivers. And really from our symptom prioritization exercise, we confirm the importance of treating these symptoms.

One thing to note in the pilot testing, we found caregivers of younger children did have a very difficult time emotionally taking the survey when we piloted it and that lesson had us increase the age criteria for the study at the end of the day. Santhera did submit the data to the FDA with their package, but FDA had concerns about the trial design, and Santhera was asked to do an additional study of patients that were on standard-of-care along with their drug. And we are awaiting the results of that trial. Next slide.

So, for our next study, we looked to explore newer methods in preference research. Discrete choice experiments are more traditionally used, and we were challenged by our advisory board, which included a member of this panel, Bennett, to explore the use of DCE within our community. Next slide.

And we actually piloted this at one of PPMD's conferences. This is an advantage to convening your community across stakeholder groups. It gives us a great opportunity to perform research. During an annual meeting, John Bridges coined this as “research at an event.”

Here, we had patients, caregivers, and medical and industry professionals take the DCE. And on the left, you see the attributes and levels, chance of the drug working, levels of benefit, risk of kidney damage, risk of fracture, and we used risk grids for the first time. So, we also wanted to test this methodology and the use of those grids in this, and the final product there you see on the right of what all stakeholder groups had to take. Next slide.

And just here's a snapshot of maximum acceptable risk in exchange for one level of

improvement of muscle benefit. Interestingly, we see patients appear to be less risk tolerant than caregivers and professionals. However, important to note that we had a low patient response rate on this survey. We only had around 10 people complete this survey. This led us to wanting to explore a larger study asking more patients themselves to take the study, and we actually collaborated with our international partners to do this across countries. So next slide.

So, this is our first ever international study, preference study in Duchenne. We partnered with seven countries and patient groups, and the study was supported by Pfizer and EveryLife, and we're grateful for their support. There were several parts of this study, but in the interest of time, I'm going to really discuss the DCE. The challenge here, with any international study, was translation of surveys and acceptability to do the international study, but we were eager to try that. So next slide.

So, the DCE we developed was updated based on feedback from the pilot. We changed the benefit levels to number of years slowing disease progression, which felt more meaningful to our advisory board and the patients we piloted with rather than the small, medium, and large benefits. And the other attributes, actually, remained the same. Next slide.

So recruitment, we had strong recruitment numbers, and it's important to look at recruitment and response rate particularly when publishing these studies. More and more FDA and others are interested in these numbers. We have a willingness of our community to take these studies. And we wanted to have a large number of patients, so that was important for us for them to respond for themselves, do the questions from the original pilot. Next slide.

Okay. So, this chart displays the preference weights across these countries, and you see differences. For instances, participants from France in the dark blue disfavored 20%

chance of kidney damage as compared to other countries, such as in the U.S. But overall, we do see some similar patterns that patients and caregivers across many countries are willing to accept risk in exchange for some sort of benefit. And we also see people start to care about fracture risk if it's around 20% or higher, which was an interesting finding. Next slide.

And here, we can see benefit-risk tradeoffs, as well. This chart displays maximum acceptable risk in exchange for only 1 year of slowing disease progression. Again, we see some slight differences between groups, France in particular, less willing to take on that risk of kidney damage than the U.S., for instance, but, overall, countries displayed relatively similar risk tolerances. The bars for fractures show higher rates of heterogeneity within the U.S. and Canada where there are large differences of opinion when it comes to that fracture risk. Next slide.

And here are the countries in aggregate form for how much risk an average person will be willing to take in exchange for slowing disease progression for a year. We see on average people are willing to take 11% risk of uncertainty, 5% for kidney, and 20% for fracture. And keeping in mind, this is for 1 year of slowing progression, and of course the goals of our drugs are to slow that progression for much more than a year. So, you can hypothesize that they may be willing to take on a drug that has higher risk for a more robust benefit. Next slide.

This chart is stratified by disease stage, which we ask questions about what stages of the disease they were in prior to taking the survey. Unlike with country, we're starting to see some meaningful differences across groups. The data indicates that people at later stages of the Duchenne disease progression may be more concerned about kidney damage, those higher rates of kidney damage, and less concerned about progression, and have a high -- that have a high success rate relative to those people in the earlier stages of

condition.

Younger families seem less tolerant for uncertainty or whether -- on whether or not the drug will work. And some of this might be reflective of the fact that a lot of our studies, clinical studies, are focused on that younger population; they have a lot more choices in thinking through this. So, if there's a high rate of uncertainty that the drug will work, it may be something that we need to tease out in further work whether that's qualitative or quantitative. Next slide, please.

So, we convert the data to maximum acceptable risk format. We get evidence that patients in the late ambulatory stage are more risk averse to kidney damage than those in earlier stages, and they'll accept less chance for kidney damage in exchange for treatment that slows disease by one year. But all stages are willing to accept some level of risk. We will be reporting results of patient and caregiver differences in this study, where we did additional analysis at a Society for Medical Decisionmaking meeting that's coming up, and we were proud to be one of the top 10 abstracts chosen within the submission. Next slide.

So we also wanted to evaluate the patient experience with taking a DCE. So, you see the lowest agreement on whether or not it was easy to answer these questions. And these are difficult to answer for many reasons. And it varied across countries. But most felt it was easy to understand. So that, too, was important. We do know that DCEs are not easy and can be difficult emotionally and cognitively to have to look through and weigh these choices, but we do see that most understood it. So I think that was an important finding and that they believed the choices were consistent with their preferences. Next slide.

And here you see the results across all countries in aggregate form. Next slide. So with that, I really do want to thank our partners and our contributors to this research. This has been quite the journey for PPMD, and we're going to continue to invest in this research. We have made it a part of our mission of advancing the science of patient input as a priority

for our organization. We believe it's an important tool in our advocacy arsenal as we continue to demonstrate patients and caregivers are willing to take on a risk and uncertainty for drugs that may slow disease progression. We do know preferences change over time as new treatments become available and as treatments are targeted to even infants and toddlers prior to significant onset of disease. So we will be measuring these as we go through, and we believe it's something so important to be able to better communicate to regulators and others in our drug development ecosystem, rather, about our community.

So now I get to hand this over to our next presenter, who I admire greatly, Juan Marcos. Juan is with Duke University, Duke Clinical Research Institute.

With that, Juan, please take it away.

DR. GONZALEZ: Thank you, Ryan.

Hello, everyone. I'm very honored to be here presenting amongst so many great researchers, practitioners, and advocates. I'm going to move ahead quickly, because we have a lot to cover. But I want to start this presentation with a short story. Next slide, please.

In 1964, the U.S. Supreme Court was asked to weigh in on a case, *Jacobellis vs. the State of Ohio*. The case required determining whether specific videos were too obscene to be protected by the First Amendment based on something called the Roth Obscenity Test. The most remembered opinion from that case was written by Justice Stewart, who said, "I shall not today attempt further to define the kinds of material I understand to be embraced within that shorthand description. And perhaps I could never succeed in intelligibly doing so. But I know it when I see it, and the motion picture involved in this case is not that."

Well, the issue in that case couldn't be further away from the topic we're here to discuss. The idea that the value of some evidence requires judgments that are hard to

codify in an unambiguous way, is not. I will argue today that this point is particularly relevant when we try to understand what it means to collect evidence on patient preferences that is fit for purpose. Next slide, please.

So, I imagine that some of you have heard of fit for purposes in the context of preference studies. It's been used as a shorthand for studies that meet some standards for the objective at hand, of course. For regulatory decision-making, there are certainly standards coded in the incredibly important FDA guidance document that was mentioned before. However, I'd argue that particularly outside of benefit-risk evaluations, we still live in a world that relies a fair amount on knowing whether PPI data are fit for purpose when we see it.

Discussions about fit for purpose, very often, are framed around the right or the wrong method for a study. There's some value to that. They also seldom go beyond practical problems, like whether the message is simple or inexpensive enough to warrant the effort. And don't get me wrong. All of those aspects are definitely important considerations. But how do we know if something that meets these critical practical aspects also produces trustworthy and meaningful preference information. Is there a test we can use to determine fit? Do we even know what it means to not be fit for purpose outside of the practical problems I mentioned before?

During today's presentation, I hope to show you that even though defining a bright line between fit and unfit for purpose can be hard, we know a whole lot about how our decisions designing preference studies impact the quality and reliability of our data. Next slide, please.

What you see here is the MDIC benefit-risk framework for patient preference data published in 2015. You've heard about it earlier today. I had the honor to be part of that effort as a member of the group who put together a summary of methods for the elicitation

of preferences in health applications.

During that time, we had long discussions about the virtues or downsides of all sorts of preference methods. And during those discussions, it became apparent that a lot of what we could criticize about published work within a specific method was about what the investigators did or didn't do when they implemented the study, not the method itself. So today I want to discuss the elements of fit for purpose that go beyond specific methods and to focus on what it means to have data that are fit for purpose, not methods that are fit for purpose. Next slide.

During the rest of the presentation, I will try to build a strawman of what ought to be considered as we determine whether specific PPI data are fit for purpose. Doing this requires considering at least three aspects of a PPI study. Think of these aspects as the three legs of a stool. We need to consider whether we ask the right questions to the patients, whether we are making reasonable assumptions about the answers we get from the patients, and whether the data we collect supports the assumptions we are making about patients' answers. Next slide, please.

When it comes to the first leg of a stool, asking the right questions, we need to consider whether the questions that we are asking are clear, consequential, and meaningful. I will discuss what each of these considerations mean and what they imply in the next few slides. But let’s start with clear questions. Next slide, please.

Clear questions provide enough information so respondents understand the tradeoffs they will be asked to make. They also provide enough information on the context for the tradeoffs respondent's need to consider. Finally, clear questions provide the right data to evaluate the tradeoffs we're asking respondents to make. Next slide, please.

Here are a few simple examples of PPI questions. Now, notice that these questions are fundamentally presenting the same tradeoffs. They're just different in terms of the

details they provide. All responses here would presumably convey PPI. But notice the difference in the details provided as we move down the list.

Now, I don't have time to elaborate on the specifics, but what I would like you to take from these questions and their details is that completeness of the answers we collect is actually directly related to the completeness of the scenarios we ask respondents to consider. In other words, the more clear we are about the questions we ask, the less assumptions we need to make about the answers we receive. The right level of detail in the question ultimately depends on the research question. But hopefully now you can see that clarity is not just about being understood by the patient, but it is also about understanding the data we get from them. Next slide, please.

When it comes to context, one important issue to consider is the framing of the question. This was mentioned before. Here, you see the example that Tversky and Kahneman highlighted in their seminal piece looking at this problem back in 1986. They found patients, graduate students, and physicians were all more likely to choose surgery to treat lung cancer if the clinical evidence was presented as the probability of living after being treated with these options -- positive framing -- as opposed to the probability of dying after each of these interventions -- negative framing.

So what does this issue tell us about evaluating the fitness of PPI data? For starters, it tells us that we may want to seriously consider showing the information both ways regardless of the methods we use. We also can, and probably should, test respondents' understanding of this information before they answer any choice questions, and we should of course talk to respondents about the information provided before we even start collecting preference data to gauge whether respondents are susceptible to the framing effects we're seeing here. Next slide, please.

A common criticism of stated preference methods is that we ask hypothetical

questions, so we ought to expect hypothetical answers. Back in 1997, Richard Carson, Theodore Groves, and John List were already thinking about this problem, also known as hypothetical bias. Their solution was to develop a new framework, broke this dichotomy between hypothetical and real actions. They argued that while the distinction between hypothetical and real actions made sense from a psychological perspective, a more useful distinction was to be drawn between consequential and non-consequential choices. What matters, they argued, is whether our questions result in preference-revealing answers. The framework established that non-consequential decisions, even if they were reported in the real world, may not in fact reveal the preferences of those making choices.

The solution to hypothetical answers was then to make our hypothetical questions consequential. This implies avoiding indifference and strategic behavior. Keep in mind that consequential questions do not require real-world consequences, but convincing respondents that their answers matter. This is largely accomplished by the framing of the question and the assumptions we ask respondents to make as they answer. Here is how Carson and others more or less operationalize the data. Let's go to the next slide, please.

When answers are seen by the respondents as potentially influencing an agency's decision and the respondent cares about the outcomes of these decisions, the respondent should see the question as an opportunity to influence the agency. I argue that we often don't need to do much to convey this level of consequentiality in our surveys. Most, if not all, of the patients we talk to when testing our instruments are eager to talk about their experiences and to contribute to the approval of better treatments. Next slide, please.

That said, one way we try to improve consequentiality and stated preference surveys is by using what is known as cheap talk. This is a way to tell people how much good they could do if they are honest and thoughtful as they answer our questions, and, conversely, how bad it would be if they don't pay attention. Researchers have shown this simple

approach has significant impact on respondents' willingness to accept tradeoffs between outcomes. So this is a nifty little tool we have available in our toolbox. Next slide, please.

Of course, questions themselves need to be perceived to be consequential. Here is an example of what that means. This comes from a study we're doing looking at preferences for allocation of kidneys from deceased donors. You can see the characteristics of a hypothetical kidney with different parameters. Notice that the two things about this kidney -- that there are two things about this kidney that are unknown, pump parameters and glomerulosclerosis. If we ask physicians, "Would you like to have biopsy information for glomerulosclerosis and pump parameters for this kidney," they would probably answer, "Sure, yes." In fact, that's what we heard when we talked to them.

Now, if instead we ask whether they would request this information if it meant they had to wait 4 hours for the results and expose the kidney to additional cold ischemia time, well, then the answers vary dramatically. So, as we determine the fit for purpose of preference data, we need to be able to understand the degree to which data are produced following this concept of consequentiality. Next slide, please.

Okay. So we're going lightning speed, but hopefully I've convinced you by now that clarity and consequentiality are key aspects to determine whether PPI data are fit for purpose. However, even clear and consequential questions are useless if the information we obtain with them is not meaningful. Although stated preference surveys are not necessarily limited by real-world constraints, as has been said before, meaningful PPI data should be at the intersection of real-world context and real-world evidence. This implies careful consideration of what is traded, how it is traded, and what are the relevant substitutes. We need for meaningful PPI data -- the need for meaningful -- sorry. The need for meaningful PPI data might seem obvious, but sometimes it is not straightforward to identify where we may be missing something that is "meaningful." Let's go to the next

slide, please.

Here is an example of the power of the right substitutes in preference questions. This was a study where we were looking at assessing the value of medications and surgery as a way to prevent health problems after a patient discovers they have a genetic mutation. This chart shows what we would call willingness to pay for these technologies when they were shown with other technologies and when they were shown as the only preventative options available. We found that the value of these technologies depended on the type of substitutes available.

As you can see here, medication and surgery have values that are significantly higher when no other preventative option was available. To make the matter more tricky, the difference, though, varied with the severity and the likelihood of health problems patients were facing, which you can see at the bottom of the chart. So, unfortunately, the right fit could require a complicated evaluation of the right substitutes in a preference question. Next slide, please.

Here is another example that relates two types of outcomes included in a preference solicitation exercise. The vertical and horizontal axes represent the probability of two adverse events. If we consider individual exposure to these adverse events, acceptability of the outcomes is highlighted there by the blue and yellow points on the chart. However, when we consider joint exposure to these adverse events, tolerability of the outcomes may be less than the tolerability of the risk of outcomes independently. Suffice it to say, this could be problematic, and so it's something that, again, regardless of the method, needs to be considered. Next slide, please.

Now, let's move on to the second stool for that strawman we're building. Let's now talk about the analysis of PPI data. The key question we must answer as we analyze PPI data is what assumptions we're willing to make to turn patient preference data into patient

preference information.

One critical issue is what do we do with the measurement error? After all, our instruments are measures of preferences. We can choose to ignore the error, and this could be fine. It's actually what practitioners typically do with some methods like time tradeoff or standard gamble or a threshold technique. Or we can explicitly consider measurement error in our analysis.

Obviously, this decision can affect the fitness of the data, but there could be circumstances where measurement error is expected to be relatively small in a specific application, so it is okay to ignore it. And that could be perfectly reasonable. But if we decide to consider measurement error, things don't get any easier. Then we need to figure out what we're going to do with that error. A lot of the analysis that considers measurement error in PPI data relies on the theory of random utility theory to be able to model responses. They derive the expected form of the errors from that framework.

Now, when we are considering error within theoretical frameworks, we enter the world of modeling, and this means that we are now also needing to worry about model specification and to what degree the assumptions and the models we use hold empirically. Next slide, please.

For example, we could rely on what is known as expected utility theory and assume that effect of adverse events in patients is proportional to the likelihood of that patient's experience in terms of how likely it is that they experience the outcome. In other words, that the disutility of every percentage point increase is exactly the same regardless of whether we're talking about increasing from 5 to 6% risk or 95 to 96% risk. However, studies sometimes find this assumption is not appropriate.

In this example, you can see a plot where we're looking at the disutility of a risk called PML. When we assume expected utility theory, in green, using Tversky and

Kahneman's weights as an alternative way to model choices under uncertainty, in white, and using empirical data on patient preferences, in pink, clearly, the expected utility theory is not a valid assumption in this application. So relying on theory alone may not be straightforward either. Let's go to the next slide, please.

And here is how model specification could matter. This is a plot of maximum acceptable risk of side effects as we increase efficacy benefits. In essence, this is patients' risk tolerance that's derived from stated preference data. With a single dataset we can model the disutility of risk, relying on different assumptions. Each continuous line in this plot represents one of these assumptions. What we see here is that these assumptions can change the maximum acceptable risk for a clinically relevant benefit from 2 to 4% in this example. In a world where approvals or rejections may come down to a couple of percentage points, this could be problematic, too. So, these are not trivial assumptions that we need to consider. Next slide, please.

I want to comment quickly on the issue of preference heterogeneity. It's been mentioned before, so I'll try to be quick about it. It's an issue in preference elicitation work, because preference heterogeneity can be very complicated. It can be something that corresponds to a very complicated process or that relates to variables that cannot be collected easily. I should mention that this is an area that the ISPOR Health Preference Research Special Interest Group is currently tackling. Sebastian Heidenreich and Marco Boeri are leading a very important effort to document how practitioners are exploring heterogeneity to synthesize learnings and gaps in this part of PPI analysis. So, I think that's important to stay tuned for that one. Let's go to the next slide, please. Actually, I'm going to skip this slide in the interest of time. I'm going to go to the last of the steps. Please, next slide.

Confirming the quality of respondents. This is arguably the most direct way of

evaluating whether all the work we've put into a preference study made our data fit for purpose. There are many different types of validity measures that can be used to evaluate the quality of the preference data, and these are actually just a few of them. There is some really good work recently published by Ellen Janssen and others discussing these and other validity measures in PPI data, so I encourage you to look at that work. In the interest of time, I'm going to skip here. Please skip the next slide and the following slide, please. One more. Thank you.

Another way to evaluate PPI data is to look at preferences across studies with meta-analyses. Unfortunately, this has not been widely pursued in our space because the literature is still rather thin for specific diseases. However, this is changing quickly. The work here looked at maximum acceptable risk in the treatment of psoriasis. The MARs are summarized by the magnitude of the benefit based on the type of psoriatic lesions that could be eliminated by treatment.

The results for this meta-analysis are rather encouraging. As we can see, clear and sensible patterns emerging from this literature. For example, we see that eliminating more severe lesions is associated with higher risk tolerance, which makes sense. And also, we see how tolerance measures for the risk of death or malignancies are so much more lower than those for severe -- for less severe lesions. Next slide, please.

To conclude, let's go back to the idea that we should know fit for purpose when we see it. I hope that this brief presentation helped you see that when we talk about patient preference data, we are generally not talking about opinion surveys. We're actually trying to measure a construct called preferences. But we don't have all the answers when it comes to evaluating fit for purpose and preference data. We know quite a bit about what may be necessary to determine the data are fit or not. We need to be able to judge the quality of our instruments, the data that they produce. And furthermore, we need to

understand the assumptions we make as we analyze these data.

Some methods will have problems meeting specific aspects of fit for purpose, but the methods shouldn't be the focus here. We have incredibly creative researchers, and I'm sure that if we are more specific about what it means to have fit for purpose preference data, there are ways to use all sorts of methods to meet those standards.

Thanks. And now I'm going to leave you with one of my favorite presenters in the PPI world, Bennett Levitan.

DR. LEVITAN: Thank you, Juan Marcos.

So, I will discuss applications of patient preference studies. And we've seen plenty throughout. So what I will focus on is what happens in some companies when they do preference work, and they suddenly realize they don't quite know what they should do with it. Next slide.

So, I'm an employee of Janssen and a stockholder in J&J. Next slide.

So, we've seen several slides of this type over the last few hours, so I won't go into any detail; just to describe that there are many applications for preference studies, all the way from early commercial assessments through our trial design, target product profile, benefit-risk, approval, and shared decision-making. Next slide.

Now, there are many approaches that can be used to apply preference studies, and we've heard several of them: Maximum acceptable risk or the reverse, minimum acceptable benefit; choice share, or when a proportion of people who choose one treatment versus another; measures that combine clinical and preference data like net clinical benefit for multicriteria decision analysis; and so on. And next slide.

There are quite a number of complications in applying these. Clinical data is heterogeneous, but preferences are heterogeneous. Clinical results have uncertainty. Preference results have uncertainty. Endpoints can be dependent. Preferences, too, can be

dependent and have a whole covariance matrix. And we have quite a number of benefits and harms, meaning the complexities above can multiply. And as Juan Marcos just described, preferences are not necessarily linear. The preference for a change from 1 to 2% may not be the same as the preference for a change from 10 to 11%. Next slide.

So what I found useful is partitioning the ways of applied preference data to inform decision-making into three classes. And this is actually work that's now part of the Innovative Medicines Initiative, or IMI PREFER project on patient preferences. The first class looks at preference information on its own. The second uses preference and clinical data jointly, but keeps them separate. And the third looks at preference and clinical data and combines them mathematically.

So I'll start with the first approach -- next slide -- preference data alone. One of the more common applications will be with qualitative preference information. So this is from a case study that was done actually about almost a decade ago, where people were broken into a few groups of size 20 and asked to conduct a benefit-risk assessment, and it started by looking at this value tree for triptans and migraine. And people did essentially qualitative preference assessment in determining which endpoints merited inclusion. Next slide.

Now in the group that represented patients -- and we actually did have patients; each group had, like, three or four people with migraine -- they said pain-free response is just not realistic. You'll measure it in clinical trials, but it's not something we expect to see in the real world. So they said take it out. However, the group that had physicians acting as regulators thought just the opposite. If you're willing to include heart attack, which is one of the risks that were included, we thought you should get rid of your migraine totally. So this was a very small example of how you can get radically different perspectives from different stakeholder groups in a qualitative preference assessment. This is relative

importance.

Now, you also can do this type of relative importance in a quantitative manner. So next slide. This is an example that was done by Genentech. At the time, they were looking at a Phase 2 drug for Fragile X Syndrome, which causes all sorts of intellectual and cognitive impairment in children, and there's no cure. They were designing a preference study, or conducting it, to learn what they might measure in Phase 3 since this was a very new disease and people didn't really have decades of experience with it. So next slide.

The preference study had six different attributes, which you see on bottom. And the blue lines are showing the relative -- the preferences as you migrate through different endpoints. Next slide.

The distance from top to the bottom is the importance or relative importance, and controls on behavior attribute was put on a scale of 10. Next slide.

The commercial and clinical people were actually convinced that the first and fourth attributes would be the most important. Lo and behold, the fourth one was the least important. The ones that were most important were the 10 and the 9.9. The point here is how valuable both the qualitative and the quantitative approach to using preference information is with no clinical data. This just looked at the preference information all by itself. Next slide.

Now, we've seen many examples in the talks today of maximum acceptable risk, and it's one of the most common and easy-to-understand approaches to apply preference information. This is a classic study that was done by, I think, Reed Johnson and Brett Hauber in Alzheimer's. And you can see as you move from left to right and increase the severity, so increase the degree of benefit of the Alzheimer symptoms that are removed, people would take a greater and greater chance of death or disabling stroke up to quite a high percent, 31.

Now, this works very nicely if you have one endpoint for benefit or composite benefit, and one endpoint or composite for safety. But it's a little more challenging if you have multiple benefits and multiple risks, as you saw in Juan Marcos's presentation. So here is an example for work that we did with Duke Clinical Research Institute for depression, though I'm keeping the details hidden. In this case, was a movement from severe to mild symptoms. And there were two adverse events on the *x* and *y* axis. Instead of a single maximum acceptable risk, what you have is a surface. Anything below that red line has benefits exceeding risk.

Now, what if you don't know the degree of benefit? Next slide. Well, the preference study gives you the ability to ask that same question for different degrees of benefit. So if we only give severe to moderate symptoms, anything below the green line is acceptable. And if it's only moderate to mild, anything below the yellow line. So, you can get tremendous amounts of information that's very useful particularly in strategic decision-making and target product profiles or benefit-risk by using a preference study all by itself. Next slide.

Now, what if you want to take into account population heterogeneity, one of the complications I mentioned at the start? Well, imagine the red line is the median maximum acceptable risk, and the blue line is representing a percentile at the 90th percentile. So in this case, if you want to make sure that your two risks are at the level that are acceptable for at least 90% of your population, you go below the blue line. So it's an example of how you can combine the concept of maximum acceptable risk for multiple -- in this case, multiple harms, and one benefit, and the population heterogeneity in preference. Next slide.

And the same concepts then apply when you have nonlinear preferences, as shown in this mock example that's very similar to what Juan Marcos showed earlier. Next slide.

Now, one of the fun things that people have talked about using preference studies for is effect size. How large a change in some endpoint merits use in a statistical hypothesis test? So, this is a mock example, and some of you may recognize this as the preferences from the FDA obesity case study, but I'm just using it as a nice figure.

Now, imagine we have two endpoints, heart attack and some novel time-to-efficacy endpoint. We understand heart attack really well, and we know a good effect size, and we don't know what's a good effect size for this new endpoint. So one way you can use preference information to address this is the following. Next slide.

So we start with a known and well-accepted effect size for heart attack. In this case, it's about 1/2%. Next slide. And then we ask what the preference change is associated with that accepted effect size. Next slide. Then we move that preference change over to the new endpoint. And then -- next slide -- we ask, "what is the change in the time-to-effect endpoint that corresponds to that preference change?" So, in this case, it's 2 years. So in this mock example, the 2-year change in your novel time-to-efficacy endpoint is preferentially equivalent of the well-accepted effect size of 1/2% in heart attack. So this where you can use a preference study all by itself, again without any clinical data, to make very important decisions in study design. So next slide.

So those are examples of how preference information alone can give you very valuable data. Now I'll show you some thoughts about beginning to bring the clinical data in. And mostly these are graphical techniques. Next slide.

So this is an example of a preference study that was done for atrial fibrillation. We did this, I think, with RTI. And in atrial fibrillation, the benefits are preventing various forms of clots, and the harms are causing various forms of bleeding. You're looking at Forest Plot, which is the clinical data. Anything on the left favors the study drug. Anything on the right favors the comparator. And the endpoints were put in order of severity by preference. So

on top were the most severe and bottom were the least severe. And you can see this stuff on the top in the middle, either on the left, favoring the study drug, or on the line, favoring neither. And it's only when you get to the least severe endpoints that they favor the comparator.

So this slide actually -- a version of this slide was actually used at an FDA advisory committee meeting to bring preference information and clinical data together. And you don't have to do anything fancy to be able to see that you're helping where it's important. So this is one approach, but it's only showing ranking a preference.

So next slide is a variation of this, where you displace the endpoints vertically by their preference values. And here you can see death and stroke are at the top, and then there's this relatively large gap where all the other preferences are. So it may not -- graphically this could be problematic because it's hard to squeeze endpoints in together, but it does make a very important point that there is sometimes a large gulf between a certain set of endpoints, preferences, and others. Next slide.

Now, it's not hard to imagine all sorts of different variations on this, so here is an effects table, where you're looking at a drug and a comparator. This is some of mock data, the rate differences between them, and then a graphical depiction of rate difference, and a graphical depiction of weight. And you could see again the big gap between the first two weights and the rest. And this is another way of keeping the information disaggregated but putting a viewer in the position of being able to mix this data in their head and start making a decision. But it's also not very hard, if you look at this, to realize we're one step away from combining this mathematically. So our next slide.

So that brings us to the mathematical combination of preference and clinical data. And you've seen some of this before. You've seen choice share. So next slide is actually a image from the paper on the obesity preference study done by CDRH. So what the

preference study can be used is to assess if you have two or three or four different treatments, what proportion of the population would use one treatment versus another versus the other.

And this analysis, coupled with others, was part of what was used for the CDRH approval in 2015 of a device. And then you could apply this to populations as a whole or subgroups with greater or less service tolerance. And this is actually a very comfortable approach for people. But you can't do this with a preference study alone. You have to have some information about the devices. So, in this case, on the right, you see virtual device A, the gastric band, virtual device B had various properties. So you have to go into this knowing both, one, some clinical data profiles or treatment profiles that are important, and two, you have to trust the mathematics that computes choice share. And amusingly, in my view, that's acceptable. But, the next approach is not as acceptable even though fundamentally, they are built on very similar mathematics. So our next slide.

Multicriteria decision analysis is one of a broad class of methods that are used actually by the EMA for some hard benefit-risk problems. The benefits and risks are converted to some normalized scale, represented by value, on the right. And the weights are applied to each endpoint. And then you take the product of the value and the weight and sum them, and then display them graphically.

So in this particular case, which is preference studies for Tysabri and other multiple sclerosis drugs, you can see a huge benefit for relapse with a modest weight, and it shows upon the right. And then the gigantic weight for progressive multifocal leukoencephalopathy, PML, with really next to no difference. And even though you care a lot about PML, it doesn't really manifest in the weight, in the sum. Now, what can you do with this? Well, you could look at it this way, but you can also go one step further. Next slide.

So here we have a probability density function or distribution of a net clinical benefit measure. Anything to the right of zero favors treatment B; anything to the left favors treatment A. And by doing that net clinical benefit, or actually, multicriteria analysis stochastically, taking into account uncertainty in both the clinical data and the weights, you can actually calculate in this example the probability that A's benefit-risks outweigh B's, are 97% of the benefits outweigh risks. And then there's a whole bunch of other ancillary analyses you can do. The problem is, this tends to be more of an academic-flavor approach than one that is at least currently accepted by a regulatory agents. Next slide.

So are we all set? Can we use all of these techniques or the ones we've heard earlier and calculate a maximum acceptable risk and apply it to clinical data? Well, not always. Next slide.

So this is from my first slide, and we have all these complications, and I'll just give one example. And given the time, I'm going to limit the -- I won't show some of the slides. I'll just explain it verbally. So, a maximum acceptable risk will say how much risk of a side effect people might accept for a given benefit. But not everybody might get that benefit and not everybody who gets a benefit will have the same degree of benefit. So what you will end up having to do is have multiple maximum acceptable risks for all the degree of benefits, and then you can't apply any of them alone to the population. Rather, you have to partition the population into the groups that have different degrees of benefit and apply the relevant maximum acceptable risk to each of them. It's something you certainly can do. Conceptually, it's not that hard. Mathematically, it can get messy. But it's one of the important details that I take into account when I think about applying maximum acceptable risk to real-life clinical data.

So let me advance to a few slides. Please go to the table with some colors on it. Two more slides. One more.

So here is my judgment of these three classes of methods, and I want to stress that it's the speaker's judgment. Preferences alone are very -- do not have anywhere near as much flexibility in terms of answering complex problems as some of the other methods. But they're very simple technically. They're very easy to communicate. It's easy to understand the transparency. And I think they're fairly well-accepted by health authorities.

Mixing preference and clinical data, it's much more flexible. It's not hard. But it is harder to communicate. Preference and clinical data mathematically combined, it's extremely flexible, but it's also extremely technically complex, much harder to communicate, much less transparent, and at least at the moment, it's low to medium acceptance by health authorities. So next, and last, slide.

There are numerous approaches by which you can use preference data to inform decisions. In general, I recommend using the simplest approach that will address the research question, but often I end up using a combination of approaches. And as you saw, as I was describing at the end, and in some of Juan Marcos's slides, the real-world applications, taking into account heterogeneity, the variance, uncertainty are not always as straightforward as we'd like.

Thank you for the opportunity to share these points. I know Shelby now wants to continue with Q and A.

DR. REED: Well, first I want to thank all of the presenters. One thing I really appreciate about today is that we're not just focusing on the beloved DCE, the discrete choice experiment. We've covered a broad range of methods. Even in the four presentations we just heard, we heard about the threshold technique, best-worst scaling type 1 and 2, swing weighting earlier today. And so, I really, really appreciate us taking a broader look at how preferences can be used to help present the patient perspective.

Even, you know, through our method seminars -- our presentations today, we saw

Dave asking, you know, what is the right question, what's the right method for answering a particular question. Ryan brought forth how to work with patients, starting with more simple types of tasks and best-worst scaling to prioritize endpoints all the way through doing a discrete choice experiment to measure risk tolerance. Then Juan Marcos brought forth an array of new issues that we need to consider about when we're thinking about whether data are fit for purpose. You know, evaluating data quality and reliability, demonstrating how modeling choices can lead to differences in findings, and thinking about, you know, how we can begin to build our literature so we can learn across studies. And then it was great, you know, with Bennett bringing it all together, how does he use this information to help make benefit-risk decisions within the company and helping regulators make these decisions through mathematical models and multicriteria decision analysis. So we have a rich set of topics that we can dive into.

So I'm going to go ahead and start with Dave. You know, going back, you mentioned one of the less burdensome approaches, which is the threshold technique. Have these studies, sort of, done any, sort of, means of validation to evaluate consistency across the thresholds that would come from, you know, from using this for benefit-risk assessment?

DR. GEBBEN: That's an excellent question, Shelby, and to date, I'm not aware of any specific study off the top of my head that has addressed that issue. I do know that some of our fellow presenters from earlier today, like Dr. Hauber, has done a study of the lit review of the threshold technique that has examined where those pieces have looked, and I do know that there are some other studies that are coming down the pike that are comparing the threshold technique and the DCE, seeing if there is convergence in those two areas.

I'm not sure if your question is asking have we seen in the threshold technique, has there been any sort of follow-up on have people then actually chosen what they said they would choose for a treatment option? Or is it something slightly different that your

question is --

DR. REED: Well, just wondering whether there was a way to sort of, you know, to compare methods to see whether one, you know, kind of lined up with the other or ask them just different questions that might provide some cross-validation.

DR. GEBBEN: At this point, I'm not aware of whether or not anybody has, sort of, done a truly explicit cross-validation in the way that you're thinking. I think that would be an excellent research agenda and excellent way for us to, yeah, fill a gap in our knowledge of exactly where those pieces would fit together.

I do think that, as we've heard throughout the day from other people, these studies often, unfortunately, they are very complex, and they take a lot of time and a lot of money, so I do think sometimes maybe the constraining factor is both time and money to sort of bake in within a single project both a full and complete threshold technique and a full and complete discrete choice experiment. So I would throw it to my fellow panelists if they know of anything that I'm not aware of at the moment.

DR. LEVITAN: This is Bennett. One of the goals of the IMI PREFER project is to address various methodological research questions. And one of those questions is how different methods, quantitative methods, perform compared to one another. So in a case study in rheumatoid arthritis that we're running, there are both a DCE and threshold techniques being used.

As you noted, it's very expensive to run these on a regulatory quality level. What I would actually hope is that some grants are offered that allow DCE preference experts to run case studies with multiple methods in addition to answering clinical questions.

DR. REED: Well, thank you.

And you know, Ryan, I want to congratulate you on undertaking an international study. We are on the verge of embarking on a few, and we know that they're very, very

challenging. One of the issues that has been brought up by all of the presenters in this session and in other sessions is the issue of heterogeneity. And it was clear that there was some heterogeneity across the preferences that were evaluated in each of the countries in your study.

What I'm wondering is, was there any qualitative work or any quantitative evidence from the survey that gave you some insight into why there might be these differences across countries?

MR. FISCHER: Yeah. No, it's a good question, and there certainly appear to be some differences, and there are lots of sources of heterogeneity that can contribute. It's hard to model all of those sources, coupled with the fact that we have a highly heterogeneous population.

This is very new data, and we are looking to dive into some of those questions. There was some qualitative work that was included. We do a lot of mixed methods, where we have qualitative pieces as well as quantitative pieces. So we're doing a deeper dive. Though, I think analyzing by stage did shed a different light on those differences in preferences. So, it's important to look at not just the country differences, but also, for us, the stages of disease, and to see where those preferences fall depending upon where they are in progression.

But, you know, in many ways -- so this was non-product-specific. We do a lot of non-product-specific work, and we wanted to test this internationally for the first time. So, there were a lot of things that went really well in that, but I think there's more work for us to be doing in the modeling to understand the heterogeneity.

DR. REED: I also wanted to remind everyone out there if you'd like to ask these panelists some questions to just go ahead and put your questions in the chat or use the app, the mobile app, to submit your questions.

So, Juan Marcos, I love that I work with you and I can ask you these questions all the time, but I'll share the opportunity with others. And that is you focused a lot on, you know, kind of measurement issues and how different modeling decisions can lead to different results in these types of studies. And then you sort of went on and suggested that, well, maybe we can do some meta-analysis.

And I just was wondering whether you had thought about sort of developing some sort of quality score or identifying, you know, characteristics, methodological characteristics across studies that would help you understand why different studies lead to different results, when, you know, even, you know, in the process of doing a meta-analysis, so you can better understand why you might see some heterogeneity in the results.

DR. GONZALEZ: Yeah. That's a interesting question. And I think it's part of the power of meta-analysis, right? It allows you to look at things that vary across studies that you can't afford to do in a single study. So, I wish we could see more of this work as a way to maybe identify some sort of list of factors that we need to consider. I think there could be a lot of important information to be obtained that way.

I think the challenge, as I mentioned in the presentation, is that the data that we would need to conduct these meta-analyses, I think it's limited. The literature is a little bit thin when you go to specific conditions. But as I mentioned also, things are changing, and when we did this meta-analysis in psoriasis, we had only about nine studies to work with. And we were able to learn quite a bit about the issues around, whether self-reporting of diagnosis is a problem, whether the severity of the -- self-reported severity of the patients who were completing these surveys was a problem or led to variation and responses. And so, I think definitely we need to do more of that. They just take quite a bit of information and effort. And so I feel like once -- as we get more data out there in diseases like diabetes or even oncology, we will be able to conduct more of this work.

DR. REED: Thanks, Juan Marcos.

And Bennett, I always appreciate your insights in how things work within pharma. And what I'm curious about is how do your colleagues receive it internally? You know, did they say, "Well, this is great, Bennett, we love all your models, but it's just way to complicated"? You know, the question is just how did they receive this information and do they want more of it?

DR. LEVITAN: They do everything I say.

(Laughter.)

DR. LEVITAN: What's very valuable is showing examples that have been successful and speaking in the language that's very relevant to the clinical team. For example, the slide I showed where you looked at two adverse events versus a given degree of benefit really speaks to a lot of clinical teams. That's their world. One maximum acceptable risk for a single benefit against a single harm sort of is cognitively nice. But it's rare from a clinical perspective that the problem reduces to a pair of endpoints. Once you show that you can have interpretable tradeoffs against three or four endpoints, which is really what the world will look like through a clinical -- from a clinical perspective, you've helped a lot.

The other thing that's really important are meetings like this. Having health authorities say, "We are paying attention preference studies. We recognize the difficulties and limitations, but we think it's valuable," has made a tremendous difference. And I can tell you, as I listen to the beginning of this meeting, I didn't feel like we were talking about some novel methodology that we're trying to figure out. I thought that we were talking about an accepted tool, and we were figuring out how to best use it.

DR. REED: Yeah. Thank you. I agree with that.

I'm going to ask a question that has been posed by one of the viewers, and that is about whether patient preference studies can be used to weight the individual event in a

composite endpoint.

DR. LEVITAN: Well, we do that in cardiovascular all the time. I call it the net clinical benefit measure, where you might have a sum of risk differences, each difference multiplied by a weight. And the trick is whether you want to build a hypothesis test for -- a test based on that, because you're really trusting something that's still kind of new-ish and is not -- you're bringing in both clinical heterogeneity and preference heterogeneity. And in a second, you're kind of assuming that the preference is a constant over the relevant population.

So I would use that as, at most, a secondary efficacy endpoint at this point. I would not make it a primary. Additionally, composites, even in cardiovascular, where they're used all the time, run the risk that some of the components may not go in the same direction as the composite overall. Typically, for example, the most severe events occur the least often. And so, something like death might favor one treatment, while stroke and myocardial infarction will favor the other, but because there'll be so many more strokes and MIs than deaths, the composite will hide that impact on death, and it'll be all the worse with the weighting. So, I'd use it, but I wouldn't make it the primary analysis. That's at least my perspective.

DR. REED: So the other issue I want to discuss a little bit, it's been mentioned many times, and that is preference heterogeneity. There was a question that was posed earlier about, you know, whether preferences are influenced by patient characteristics like their education, clinical affiliation, religion, and you know, their social background. And to the extent that they are, how can we evaluate whether we have a representative sample?

DR. GONZALEZ: Well, I can try to answer that question. So, my view on this is that we have a difficult problem when it comes to heterogeneity and preferences, because all of everything you mentioned in that long lists of potential covariance that could explain

heterogeneity could be related with preference heterogeneity. But then again, they may not. The challenge is that preferences are internal, and so they don't need to correlate with things that we observe necessarily.

And so when it comes to collecting information that allows us to explore heterogeneity of preferences and make our results more generalizable, I think the answer for me would be the same. We need to be able to get a large enough sample, and we need to try to get as many different types of patients as possible, because we will depend on the natural variation of these different phenotypes, if you will, preference phenotypes that out there, to be able to detect the differences in preferences among these groups.

I always argue that generalizability in this context doesn't necessarily mean that your average preferences represent the average preferences of the general, sort of, the population that you're trying to represent. That would be ideal, but unfortunately, in most cases, we don't know how to even ascertain that.

So instead of going that route, I'd argue that we need to have a sample that is heterogeneous enough and different enough so that we have a set of preferences that can be applied to different contexts and different situations based on what we know about the population of interest.

DR. GEBBEN: And I would just follow-up on Juan Marcos's point about that population of interest. I think part of it would be if it is a medical device that is targeted at a specific disease characteristic, the sample should be targeting that portion of the patient population that has that, or if there is a suspicion that there is a piece of the patient population that might be different, that that sort of be baked into the research question and baked into the sampling frame so that that information can be captured.

Again, we have to, sort of, think about, you know, who is the audience and what is the sort of end goal of these sorts of studies. If part of the end goal would be you want to

make a labeling claim, you would probably want to structure your sampling frame to allow yourself to make that proposition to the relative audience, which, you know, in this case, is probably going to be a panel or some other body within the FDA.

Keeping in mind those sorts of questions as you -- again, probably as I harped on too many times already, what's your research question, and then let that sort of help to guide how you set up that sampling frame.

DR. REED: Thanks for these comments. One more question I want to squeak in here at the end. And that is, you know, how to -- and Ryan, I think you could probably address this: how do you recruit hard-to-reach patient populations?

MR. FISCHER: Yeah. It's a great question, and I was going to add to this. So just to tack on to the other question of around that sample, I think the pilot testing portion of the process is really important and making sure that you can pilot tests across those ranges of socioeconomic status is really critical, and that's why partnering with patient advocacy groups is really important.

In terms of the hard-to-reach places to really get patients to take these studies, you know, for us, a lot of our population that, you know, is -- you know, has more resources, more educated, et cetera, are -- we're skewed higher in that sort of place with people taking this survey. But we have been able to work with clinics to recruit at the clinic level about our studies so that we can get a more diverse sample at the end of the day. Hopefully that's helpful.

DR. REED: Thank you. I did.

Bennett, did you want to add?

DR. LEVITAN: So we've had some challenging recruitment problems for a preference study for people at risk for a disease. So a very common scenario is disease interception or secondary intervention. Some of these asymptomatic, but they're likely to get the disease

is some period of time. But they'd be willing to take side effects now to get benefits later. And that means you need to find people who have been screened for that disease, and usually that is rare.

So, work that Rachael DiSantostefano recently published on Alzheimer's was done initially in a pilot population of healthy adults. What we really wanted to do was do it in the screening phase of clinical trial, both before and after people were screened for amyloid. So, you'd see their baseline preferences and then how their preferences changed if they were positive or negative for being at risk for Alzheimer's. And then that's a fine approach, except people are terrified of you screwing around with their screening exercises in a trial especially where it's hard to enroll, like in that particular problem.

And so, we ended up holding off on that, but that's one of the ways that you can get tough populations. If you're already getting a clinical trial to look at a tough population, then you could take advantage of that machinery to run the preference study in that same population.

DR. REED: Thanks, Bennett.

And thanks to all presenters. We're going to have to close now. There's a short break until 3:15. Thanks, everyone.

(Off the record at 3:04 p.m.)

(On the record at 3:16 p.m.)

DR. ORSINI: Hello, and welcome back to the fourth, and final, session today, where we're going to focus on implementation, collection, and utilization of patient preference information beyond the evaluation of product-level benefit-risk in the regulatory space.

Each of our panelists will present on their experience and relevant research, particularly in thinking about patient preference at the disease level. And there will be time for question and answer at the last part of the session. So please send through your

questions as you think of them. All attendees will be entered in mute, and you can definitely use the chat box to enter your questions as you think of them.

If you go on to the next slide, first you'll be hearing from Dean Bruhn-Ding, the President of Regulatory Affairs and Quality Assurance at CVRX, Incorporated.

Our second panelist, Ravishankar Jayadevappa, is a research associate professor at the Perelman School of Medicine, University of Pennsylvania, as well as a member for the Abramson Cancer Center, a senior fellow at the Leonard Davis Institute of Health Economics, a fellow at the Institute of Aging at the University of Pennsylvania, and a core investigator at the Center for Health Equity Research and Promotion at the V.A. Medical Center in Philadelphia.

Our third panelist today will be Melissa West, the Acting Vice President for Research, Discovery, and Innovation at the ASN Alliance for Kidney Health.

And finally, Dr. Louis Jacques, the Chief Clinical Officer and Senior Vice President at ADVI, a healthcare advisory services firm, where he's also a partner.

So I'll hand it off now to Dean to start out with his first presentation.

Go ahead, Dean.

MR. BRUHN-DING: Thank you, Lucinda. And hello to all Summit attendees. I'd like to thank FDA and ISPOR for the Summit today. Next slide.

As Lucinda indicated, I'm the Vice President of Regulatory Affairs/Quality Assurance for CVRX, a small medical device company in Minneapolis, Minnesota. I've been in the medical device industry a little over 36 years and have had the pleasure of working in several departments and key areas of those companies over the years. I've been involved with medical device patient preference studies just over the last 4 years. Next slide, please.

I had the honor of chairing a novel work group for MDIC. It is important to establish a foundation of why we did this project. The objective of the project was to advance the

science of regulatory patient preference assessment by giving medical device industry sponsors, regulatory agencies, and preference assessment experts another example of a disease-specific patient preference study. We wanted to build on the past case history and provide another example of a patient preference information study, like the Parkinson's patient preference study, for the medical device ecosystem. Many stakeholders were involved over the course of this project. The results of the study for the heart failure patient preference study was actually presented on September 17th, 2020, as part of the MDIC annual meeting, and the results are available on the MDIC website. Next slide.

Who was involved in this project? This was a first-of-its-kind collaboration spanning many medical device stakeholders afforded in the safe environment of MDIC for developing good regulatory science. In particular, this was a partnership of six industry sponsors collaborating on a patient preference information study with patients, FDA, and Duke preference experts that would provide valuable heart failure patient preference information for all to use.

We would like to thank our patient scientists who provided input and guidance for the project along with CDRH, FDA, Patient Engagement, and the MDIC staff. And lastly, I want to give special thanks to the six sponsoring companies and FDA for providing the funding for this important project. And in particular, I'd like to thank my fellow co-worker members out of the work group, Dr. Phil Adamson, Dr. Ken Stein, Dr. Dan Schaber, for their valuable participation throughout the entire project. And lastly, to Dr. Shelby Reed, who led the team from Duke CRI that wound up implementing and executing the project for us. Next slide.

The Heart Failure Patient Preference Study was developed to inform on a potential heart failure clinical trial design and provide a regulatory reference for FDA. Our challenge as a medical device industry is to use PPI studies across the medical device lifecycle so that

patient perspectives are infused into the entire ecosystem. That's our challenge.

I'll be available for questions at the end of the presentations. Thank you.

I'd like to now turn it over to Ravi from the University of Pennsylvania.

DR. JAYADEVAPPA: Good afternoon, and thank you very much for giving me an opportunity to present results of our study.

And this is a patient-centered preference assessment. We call this a PreProCare assessment intervention trial, helping especially for prostate cancer patients in real clinical settings to choose their treatment, and all patients are localized prostate cancer patients. Next slide, please.

And, we all know that currently in the U.S., prostate cancer is the most common cancer among men. And in 2020 alone, we'll be seeing approximately 191,000 newly diagnosed localized prostate cancer patients. And the main age of diagnosis is around 69 years. One of the important things in the localized prostate cancer area is that several treatment options are available. And each treatment has the benefits and the risk associated, like in terms of comorbidity and long-term outcomes. And no one treatment has shown to be superior to the other treatment. And some of the common localized prostate cancer treatments are active surveillance, watchful waiting, and then we have types of surgery, as well as types of radiation therapy.

So the patients often kind of like have a task to derive how to weigh the risk and benefits of these treatment options available for prostate cancer. So, to facilitate the shared decision-making, we have developed a PreProCare, that is, patient preference intervention for a newly diagnosed prostate cancer.

And the objective of this study is to study the effectiveness of this preferential assessment intervention. And the second, identify the preferred features of prostate cancer treatment that will aid in shared decision-making. And also, the important objective

as well as the question that we are asking is: Will preferential assessment intervention improve patient satisfaction with care and satisfaction with their treatment decision, as well as reduce regrets, and finally, align treatment choice with their prostate cancer risk. Next slide, please.

And this is a randomized controlled trial, multicenter, randomized controlled trial. So, we recruited all the newly diagnosed prostate cancer patients. They are localized prostate cancer. And after their baseline assessment, they're randomized to either usual-care controls or our PreProCare patient-centered decision-making tool. And we recruited about 360 in controls and 360 in intervention group. The total is like -- the total patients we had recruited are more than 720 patients. And the participating centers are University of Pennsylvania Fox Chase and Presbyterian Hospital, as well as Philadelphia V.A. Next slide, please.

The intervention consists of the preference assessment intervention, which is a web-based tool and is an adaptive control analysis. And this consists of five interrelated screens on the tools: the interaction section, where it provides the overview of the prostate cancer and the different treatment options, and then the -- and it's followed with the instructions of how to complete this preference assessment tool. And end of that, the first step of the PreProCare is that it identifies all the attributes that are important for patients. The next slide, please.

And that screen consists of -- like, they go through the treatment options, and as well as the attributes. So, it gives a scenario like, example, “suppose two treatment options are safe, and how important is survival for you?” And then the patients can rate from "not important" to "extremely important." And based on these attributes that are, like, specific to the individual patients, it develops the trial scenarios, that is, hypothetical trial scenarios treatment, that is the trial scenarios, too.

And then after the patient completes the trial scenario, it develops patient-specific attributes. Example, for this patient, at the final right-hand side of the "final attributes" column, you can see for this patient, "out-of-pocket" was least preferred attribute compared to "urinary function" and followed with “cancer recurrence" are the top two attributes. Next slide, please.

So we randomized to two treatment groups, and 360 received -- all the patients received this intervention before their treatment choice and right after their diagnosis. So, the window was, like, was very small, so as soon as they learned about their prostate cancer diagnosis, we -- this intervention was administered. And the primary outcome that we looked at was the general satisfaction with care. And as you can see, we assessed at the baseline, as well as up to 24 months. The intervention group consistently reported higher satisfaction with care across all the time compared to the control, usual-care group. Next slide, please.

And in terms of satisfaction with the decision, as well, like, the intervention group reported higher satisfaction with their decision, but a lower regret across all timepoint, especially at 12 and 24-month period. Next slide.

And another important is if we look at the treatment trials also was affected by our intervention. And the more low-risk patients were in the intervention group, and more likely to select "active surveillance" compared to "active treatment."

And in conclusion, our preference assessment is a key component of patient-centered care, and it demonstrated improved satisfaction with care, as well as satisfaction with the decision as well as treatment choice.

Thank you. And the next presenter is Melissa West, is the Acting Vice President for Research, Discovery, and Innovation at the ASN Alliance for Kidney Health. Thank you.

MS. WEST: Thank you so much.

And thank you to the organizers for today's session. It's been fascinating, kind of, listening to all of the topics and presentations. And I really feel like we're kind of standing on all of your shoulders as we're trying to push our work forward into kidney disease and kidney failure space.

So, I am Melissa West. I am serving as the Acting Vice President for Research, Discovery, and Innovation at the American Society of Nephrology and over the last 8 years have been managing and leading the efforts of the Kidney Health Initiative. So, Kidney Health Initiative is a public-private partnership with the Food and Drug Administration and the kidney community.

As shown on the right-hand side of this slide, we have over 100 members who make up about 50% industry, who are interested in dealing with various innovation at the regulatory intersection. Also included in our membership are patient organizations, healthcare professional organizations, and others, and really our job is to try to facilitate the future passage of drugs, devices, and biologics. Next slide.

So, I'm going to highlight kind of some of the projects and the things that we work on because our work in the patient preference space is at an earlier stage. We are just finalizing our survey instrument now, and we'll be looking to field that in early '21. But I think it really stands, again, on not only the shoulders of this community and the work that you all have been pushing forward in terms of patient preference methodology and philosophies, but also the work that we've been trying to do in the kidney disease space, which has really seen a lack of innovation over the last 50 years.

I mean, for many dialysis patients who still go to in-center hemodialysis unit, the machines look slightly different, but there hasn't been drastic change. And really with our partnership with CDRH and others, we've really been trying to think about how we can transform care.

And so, some of the work that we focus on within the Kidney Health Initiative is focused on endpoints, really bring in patient perspective very early on. For those that heard Todd Snell's presentation earlier today, we did facilitate that workshop that really stimulated the initial work that NxStage did in their patient preference study.

But we also have been developing technology roadmaps. And one technology roadmap in particular that we've been focusing in on is in the area of future renal replacement therapy. So this would be thinking through, again, this transformation that we'd love to see to get patients more independence, a higher quality of life than many of our in-center hemodialysis patients get, helping to facilitate more patients to be able to care for themselves at home should they wish.

And so a patient preference initiative was initiated in earlier this year through partnership with the Food and Drug Administration, where we will actually be developing this survey for a future wearable renal replacement therapy device. We are hoping that, again, using kind of a lot of the work from this community, we're trying to think early about how not only can we bring the patients into the process, because there is not a wearable hemodialysis machine or peritoneal dialysis machine on the market right now, but we want to bring in this benefit-risk discussion earlier on in the process to ensure that we all really understand what elements of the product and the attributes are most important to them.

We also want to bring in the conversation around the payors and using this patient preference survey there, as well, in order to really better understand how payment and reimbursement can align. And ultimately, through our work with not just developing this survey, we really are hoping to build some capacity.

This is a community that really would like to be able to be able to voice their opinion more often to developers, and so through our efforts and partnership with the Food and Drug Administration, we're hoping to build, kind of, a sustainable strategy. Many of the

speakers earlier today also referenced the challenge of these surveys and how you convert them in language to patients so that they can really understand. So we're hoping that we can think through not only those techniques and pilot them, but also bring our developers in industry in earlier so that as they're thinking about developing, say, a wearable kidney, you know, that they integrate patient preferences early, and ultimately kind of fill the system or an ecosystem that would really be able to catalyze future of innovation in this space.

So I really, again, appreciate -- I'm looking -- very much looking forward to the panel discussion this afternoon.

And at this time, I would like to introduce Louis Jacques, who is the Chief Clinical Officer at ADVI Consulting. Thank you.

DR. JACQUES: Good afternoon, and thank you.

I do think it's interesting to have a payor perspective at the end, because I think the question really is, if you plan a party and throw a party, is anybody going to show up, because at some point, someone has to pay for it.

My disclosures are up on the screen. In addition to those, I worked at CMS from 2003 to 2014, 10 of those years as a manager in national coverage, and from 2009 to 2014, I ran Medicare National Coverage. During that period of time, I also spent a little bit of time detailed to FDA for CDRH's Entrepreneurs-in-Residence Program. Next slide, please.

I think from the payor perspective, a lot is going to depend. In other words, you know, it's not difficult to say that we would like to see medical devices or medical therapies, whether they're drugs or whether it's even hands-on manipulation, we would like them to reflect attention to those things that are most important to patients. And we know from experience that the things that are most important to patients are not necessarily the same things that are important to physicians or to clinical trialists or to various agencies of one

type or another.

So, given a general sort of curiosity about this space -- I don't think the payor would dismiss it out of hand -- you end up with implementation questions: How can you adequately determine it for policymaking purposes? Is one going to do a randomized study of every patient preference outcome before one then graduates into some other bucket where it might be used? I mean, that seems to be impractical. Yet we know from our own history that sometimes what seems intuitively appealing turns out to in fact be wrong.

How can we account for preference heterogeneity? One of the earlier slides this morning talked about roughly -- I think it was something like 75% of parents preferred, essentially, a physician office strategy for tympanostomy tubes. Well, that means that a quarter didn't, okay?

So from a policy point of view, when it's -- you're not just saying, yes, you can do this; you're having to essentially adjudicate premiums and other things around, well, what is our case mix actually going to be? You know, how small does a patient preference percentage needs to be before it becomes trivial to a large institution, even though it may be very meaningful for that individual patient?

So have to sort of sort all that stuff out. It's sort of like saying you should engage with your children on vacation. Well, what do you do if your children don't agree on where they want to go, and the only place they want to go happens to be a place that far exceeds your budget? Then what do you do there?

So, how do you integrate all that stuff into the primary increased specified outcomes of clinical trials? One of the things that frustrates payors is a pivotal trial will fail its primary. It will literally fail. And then everyone engages in this post-hoc data dredging to say, hey, look, we were better on a subpart of SF-36 that we sort of serendipitously happened to collect. Well, congratulations. You now have a hypothesis. Go run a trial with

that as your primary prespecified outcome, and we might have some more interest in talking to you.

What do you do with infants, young children, and cognitively challenged persons? When I was a child, my only priority and preference was to avoid pain. If you could do anything to be without phlebotomy, that's my preference. I don't care if it works or not. I'm a 4-year-old. I don't want pain. And while we normally view parents as acting in the best interest of their children, we know from reading the newspaper that, unfortunately, that is not uniform. Some parents, frankly, don't appear to have their children's best interest in mind. And there may be other pressures going on that may change their preferences vis a vis what the child would actually want.

Are we going to need patient-reported outcomes in order to actually measure patient preference outcomes? I mean, it's unlikely a patient is going to say, "Well, my preferred outcome is an ejection fraction of 45%." That's not how patients talk. They're likely to say something else like “I don't want to be fatigued,” "I want to be able to climb stairs,” “I want to be able to engage in those day-to-day activities that make life meaningful." Well, how does one measure that? You don't measure it with an echocardiogram. At some point, you're dealing with patient-reported outcomes, and then all the challenges that come with patient-reported outcomes.

From a payor point of view, if you're a commercial payor, how much does it cost to do all this stuff? Is this going to essentially blow my budget or potentially create some downstream benefit that's not going to accrue to me because that patient isn't going to be in my health plan in 2 years? So there's a lot of questions that will impact this. Next slide.

So the good thing for everybody is that Medicare loves patient preference. Medicare has loved patient preference for at least 10 years. CMS has repeatedly endorsed shared decision-making in national coverage determinations for Medicare. And where does

this shared decision-making start? It starts with the patients' values and the patients' preference around their own goals of care, okay?

And in spite of that, interesting for this particular webinar, there was significant pushback when CMS started to adopt, essentially, shared decision-making. And I was sitting in a meeting one time. I had a CEO on one side and physician KOL on the other side. And the conversation was essentially, "Well, we know what patients want. Well, you know, maybe you don't." It is different than traditional informed consent. On occasion, physicians will, sort of, you know, get their hackles up a little bit and say, "I know how to do informed consent." And I think there'll be some education needed to get everybody onboard with the idea that patient preference is not the same thing as patient consent.

So, the application process for Medicare coverage in IDE trials is an opportunity where you might want to incorporate your discussions about outcomes if, in fact, you have a patient preference instrument that you want to be, essentially, the primary outcome in your IDE. CMS is more than willing to talk to you. They now cover something, like, 340 IDEs. It's a national process. It takes about 30 days. Most of the requirements are brainlessly simple. It's like register on clinicaltrials.gov, respect the common rule of protections for human subjects in clinical research. But CMS loves this sort of stuff. Next slide, please.

And here are some examples of where CMS loves this sort of stuff. In every one of these decision memoranda, which date back quite a long period of time, CMS explicitly talks about shared decision-making. You know, patients, as they are weighing risks, you may have a patient who is very terrified of the possibility of having a stroke. You may have another patient who is particularly concerned about bleeding. You may have someone else, who, for whatever reason, has a fear of surgery or a fear of surgical procedures that other patients don't normally exhibit. How do you respect all of these things?

And the point of these discussions in Medicare policies are that for things like before you decide that you're going to implant an ICD, before you decide that you're going to do a left atrial appendage closure, have a conversation with the patient and actually decide with the patient where their own values lie, what their goals of care are, and those patient preferences should drive the choice of therapy, even if that means, as a proceduralist, you're going to refer that patient to a noninterventional cardiologist because that's the place where the patient is best going to have their interests served. It means, as a physician, you have to put your own interests aside. And you may even, at some point, have to refer the patient outside in order to make sure that you fully respect that patient preference. Next slide, please.

So, here are some challenges. So, if a patient, whether it's a patient with renal failure, heart failure, anything else, says, "You know, feeling energized is important to me." Well, how do you measure "feeling energized," okay? Do we measure hemoglobin? I'm going to suggest the answer is no, and that's why I have it in brackets at the end, because we know from multiple clinical trials that artificially inflating hemoglobin level doesn't accomplish the same state of affairs as what a patient would experience if they had a naturally achieved hemoglobin level of the same amount.

When we attempt to manipulate a biomarker, we sometimes actually cause problems rather than helping the patient. In healthcare -- and I think some of the Medicare reporting requirements are emblematic of this -- metrics that are easily measured tend to get measured. So, the challenge is: How do you make sure that what you're measuring is being done because it's the best way to ascertain that measure as opposed to, well, this is in every electronic medical record, it's easy to do, it'll make three leaps of logic and a somersault of faith to say that all of these things align with each other?

How do you balance counter-preferences? I mentioned -- I talked a little bit earlier

about people who don't want to have a stroke, the people who don't want to bleed out from anticoagulants either. How does one balance those things especially if there is not an ideal, or if there is not evidence to support that there actually exists an ideal option that essentially negates both of those concerns from the patient? Next slide, please.

And this is my last slide, aside from just my contact information. I think rigorous assessment of patient preference is challenging, and translating that preference into a robustly measurable outcome is vulnerable to bias from a number of sources. I think implementing preference-based health plan policies is going to be even more challenging, given the need to respect heterogeneity.

Medicare loves outcome data that reflect the beneficiaries' experience of disease, their experience of priorities, and their response to therapies. These might include KOL measures of independent function or specific adverse event risks, for example.

I think PROs are going to be needed, simply based on the way that patients tend to describe their preferences. As a payor, I would much rather see that than, you know, MACE at 30 days or procedural success at 30 days, unless MACE at 30 days happens to track very, very closely with the patient's own feelings about this.

So on that, let me go ahead and pass the baton, I think to Lucinda.

DR. ORSINI: Yeah, hi, yeah, thanks, Louis, that was great.

And thanks to all of our presenters.

I would like to remind everyone that you can go ahead and put any questions that you have or comments in the chat function either within the webcast, or if you want to use the app, those will come right through to me on this screen.

So, I just wanted to first say, you know, this is sort of a much different session, I think, than the sessions we've had the rest of the day, talking about using -- gathering and using PPI in certain disease states in a precompetitive space, you know, gathering that

information even in a public-private partnership, but certainly an interesting topic. And I want to get to that in a minute.

And using PPI in real time to help with shared decision-making and patient-centered care hopefully to improve satisfaction with treatment certainly seems to fit with a lot of the things, Louis, you were saying about payors are interested in. And then the payor viewpoint on PPI for coverage, what's most important to patients, but also, you know, are they capable of making sort of those rational decisions in coming to what they want, which is, of course, rational, but is it even the right one? And then how do you pay for all that coverage?

So, you know, since Louis, you finished off, Ravi proposed or is working on, you know, sort of a tool, a shared decision-making tool or collecting patient preferences in real time and trying to help make treatment decisions. Does that appeal to you as a payor? Are you worried about that? What do you think about that sort of clinical real-time data collection?

DR. JACQUES: It doesn't worry me at all, I mean, in fact, as long as protections are there around the vulnerabilities. I mean, ultimately, the issue is: Can we confidently conclude from the data the same conclusion that the advocate would want us to conclude? As long as that's done appropriately, we don't have a particular problem with that sort of thing. It was the same thing with Bayesian types of analyses. And CMS has no particular opposition to, you know, Bayesian analyses. It's just, you know, be transparent about how you arrived at your prior probabilities and something along those lines.

DR. ORSINI: Yeah. And then, Ravi, how easy is it to have patients collect that information or use the tool in a clinical setting? What's your experience with that?

DR. JAYADEVAPPA: Yeah. One of the important, we give several options for them. They can do it at the clinic if they -- all that they need to do is 30 minutes before the

appointment, scheduled appointment. They can come to the clinic and they can -- they have a kind of room that's dedicated for this. As well as if -- we can also provide them a user ID and password unique so that they can complete this even at home. And we are now doing this on the mobile platform, as well, like iPad or iPhone, so it's easier for them to -- even if they want to have a chat with their spouse or other caregivers before they, kind of, tradeoff their -- select their attributes, that can be facilitated, too.

DR. ORSINI: That's great. Thank you.

And I mean, of course, it's one thing to have a preference, but then for your physician to actually help you follow through on the decision in case they have a different, you know, their own opinion about what should happen, is that an issue? Are physicians using this? What do physicians think about using this for decision-making?

DR. JAYADEVAPPA: Yes. That's a really, really good question.

DR. ORSINI: If you don't know the answer, I don't know.

DR. JAYADEVAPPA: Yeah, we are trying to assess that in our, like, you know, in our, like, future studies.

DR. ORSINI: Yeah.

DR. JAYADEVAPPA: But one important thing happened with our PCORI-funded grant that I just published, with all the urologists and the radiation oncologists, they are all part of the study, so they were involved in designing the preference assessment web-based tool. So, they kind of knew what -- like, the outcome of it, how to interpret the results, and how to have a shared decision-making conversation with the patients. So that helped.

I agree with you. I think physicians also need some kind of training to overcome their own bias, some kind of training, aggressive versus non-aggressive, as well as other age-related and racial/ethnic bias. So yeah.

DR. ORSINI: Sure. Yeah.

DR. JAYADEVAPPA: That's an important we need to go through. As a physician, I definitely recognize that.

DR. ORSINI: Great. Thank you for that.

And now, before I come to some of the questions that are coming through, Melissa and Dean, you both are sort of working in a similar space, so almost a precompetitive space or a collaborative space to gather this type of information, letting it be, then, open to others to use it, who are working in this disease space. How is that working? I mean, are you able to come to the types of decisions in designing the studies or coming -- the outcomes? What are the challenges? What are the opportunities there?

MS. WEST: So I'll start. I also want to comment on the last point --

DR. ORSINI: Yeah, please.

MS. WEST: On the physicians' bias. I can remember being in a meeting at FDA, and it's probably been 5 years now, where I was getting first introduced to some of these concepts. And I remember Dr. Levitan standing up there in front of the group and saying "it's almost as important to understand" -- I'm sure I'm getting this wrong, but I'm telling you what I took away -- "it's almost as important to understand what a patient's preference is as it is to understand the physician who presented that opportunity to the patient, because if the physician was risk averse and presented the study in a way that the patient could read it, they may get a very different answer than a physician who is much more of a risk-taker presenting a patient preference survey to a patient and then, therefore, they got the answer." It's always stuck with me, and I've always kind of continued with that.

So, for us, within the Kidney Health Initiative, we are kind of embarking on this patient preference initiative really with already a history in place. We have been working collaboratively across our community very successfully with the FDA for the last 8 years. And so, by the time we're getting now to this point where we're starting to work together

on a patient preference initiative that the relationships are somewhat established.

And really our patients are the ones who are leading the way, who are asking for this work to be done and really advocating that they have a voice in the work. And so, I think that also is really kind of level-setting to all of us, because in our case, within kidney disease, we're on the forefront of hopefully a whole new set of innovations. So, we're embedding these practices, and hopefully infrastructure to support it, way before the technology has arrived.

And so, you know, some of the challenges that we're facing are that we're developing a patient preference study in the agnostic of an actual device. So, we can't touch and feel and think through. So, we really have to rely on the developers who are in the space who may still be at a very early conceptual phase to talk through what are some of the device attributes. So that's been a little bit challenging. But it's also allowing us to kind of grow the opportunities. It's allowing us to grow together through the process, because we're attempting to be as transparent as possible before we field this study to really think through both, you know, getting patients to try to help us, say, describe what they think these devices will look like in patients' language, talking with developers at the same time about what, you know, they may have different iterations of devices that are coming, so talking through it with them what some of those device attributes might be, and then thinking through it from the regulatory perspective.

You know, again, backing into those critical research questions, you know, what are the kind of critical research questions that the regulators will need answered through these studies in order to be able to help the decision-making? And ideally, if we all go on that path together, then by the time there is a product and we are engaging with the payors, we start to say, okay, now we have a product that's moving from -- you know, into clinical trials, let's embed this patient preference work from the beginning. You know, I think we'll

have a better shot of success versus doing it kind of retrospectively.

So, it's challenging, because we're in -- you know, again, we don't have a product that we're looking at or we're trying to adapt or evolve from that perspective, but we did have the relationships and somewhat of the trust that was already built in place.

DR. ORSINI: Yeah. Great. Thanks for that.

Dean, did you want to comment?

MR. BRUHN-DING: I can comment on a couple of things. First of all, the MDIC program that I was a part of, that was a very interesting collaboration in a safe environment that was provided by MDIC. And we have the advantage there that FDA was involved from the get-go. The six industry sponsors were obviously involved. We did have patients involved from the get-go. So, it was a very collaborative program. And as I think about the competitive space, it was done from the standpoint of kind of genericizing a device. The risks that were involved with regard to heart failure, the two that we really picked on was a two-day hospitalization complication and mortality with regard to a heart failure, you know, death.

So, I think with the MDIC environment, we were able to, you know, pick attributes. That was the most difficult part of the competitive space, is what attributes are important. And for a lot of us, we had to be educated. Attributes that patients care about are totally different than clinical -- well, may be totally different than clinical endpoints. And so, we had to come to terms with that.

And as I think about, you know, the relationship of patient preferences, how you can measure them, what kind of metrics are involved there, it's important if you can get some of those that they crosswalk over, and will be tied into some clinical endpoints that will be of importance. So, I think that was the most difficult part of the program under the MDIC heart failure project that we did. The risks were relatively straightforward.

It was interesting. I felt the -- all of us out of the six sponsor companies were competitive with regard to heart failure devices and/or interest, and I thought it was very interesting that everybody was very forthcoming in providing good information and were very supportive of not only the entire program, but participated fully in the process. So that was helpful.

DR. ORSINI: Okay.

MR. BRUHN-DING: From an individual company perspective, one of the things -- I've been involved with patient preference a little bit over 4 years, so we were doing some work at CVRx. What the MDIC project didn't necessarily provide for all of us is each one of us as a sponsor company probably had, you know, in mind some device type and/or device features that would be important to possibly test.

So, the way we ran the study, we weren't able to necessarily get at specific device features. So, I think from a competitive space, it made some sense, depending where were you at in the development process, where you're at in the process dealing with FDA in the pre-IDE environment, are you going to try and incorporate it into a clinical trial with regard to the patient preference information, or are you going to use it maybe on the back-end to possibly help your marketing and/or your labeling activities, you still need to get FDA involved early and work with them in the pre-IDE process to get that worked out. So, from a competitive perspective, I can see some things that device features, you would, you know, probably really want to look at, you know, from a specific company perspective.

DR. ORSINI: Yeah. So it's not, it's not a full panacea. I mean, you still have -- there's work to do beyond what you're collecting, yeah.

MR. BRUHN-DING: Absolutely.

DR. ORSINI: Yeah. Great.

So I'm going to go now to some questions. Thanks to all of you for indulging me with

my questions.

Here's one that comes from the -- our audience, so I'll go slow, because it's complicated. So, we know from empirical research, for example, economic research, that people at the end of the day often don't make rational choices based on all of the evidence, as patient preference studies would suggest. How should other data, such as real-world evidence, supplement PPI in the decision-making for devices in both the regulatory and, you know, beyond regulatory decision-making? Do we need to sort of validate or add in more information to understand where people's choices are falling?

I don't know. What do you guys think?

MS. WEST: Yeah. So I mean, I guess I'll take a little bit of a stab at that and say that, you know, I think that FDA, CDRH in particular, has a real rich history especially in the area of coordinated registry networks and thinking about how again you can kind of work together to pull data sources that are kind of disparate and try to query them and try to understand kind of how all those pieces of information come together.

I would say, you know, I guess I could say, hypothesize in our space for kidney disease, where we are paid for the -- the kidney failure patients are paid for through the ESRD bundle, so there is a lot of data that's available from a claims perspective from that piece.

If you think about us being on the forefront of innovation and devices being developed, if we could also build registries that would allow you to have those unique identifiers built into the devices, and you could, you know, identify a way to understand how to track them back to the patient, and that patient's claims data also could be connected, and then you start to add in the patient preference information, you start to have a really rich story around not only that individual choice, but how their interacting with their device, how that device is serving them, as well as kind of generating each

outcome.

So I think in the grandiose sense picture, it makes a lot of sense. I think for us, we're again, we're lucky in the sense that we're on the forefront of change, and so we can kind of build in some of these concepts. But I do think real-world evidence supplemented with patient preference could be very powerful. We haven't had the experience yet, so I don't know exactly what could be also all of the risks that could be associated with that. You know, it's building the systems, I think, that become really important, building those platforms and making sure all the data can really talk to one another, which I think is extremely challenging, but doable.

DR. ORSINI: Yeah. Great.

Anyone else have a thought about --

DR. JAYADEVAPPA: Yeah. I would like to --

DR. ORSINI: Yeah, go ahead.

DR. JAYADEVAPPA: -- add a small thing about that. Like, patient preference is like in -- I'm discussing with respect to prostate cancer -- is in identifying the attributes. So, that in summation is really, really important work when they go and have a conversation with the shared decision-making with the patients, so that the physicians can tailor that with the evidence-based -- what treatment option is good, for example, low-risk, intermediate-risk, high-risk prostate cancer. So, if a patient is not interested in surgery at low-risk, they can opt for active surveillance. So that's where I think the physician component comes into picture. That's where the evidence-based care integrates with the preference-based care, kind of like shared decision-making I think is going to strengthen that environment.

DR. JACQUES: Yeah, I don't think we need to reinvent the wheel. I mean, if one is looking at orthopedic implants, you know, hips, knees, whatever, the primary outcomes you're going to tend to see are things like ODI, the Oswestry Disability Index, WOMAC,

things along those lines. And I think if you ask a patient with a bad knee or a bad hip, "What are your preferences for outcomes?" I'm willing to bet a significant amount of money that their preferences are going to be: "I want to be pain-free," "I want to be able to walk up and down the stairs," "I want to be able to get in my car," "I want to do all those sorts of things."

So, it's not like we've been ignoring those things for, you know, that great period of time. In fact, payors are reviewing that sort of evidence and have been, you know, for well over a decade.

And I think in -- especially in instances where the major impact of a disease is something that the patient experiences as a limitation in their daily life, I think those things have been sort of more obviously aligned to patients. They don't walk in and say, "You know, I have an abnormal X-ray, and I have, you know, a little bit of erosion in my whatever." They say, "It hurts when I go up the stairs," you know?

DR. ORSINI: Absolutely.

MR. BRUHN-DING: You know, Lucinda, I'd like to throw in a couple of comments here.

DR. ORSINI: Sure.

MR. BRUHN-DING: I think Melissa hit it right on the head with regard to, you know, coming up with more or less metrics, possibly, and registries that you might find in real-world evidence. And if you can correlate or tie those in to patient preference work, I think they're actually complementary and not actually supplementary. But they actually complement each other.

And to get to the regulatory question here, the part that would really be key for industry, and also the patients, would be if you can take real-world evidence combined with patient preference evidence, and then be able to, let's say, do a PMA supplement and

actually get a revised indication or expand the indication for use, that actually gets to the meat of the matter, which I think actually Dr. Shuren was driving to. Real-world evidence can actually be a real beneficial tool to industry. And I think the way we have to do is you have to have enough metrics so that you can correlate it, not only safety-wise, but effectiveness-wise so that it has meaningful results that you can submit to FDA, revise your labeling, expand your indication.

DR. ORSINI: Perfect. Thanks. I think we answered that question pretty well.

All right. Louis Jacques, there's one for you. You mentioned concerns with bias. What is your perspective on the methodological robust approaches to address bias, as mentioned by speakers earlier in the webinar?

DR. JACQUES: Okay. And I only caught some of the earlier ones, because I actually have a day job, and I had to go in.

DR. ORSINI: Oh, okay, well, do your best.

DR. JACQUES: Yeah. I mean, I think there are concerns around it, and I think there are concerns around motivations for bias, because from a payor point of view, as I alluded to earlier, what we tend to see is a trial that failed its primary outcome, and then essentially trying to data dredge. And I think that the motivation to just, to find some way to rescue this thing can sometimes lead to, shall we say, shortcuts in thinking.

To the extent that we ascertain some of these things through web-based surveys, e-surveys, things along those lines, I know from experience with older relatives, you give them a survey, they're going to give you their Social Security Number. Okay. And there are some who simply are not capable of using some of these remote instruments. And I know that because I'm related to some of these people. So, if we don't include them, and these people tend to be -- have multiple comorbidities, we're basing our preferences essentially on a selection bias that has excluded them.

Same things with cognitive impairment. There's a whole lot of interest, both on the drug side and the device side, around things for dementia. Well, how do you actually best ascertain patient preference in a demented or cognitively impaired patient? Are you going to see the translated preferences of a very burdened caregiving family instead?

You know, when I practiced palliative medicine, I would see times where the patient's goals were diametrically opposed to the family's goals. And many times for the patients, because this was in an oncology setting, the patient would say, "I've done enough. If I'd known it was going to be like this, I would not have gone down this path in the first place." But the families, for various reasons that I could speculate on but I won't, were absolutely opposed to doing the things that the patient wanted, which was, "I want to go home," you know? So, I think especially when we look at vulnerable populations, you know, I think we have to be very careful about what we're actually finding.

DR. ORSINI: Ravi, do you --

MS. WEST: So I'd like to just --

DR. ORSINI: Oh, go ahead --

MS. WEST: I just want to add onto that, because I think in some ways, our group is here representing the patient perspective on this. And I think one of the things, though, that we need to encourage ourselves to think about is that if we really are collecting this patient preference information early and often, and we are in regular discussion with FDA, and then the payors, we actually will develop better products.

And even as mentioned around, the challenges around getting out to patients and making sure that they can even complete these very complex surveys, I think one of the case examples that came up earlier, which was obviously in our community, was NxStage was going after a technology advancement to get a label extension, and they were ultimately able to use a patient preference survey because they identified a subset of

patients that would be willing.

So, I think we have to think broad. I think we have to think about being inclusive in the getting -- you know, really developing these surveys on as, you know, a sixth-grade reading level, so people have the opportunity to enter and complete them if they can try. But I think ultimately, you will find that there will be not only the subset on the one extreme that says, "Yeah, this fits for me. I can complete it. I know what I'm getting into," but you will start to build this community of folks who now understand what it means to even get into these kinds of conversations.

And it's going to take the physicians, who have to come along with that.

DR. ORSINI: Yeah.

MS. WEST: And they really have to be a part of this so that these surveys are even presented in a way that, for an individual at a lower reading level or disparate communities or can't see very well, or trying to do this on a mobile phone, you know? They're going to take the right presentation from the physicians to at least try it if we really are going to try to develop better products for patients.

DR. ORSINI: Um-hum. Yeah.

Ravi, I don't know if you'd have any insight into that given that you deal directly with actual patients, you know, or trying to get this information?

DR. JAYADEVAPPA: Yeah. Like, the one thing is it always adds knowing the patient's preference. I know there are, like, bias due to some of the blind patients, the -- patients, as well as those who are with demented patients. But still add to that, we may not have the instruments or the tool right now to help incorporate those biases, but still, we can aim to limit it and also try to involve caregivers. And it is important for caregivers to understand what the patient's likes and dislikes are, what their preferences, what are their -- the attributes. At least to know and respect that is very important. Now, you don't have to

agree with them. At least you should respect their preferences by integrating them, as well as their caregiver's and the physician's.

So I think it's a complex process for some populations that's been discussed here, but we are almost there in getting that integrated.

DR. ORSINI: Yeah. I agree. I think we can't discount the caregiver. I think, you know, Louis, your point is a good one, you know? Who is filling this out? If the patient themselves can't see on their phone or if the doctor has to translate something -- now, I don't mean, like, you know, linguistically, but you know, a concept, and making sure that the patient can understand it without the doctor having to necessarily to put their own bias in the middle of it to try to explain it. That's going to be tough.

DR. JACQUES: Yeah, and I think there's a lot of technical information that we can't expect the patient to have, because, frankly, many physicians don't have it. If we tell someone these are equivalent therapies, and one is IV, one is subcutaneous, one is inpatient, one is outpatient, those data are likely derived from noninferiority studies. And they probably aren't exactly the same. It depends on the inferiority margin. It depends on a whole lot of things.

So is the complete conversation with the patient -- these things are statistically interchangeable, but there is a difference in their point estimates. Because if you look at how to -- cancer therapies, they will, they will push very far for even a very small absolute number of differences in effectiveness. So, if one has a noninferiority margin of 10%, well, for truth in advertising, somehow we need to convey that concept to the patient. And I'm not sure how do we do it if you haven't run a superiority trial.

DR. ORSINI: Well, even the concept of risk or the difference, relative, you know, differences is hard to understand, even for people who are deeply involved in the actual conduct of some of these studies sometimes. So for patients, it'll be even harder, and their

caregivers.

I think we might have another question here we should try to get in. And this is for everybody. Are patient preference studies different when used for FDA or for CMS or payor purposes? Are they used in the MEDCAC meetings? Or how are they received by other academics? So that's kind of a mixed question. But I guess let's start with regulatory versus payor coverage decisions. Is that the same study? Is there something different that needs to be done?

DR. JACQUES: I think the reality is that they will be the same study.

DR. ORSINI: Right.

DR. JACQUES: And from a regulatory point of view, I think the conversation between the sponsor is more if I do a PPI informed study, because you're still doing a clinical trial, you're not exploring PPI, you presumably have used PPI data from whatever source to say, "These are my primary outcomes that I'm prespecifying." So, with FDA, there's more likely to be a conversation of will that be permitted or not. And if FDA says no, I think it would be a crazy sponsor who would say, “well, the heck with that, we're going to do it this way anyway.”

I think on the payor side, what's more likely to happen is that these studies are simply going to land in their laps. And aside from IDE studies, where CMS may have had -- have a conversation with the sponsor, it's going to be whatever evidence is out there of varying levels of quality and relevance is simply what you're going to have to sift through.

DR. ORSINI: Um-hum. Yeah.

Does anyone else want to comment?

(No response.)

DR. ORSINI: No? Yeah, I mean, I think -- go ahead, Dean. It looks like you're coming off mute.

MR. BRUHN-DING: Yeah. You know, I think Louis hit it right on the head, you know? From a regulatory perspective, you're going to -- the sponsor will try and work that back and forth with FDA with regard to how are you going to do your clinical trial, what are the important, you know, endpoints, and if the patient preference study informs us and FDA as to what those metrics should be. And we agree, then, you go forward. I think with CMS, I know from our company perspective, we have tried to involve CMS early on in the process. I think there's some advantages to doing that. However, I think FDA tends to drive the study with regard to, you know, the endpoints and what's going to be agreed to. And I do agree with Louis. A lot of times CMS gets the results, and it gets placed in front of them.

DR. ORSINI: Um-hum. Yeah. It's probably -- there's not a lot of reason to go back and redo a patient preference study in a product you've already sort of developed in a certain dataset, I would imagine, you know, because the data is what they are unless you find something different or some aspect that you might not have thought about to get more patient perspectives on.

So let me ask this question. You know, should we be doing these studies on just about every product to understand how to drive the actual outcome, you know, definitions and what will be important to patients? Are there reason to not do these types of studies? Or should we always be doing them? I don't know. That's an interesting question.

MS. WEST: The one thing that I'll bring back around is the value of precompetitive collaboration. And I think that, you know, wherever possible that sponsors can come together and can sit around a class of products and to be thinking through what information they don't have and how could a patient preference survey complement instead of supplement that information -- and again, thinking through even the other data points -- I think that would be the perfect place where you would start to engage your payors, like, as well. So, again, they don't end up with it landing on their lap, but that they have the

opportunity to influence.

You know, there's going to be a place where the survey instrument will only be so valuable, because they're going to be testing doing that qualitative work around that survey instrument within, again, in the kind of the place where we are, without a true product behind it, that don't have the class to be thinking about. But then it becomes a way that all of the sponsor could then come behind it and make it very specific to their product and be able to tradeoffs.

You know, again, I think we're talking in the hypothetical, in the ideal, and recognizing that that's not always the case. But I will kind of say that I think there is some value for that precompetitive collaboration that might be especially probably at that payor intersection, as well, which you're translating all the way through from FDA into commercial payment.

DR. ORSINI: Yeah.

DR. JACQUES: And I think some of that's been done. If you look at recent MEDCACs, CMS has not necessarily done them to get advise on should we cover this or not. It has been things like "what are the desirable outcomes in clinical studies of heart failure," the desirable outcomes in clinical studies of lower extremity arterial disease, lower extremity venous disease, et cetera.

And those actually have been opportunities for KOLs to actually engage publicly with CMS and try to get some consistency of thought, because one of the more frustrating things from a payor point of view if you've got seven trials and used seven different outcomes. And they were assessed in different ways. You have questions about whether the metric was validated in one, whether it was something else in something else, and you have a body of evidence. You have seven silos and if there were agreement on looking at those outcomes that reflect the patient's experience of the disease and the patient's experience

of the treatment, frankly, CMS would fall over in delirious joy.

DR. ORSINI: I'd like to see that.

DR. JACQUES: Here I'll -- even though I don't work there anymore.

MR. BRUHN-DING: You know, Lucinda, I'd like to just, you know, comment on what Melissa said. I think the precompetitive space is difficult for companies to get involved with, you know? There's issues of antitrust and collusion and price fixing, and things like that that you have to be sensitive to. It was interesting to be able to go to MDIC under a safe environment and be able to do that so that the issue will be can we create, you know, entities such as MDIC or does MDIC have the capacity to do more of these disease-type studies that could be beneficial across the entire medical device base? You know, that's yet to be seen, because, you know, again, there are unfortunately legal issues that we have to be really careful of when you're dealing with precompetitive space with companies that are competitors in a certain area. And I know AdvaMed, MDIC afford the luxury to do some of those joint-type projects, and it's important if we have key disease states to maybe approach to those kind of organizations to see if there's an appetite to do them.

DR. ORSINI: Excellent.

So we have another question that just came in. Is there a way to seek payor feedback during design of patient preference information studies? And I mean, we're doing it for regulators. We probably should be doing it with the payors, as well.

DR. JACQUES: The answer for Medicare is yes. The answer for commercial payors is we're not sure.

DR. ORSINI: Um-hum.

DR. JACQUES: Many, many years ago, FDA launched, sort of, a commercial payor task force that included a fair number of, sort of, the big names that one usually thinks of either among the commercial payors or in healthcare technology. And what's been a

challenge there is that despite multiple requests, I have yet to actually see a product meeting like a lessons learned, do it at a panel and all the various meetings, or something like that.

And I think when you're dealing with three secretive bodies, you have commercial payors who obviously want to keep their secrets, sponsors who want to keep their secrets, and FDA, who doesn't want to say anything to anybody because it's all privileged information. You are not going to get much in the way of lessons learned.

In general -- and I do a lot of commercial payor work -- commercial payors don't see it as their problem to spend their time telling you how to do your job. You know, that's just the way it is. CMS is more than happy to talk to you. CMS has historically suggested that people even come to CMS before they go to FDA, because there are some issues that actually trump FDA, like scope of benefit issues. You can be a wonderful product, but if you don't stick within the legal scope of the Medicare benefit, there's not a darn thing Medicare can do. If you fit in the scope of benefit, but you fit in a bundle, okay, what's going to happen to you?

I mean, I suspect some of the people on the call remember FDA's ESRD challenge from quite a few years ago. And we had a joint meeting, FDA, CMS, and three sponsors. And what the questions from the CMS payment physicians was: "Well, Medicare pays for renal care in two big buckets. You're either dialysis or you're a transplant. So, if you're an artificial kidney, are you a transplant or are you dialysis? Because that's going to dictate what bucket you fit in." And for certain sponsors, knowing that they're not going to be able to separately bill for something because it is bundled, is a very important input into their financial calculations as to how they go forward.

So CMS is more than happy to talk to you about it. Commercial payors, you know, good luck if they want to talk to you.

DR. ORSINI: Yeah.

Dean, were you the one that might have had some experience outside the U.S. with some of the other assessors? I don't know if you've had any experience trying to get any feedback from them. I know we're U.S.-based here, but --

MR. BRUHN-DING: We're U.S.-based. We have not really had any, you know, feedback on patient preference studies from the international folks.

DR. ORSINI: Okay.

MR. BRUHN-DING: But I will tell you this, just based on my discussions with international people. The Europeans, especially the Class III-type devices, which are devices, they are aware of patient preference, and they are interested in it. And it probably will have a bigger impact on the health technology assessment side of the business, not so much on the regulatory, the notified body, aspects.

DR. ORSINI: Okay. Great. All right. So I think we have 3 minutes left. Does anyone -- just want to go around the electronic room here -- want any last thoughts or feedback from the day?

So, Melissa, maybe I'll start with you.

MS. WEST: Yeah. This has been a great discussion. I've been thinking about my response to Louis's last comments around the value of payors being included earlier. I'm still going to advocate that they need to come to the table. They need to be there whether they want to say publicly or secretively what they're working for out of these patient preference surveys. I think it's our job to pull them kind of out of the woodwork and extract as much information as we can.

I think overall the day has been fantastic. I think, you know, working through kind of the case studies and the methodology and really thinking through, you know, I think we're all challenged with the same thing, which these are very complicated, complex, sort of you

know, pieces of information that we're trying to get from patients and trying to figure out the utility. So the more that we can work together and share kind of lessons learned and think through, you know, the value of all of the different stages of development I think becomes truly powerful in translating what worked in one space into another one. So really appreciate the forum and the opportunity to participate.

DR. ORSINI: All right. Thanks, Melissa.

Ravi, do you want to just quickly have any last words?

DR. JAYADEVAPPA: Yeah. A couple of important things is one thing we, kind of, demonstrated from a large randomized controlled trial is integrating patient preferences and shared decision-making environment. Always include satisfaction with care and satisfaction with the physician, as well as it tailors the patient's preferred treatment.

And that's important message, I think, so that kind of work for regulatory as well as payors. So here we go, like, if we -- if you integrate your treatment choice with the patient preferences, I believe you always improve the satisfaction with care and satisfaction with the decision. And one important aspect here, we learned, is like there is an educational component from the physician point of view. They need to, kind of like create how to integrate the patient preference, respect the patient preference in the decision-making environment, and that is very, very important.

DR. ORSINI: Great. Thanks for that, Ravi.

Louis, you want to -- last words today?

DR. JACQUES: I think, philosophically, it's a good place to go. I think the challenge is going to be practically how you do it in a manner that keeps everybody, you know, sort of aimed in the same direction. But I think, ultimately, it's a good thing. Much rather see these than, you know, 30-day procedural success outcomes.

DR. ORSINI: All right. Thanks for that.

And Dean, you get the last word.

MR. BRUHN-DING: Perfect. I think from an industry perspective, today was really good. There were several examples of how patient preference studies could be used. I think it's going to be critical that there are published, public examples that come in the public domain of how patient preference influenced clinical trial design, how were patient preference studies used by FDA in the regulatory review of at least PMAs, possibly 510(k)s or De Novos, and what goes into the labeling, either the physician instructions for use and/or the patient labeling, I think is important, too.

And then, lastly, we've had a lot of discussion on reimbursement. I think the impact on CMS and the private payors, ultimately, that is a good place to go also. It'd be nice to see good, positive examples for patient preference information used in all three of those areas.

DR. ORSINI: Great.

Thank you all to the panel here today, and well, that's our last panel. There's still a wrap-up from Michelle Tarver, so I'm going to hand that right over to her now. Thanks, everyone.

DR. TARVER: Thank you for that. It's been a wonderful day, and we really do appreciate everyone sticking in and holding on to the end of the day.

We heard today from many stakeholders about the importance of the patient's perspective across the total product lifecycle. We've heard that it's not just domestically a focus, but also internationally. And that patient preference information is just one approach that we can weigh in the patient's perspective across the total product lifecycle of medical devices. But it's research. It requires expertise, thoughtful content and construct, and that it is, when it's well done, evidence that can be used in regulatory decision-making.

We also heard that it's voluntary. It's not a required part of any of our regulatory

evaluations. But there are opportunities for us to use this technique to inform many different aspects of not only medical device development and evaluation, but also for us to look at beyond the regulatory context to the clinical care paradigms, as well as the payors.

The ways in which we saw that it could be potentially impactful on a regulatory context were to inform the device development pipeline, may help set performance targets, and may inform the benefit-risk decision-making. You heard at the very beginning of our day that this was a novel method about a decade ago. But from the multiple examples you've heard, there is a lot of rich information that's been generated over that decade that has increased our confidence in this type of information and our ways in which we can use it.

But I would suggest to you that there's new opportunities we have. We heard that there are new settings in which it could be used, particularly in early feasibility studies or breakthrough devices, or De Novo submissions for medical devices. It may help us to understand what sample sizes may be useful for a pivotal clinical trial. It may be an opportunity for us to look at other methods besides the ones that we have typically seen in our submissions. There's the opportunity for us to explore how we can crosswalk patient-reported outcomes that are typically measured in our clinical studies to patient preference studies' attributes.

We have posted on our website a priority patient preference-sensitive list of areas that we think patient preference information could be most impactful. We do encourage everyone to take a look at it and see if there are areas that align with your development pipeline and provide an opportunity for us all to learn from one another and ways in which patient preference information can be brought to bear.

We also heard that there are many other types of information that we see in the submissions for a medical device, and all of this is complementary. We should not be

looking at an "either' or an "or," but instead, an "and" paradigm for patient preference information.

We heard about ways in which it can be useful in an analytic framework and as a shared decision-making tool. But most importantly, I think the message that rang loud and clear is the importance of us collaborating, working together as a community to advance the science, the methods, and the applications of patient preference information.

Collaborative communities, as you may be aware, is one of our strategic priorities. And we heard time and time again how impactful the precompetitive space can be to really evolve and attack shared challenges and create solutions that resonate within all people within the stakeholder communities.

I want to really thank my ISPOR colleagues and our FDA staff that have worked really hard to put this meeting together. In particular, I want to call out Amy Pavlock and Christina Webber, who did a fantastic job keeping us all in line, on topic, and efficient over the course of this day.

I encourage us as we move forward from today to not only consider patient preference information, but also consider robust patient-reported outcome measures. We have a workshop tomorrow, and we hope you will join us, that will be talking about patient-reported outcome measures and the ways in which they can impact the regulatory contexts across multiple devices types, disease types, and using different approaches to create a least-burdensome and efficient way of developing these tools, as well as ways that we can integrate them into other platforms.

We are all working together to work beyond the regulatory context to the point of care so that our patients and our providers can make the best choices to protect and promote public health. Thank you all for joining us today. Good day and good night.

(Whereupon, at 4:36 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:

VIRTUAL ISPOR FDA SUMMIT

USING PATIENT PREFERENCE INFORMATION IN MEDICAL DEVICE REGULATORY DECISIONS:

BENEFIT-RISK AND BEYOND

September 29, 2020

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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.

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TOM BOWMAN

Official Reporter