



PDUFA V Clinical Outcomes
Assessment
Development and Implementation:
Opportunities and Challenges
Public Workshop
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Campus

Meeting Transcript

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Welcome Remarks and Introduction

- **PDUFA V context and goals of the meeting**
- **Overview of background package, expectations of meeting**

Elektra Papadopoulos: Good morning. I'd first like to introduce Dr. Janet Woodcock. Dr. Woodcock is the Director for the Center Drug Evaluation and Research in the FDA. She is a rheumatologist and has held numerous positions at FDA. But I think most of all she has really shown tremendous creativity and resolve in finding new and efficient pathways in drug development. So without further ado.

Janet Woodcock: Thanks very much Elektra and good morning everyone. I'm really glad, sounds like an enthusiastic crowd over here. I'd like to welcome the speakers, the FDA participants, our NIH colleagues, the patient advocates who are here, the industry representatives, consortium members and academics. And I think it shows it really takes a village to get this done. But welcome to the workshop on Clinical Outcome Assessments. Our co-chairs are going to go into detail into the background of the meeting and what we're planning to accomplish today. But I'd like to provide the big picture of how that fits into the overall concept of what we call Patient Focused Drug Development. Something we've been trying and I think Elektra has alluded kind of moved towards say in the last five years.

Now almost everyone has experience of being sick and being a patient often. And many people have sought help from healthcare professionals. And if you are sick enough, whether your illness is acute or chronic, you'd welcome some medicine to relieve your symptoms to help you continue with your daily life and maybe even cure what's wrong with you. And that, those things along with extending life, that's the purpose of medicine. Really, it is to help people. And at FDA, we codify this in our typical lingo by saying, clinical benefits, which basically, by which we mean something that benefits a person who has a medical illness, means improving how people feel, function or survive. And that has always been FDA's mantra, that medicine should do one of those things. While measuring improves survival it is by no means straight forward but you can do it. How do we determine if a person feels or functions better? We want to improve how they feel, function or survive but how do we determine if the medicine makes them feel or function better?

Well the many ways of doing this has been developed over the years. Of course we approve a lot of symptomatic therapies so obviously we found ways to measure how medicine improves symptoms. And these have led to many successful drug development programs. However in many cases, a lot of assumptions have been made. We really can do better. Many of the outcome measures we've used over the years have become homegrown, that

doesn't mean there's anything wrong with them. But it isn't really clear how it relates to the actual experience of the patient. And my favorite one as a rheumatologist has always been the physician global. If that was an outcome measure, it would be how does the doctor feel about how the patient feels? That was actually used as one of the measures to approving drugs for Rheumatoid Arthritis and to some extent and composite still is. Really that's as they say several degrees removed I think from the actual patient experience.

We would like measures that measure the authentic way people feel. Many of the assumptions were, that this test or that test or this scale or that scale would really reflect the authentic experience. There was little, I think, rigorous or structured attention to factors like, how do different people experience the disease? We always think, well it's a disease and it has this course. That what you were taught in medical school, so everybody who has the disease has exactly this, but of course, that isn't at all true. What are the main symptoms that people would like to have alleviated? What is really bothering them about their disease? And it turns out sometimes this is radically different from what's bothering their doctor. That may be very important like this decline in kidney function, but many of the other things, it's really important to figure out what the patient wants to have alleviated.

This one has always been really hard to measure. How's daily function impaired by the disease, and then conversely, how is function improved by an intervention? What is impact of current medication on the patient from the patient's point of view? Sometimes the treating physicians may love this medicine, but it makes the person miserable and it actually doesn't improve how they feel or function. We want to know what is the impact for current medication for good or for ill or if we're going to try to develop better medications? It's clear you have to start with an understanding of the impact of the disease on the people who have it. Also, what they would value most in terms of alleviation before you set up a measurement as we go into the future to be truly patient focused. You should be sure to capture both the range of problems and the range of preferences of people since no one is exactly like nor do they experience the disease identically. There are several dimensions of this, both the personal and the disease dimension.

Under the fifth iteration of the prescription drug user fee program, which we call PDUFA V affectionately, we've been holding patient focus drug development meetings which many of you know about. We had an agreement with the pharmaceutical industry that they would fund us to hold up to twenty such meetings during the five year period. We wanted to explore these factors in the needs of patients. What this has revealed, I think, is that patients are true experts in their disease, people with chronic illness in particular. Obviously one of us had chicken pox. You can get it and it goes away, you don't get it any more fortunately. Or you get herpes which could be a side effect of having chicken pox. That's the first time you've had it, and so you're not an expert. People with chronic disease, people who are living with disease, they really are experts. We've learned a tremendous amount about the range of patient experiences from these meetings, and we published the Voice of Patient follow up, however we recognize that that doesn't get us to a measurement. We need a formal and structured way to collect patient input and patient experiences and patient preferences. That's what I call the front end is understanding the patient experience of the disease but understanding it in a very structured manner.

On the other end, the back end, you might say, of drug development, if patients are the front end, then we have been implementing a structured benefit-risk framework when we review applications. That's when all of the trials are done, all of the measures are measured and everything, all of the statistics are run, and then we're looking at that. We're trying to have a short summary where we've talked about the benefits experienced and the harms because there's always some trade off with medicines, in a very structured way that we can then publish. In this framework we very deliberately construct it to be able to incorporate that structured patient input at the front end of that benefit-risk framework at the front, because really assessing the benefits and harms of drugs should incorporate the patient point of view. A pilot of this is ongoing, and we are going to roll this out to a larger scale. Hopefully this will lead to a very accessible summary of the benefits and the potential harms of the medicines that are newly approved so that people have some idea. Without that front end of understanding what patients prefer and what is bothering them, we don't really have a deep understanding.

Those are the two ends of the spectrum, the disease experience on one end and then the assessment of the development program and trials on the other end. In the middle of the process is really collecting the patient experience during the trials of the drug. That is really a clinical outcome assessment, and that's really the primary subject of this meeting. We need to understand patient experience with disease now, and we need to understand in a structured way how people are experiencing the medicine, experimental or investigational medicine that they're receiving for good and for ill, and then do a structured benefit-risk assessment of the results of that drug development program.

These part in the middle where you're collecting information about the impact of medicine on the disease really needs, again, to be valid the way the information is collected and ideally reflect the range of patient experiences with the disease. That I think is where we've fallen down most with our various indices in the past. We may remain focused on different aspects of the disease that are medically important or that the physician community has felt defined the disease and not really looked from the patient point of view. I know that the PRO consortium they are doing some things on multiple sclerosis, and I went to that meeting. Many of those patients there, some of whom were physicians said the information that's gathered in those trials don't really inform us as a patient about what to expect about whether this is really going to help the things I care about in a year or two.

For many of these medicines, that have significant harms associated with them, people really want to know the experiences of other patients and what they can expect when they take the medicines. This is a non-trivial exercise to collect this information in a valid, reproducible manner. You have to know the first part, you have to know what bothers people how the disease is affecting people from their point of view. People want to know the experiences of other people who took the drug. If you put all these things together, patient-focused meetings and weaving that into a way that we can collect valid and structured information for the patient about what I call the burden of their disease, how does the disease make them feel bad, how does it impact their functioning and so forth. And then in the trials, collect structured and valid information about how it's relieving that

burden. Also, of course, in the trials we collect information on the harms of the drug so that we can understand the balance.

I think if we do these things and then we do a structured benefit risk assessment at the end, our medical reviewers do that so that all that is laid out very clearly for everyone, I think if we can achieve that, we really will have patient focused drug development. The information that comes out of the drug development program can be directly relevant to a person with that disease who's considering taking the medicine. Really, that's what we're trying to achieve here.

Thank you all for attending. I think this is a very action-packed day, a lot of things to discuss here. I think they all, that's the big picture of where we're trying to get with this. I know that some people are discouraged and they feel that this is really hard and so forth and et cetera. Remember who we're doing this for, we're doing this for the patients. We're trying to make sure they have information they need to make choices about whether or not to take the medicine. Thank you very much.

Theresa Mullin: My job in the next few minutes is to give you a little bit of context, the historic context of PDUFA V for this meeting and briefly about the goals and then turn it over to Elektra to go into more detail on what we're going to be covering today. I have to say, when we were planning this meeting, I was impressed by how many people we have speaking on these panels. You probably want to speak, too, if you're not on the panels, so I'm going to try to make this quick because I think we have a lot of things to talk about today. Let me get the clicker to work if I can.

This PRO commitment is what is in the commitment letter if you've ever taken a look at, gone to the website or you've Googled PDUFA V commitments, it comes right up for you. This is one of a number of efforts that are listed here that were part of an agreement in a package that FDA had put together in discussions with industry and with extensive consultation with patients and other stakeholders throughout the process, a set of things meant to enhance our drug review process and to enhance and support drug development. One of these initiatives, the one listed at the top, was to do with adding more communication and interaction responses during drug and review. This was focused on new molecular entities and BLAs. That's really a review process.

The next set of things you see here is really about what we were calling regulatory science for expediting drug development. As you can see, there a number of initiatives here. One is communications; more communications early on, supportive communications with the sponsor during drug development methods for meta-analysis, biomarker pharmacogenomics support and expansion of our capacity to do our reviews there, and use of Patient Reported Outcomes was what we called out as part of this set of commitments we've also programmed to really help focus on and encourage our review around development of drugs for rare diseases. I'm also highlighting benefit-risk assessment.

As Dr. Woodcock mentioned here, there's some connection between these efforts, the PRO work, which we've expanded to really refer to the whole basket of Clinical Outcome

Assessment tools and its connection. I'll talk a little bit about that benefit-risk. Also, we had some enhancements of our post-market safety efforts as well, as you can see there. What we were really trying to do with this initiative related to PROs in the context of PDUFA V? We noted, and this is the problem that we were trying to address, that study endpoints that were really focusing on the patient experience were increasingly important, but they really required rigorous evaluation and there was a pretty high failure rate with sponsors including these instruments. Yet they weren't really that vetted before they went into phase three. How can we really avoid having that happen? How can we avoid phase three failures? By a really earlier consultation seemed to be the way to go and a more predictable sort of criteria in what do sponsors need to do? We were hearing that they wanted to reduce the uncertainty about what they need to do.

The themes our enhancements under PDUFA V were first of all to just increase our capacity. If you work in this field, there is a rather limited number of people who actually have the training to do this kind of statistical, psychometric sort of work as a specialty. Building that out was one of the things we are trying to do and in addition to hold this public meeting to really talk about our current qualification standards in the context of drug development for clinical outcome assessment tools. I'll talk about it in context of new measurement theory and what we want and expect there and just the implications from multinational trials.

This, as it happens, just fits very nicely to the agenda that you have for today. It just happens to fit the agenda. We added on the end of that, this sort of other item, which is what did we learn from patient-focused drug development at those meetings? We're halfway through those meetings, and so we'll talk about that more at the end of the day. We want to connect these things for you as well. Just briefly on that PDUFA commitment, as part of the benefit-risk assessment item, we recognized in that, that the patient experience with therapy was rather critical and unique and, perhaps most important, perspective because they both need the drug, will benefit from it, and will if there's any harm to the experience. We haven't really very many mechanisms to collect this kind of information.

We have a patient representative program where we involve patients in decision makings around a particular product, but because it's a particular matter, ethic rules require that there be a fairly extensive amount of conflict of interest screening for those folks. Also, we can't always find somebody who's actually got the disease. They have one perspective on the disease. You can see where there's a limitation. We wanted to open it up and get a much broader input into what it's like to live with this disease, as Dr. Woodcock was saying. We knew there's a range of experience. This twenty meetings or so, we're going to do more than twenty in the five years, is giving us a way to learn about that, get more insight about what patients are experiencing, so we have ideas that we'll talk about later today.

And finally, this slide is meant to help provide a context for how we see these initiatives fitting together. This is the benefit-risk assessment framework that Dr. Woodcock was referring to, and this is the framework that we're now beginning to use as part of the review process and as she says happens at the end. To give you a sense of how these two initiatives as currently constructed fit into this, this is what this is trying to do. You can see that there

are five dimensions to our assessment. There's an analysis of this condition, which is about how severe is this condition? What is the impact on the patient? Current treatment option gives you a sense of the unmet medical need. What therapies are available today? How well do they work at treating what matters most to the patient? What is the evidence of benefit? What is the evidence of what risk safety data we have to understand the harms that may be caused by this therapy? How can we, if we can, manage those risks so that the benefits outweigh the risks?

Those are our five dimensions. The first two are explicitly addressed in that patient-focused drug development discussion we have all day. Only the patients get to talk, and they talk about what it's like to live with the disease and what are they doing to treat it today and how well is that working. You can see, that really helps bring the clinical context, it helps reviewers understand, and it really it helps frame benefit-risk assessment for them. The COA work in PROs really would inform benefit when you collect it during trials and maybe even serve as endpoints that we could use as a basis for approval. One of the things we're trying to look at now is how can we bridge and go from that initial input trying to turn that into, translating that into maybe measures that could be used in studies and thus go from being patient-focused drug development input and advance it and collect it systematically so it could serve to support the benefit assessment. With that framing, I'll turn it over to Elektra. She's going to tell you more about what's going to happen for the rest of the day. Thank you.

Elektra Papadopoulos: Thank you Theresa. I'd like to thank you all again for coming. I think the fact that everyone is here really speaks to the importance of this topic. I'd like to first step back and talk a little bit about the background of today's meeting and its purpose. Leading up to the meeting today were a series of two Brookings Institute meetings, workshops. And these were multi stakeholder workshops aimed to gather information and discuss where we can improve the use of Clinical Outcome Assessment to really capture the patient's voice. As part of this we discussed various topics ranging from communication to scientific standards for Clinical Outcome Assessment and how we can more consistently apply these standards as an agency. I'd like to just allude to some of the points that Dr. Woodcock has already made. Really there are many considerations for Clinical Outcome Assessment that are specific to their use in clinical trials that are unique and may not be applicable equally across other uses in Clinical Outcome Assessment such as use in clinical practices, epidemiology and so on and so forth. These considerations really are targeted to clarity of the concept that we are trying to measure and the rigorous assessment of that concept so that we can detect treatment benefits in clinical trials. And subsequently label both benefits and communicate them in a way that is accurate and not false or misleading.

The 2009 FDA guidance for industry on Patient Reported Outcome is intended to help guide the FDA and industry on how do we review these Clinical PRO's specifically, and many of these principles can be applicable to other types of Clinical Outcomes. And so today we really here to have an open and honest discussion of some of the challenges and opportunities that we face with both the development and implementation of Clinical Outcome Assessment including Patient Reported Outcomes. And we are committed to

working with all stakeholders to overcoming these challenges. So your perspective here today will be carried forward in shaping our activities in the future with regards to implementation of COA's and patient focused drug development. So in the first sessions we will be discussing the evidentiary standards described in the PRO guidance and how they might be applied with greater consistency and we'll be discussing communication between agencies and drug developers as well as instrument developers; what is working well and where we need to be and where we need improvement.

Also in session 1 we will introduce what we call the Clinical Outcomes Initiative and this is a proposed approach to promote scientifically sound Clinical Outcome Assessment development and the advancement of science and policy. We will also discuss the creation of a proposed online resource called a compendium of Clinical Outcome Assessment which will include previously labeled tools which we feel are, continue to be potentially acceptable for future drug development. And these are not necessarily qualified tools but might be considered and in addition the compendium will include qualified tool. This will also really increase transparency and be useful as a communication tool and hopefully reduce some of the regulatory uncertainties faced by companies hoping to develop new drugs.

We'll then transition into session two where we will take a deeper look at the proposed compendium and we really hope to elicit your input, on both the limitation and utility of the compendium as well as its content and how it can best be implemented as a communication tool.

Then in session three we'll obtain at multiple stakeholder perspectives on the challenges and opportunities related to the COA's and how we can draft these challenges in multinational clinical trials and how we can better harmonize with our international regulatory colleagues. And then as Theresa alluded to in the fourth and final session we'll hear perspectives, again multi stakeholder's perspectives on bridging the gap between patient engagement and patient focused Outcome Measurement in clinical trials.

So at this point I'd like to thank my colleagues on the study endpoints team for making this meeting possible and I'd especially like to acknowledge Dr. Michelle Campbell on my team who has worked tirelessly to organize this meeting, no easy task for sure.

Finally I have a few housekeeping notes. Today we have Stephen King team for questions from the press. There will be an opportunity for open public comments towards the end of the day and if you would like to make comment during this period, please sign up, there's a signup sheet by ten twenty five or so at the registration table. And we'd like these presentations to be relatively brief on the order of about two minutes.

You will also find in your folders colored index cards that you may use these to write down questions for speakers and panelists. And then they'll be collected at the beginning of our short breaks and lunch break session.

And finally you will have in your folder an evaluation for the meeting. Please complete that and return to us at the registration table. So I would like to now transition to session one and I would be the moderator for the session. So if you could bring up the overview.

So as Janet alluded to earlier, treatment benefit is really demonstrated by evidence that a treatment has positive impact on survival or how patient feels or functions in their daily life. And this treatment benefit is then used to make risk and benefits decisions regarding a new drug.

So how do we measure treatment benefits? There are various types of Outcome Assessment. Obviously there are survivals but we also would like to know additional information about how patients are feeling and functioning these are best collected through the Clinical Outcome Assessment. In addition, there are surrogates and these are often bio markers intended to serve as substitutes for how patients feel, function or survive. This really will not be the focus of today's meeting however.

I'd like to go first do some definitions to make sure you're all on the same page. A Clinical Outcome Assessment is any assessment that may be influenced by human judgment, motivation or choices and they may support either direct or indirect evidence of treatment benefit. And there are four types of Clinical Outcome Assessment. There are those reported by the patients themselves, clinician reported, observer reported such as by a parent or caregiver and then the performance outcome measures. And these are all defined on our FDA website.

From a regulatory standpoint, what are evidentiary standards to documentary benefits? Treatment benefits must be documented by substantial evidence of efficacy and this is defined in our code of regulation. And the evidence must be obtained, from adequate and well controlled clinical trials. So as part of this definition, we need to ensure that the methods of assessment are well defined and reliable. So when is a Clinical Outcome assessment adequate for use? As we said, it needs to be well defined and reliable but what doesn't that really mean? Essentially it means that there is empiric evidence to demonstrate that the score piece by that instrument adequately quantifies a concept of interest, specifically the goal of the measure within a targeted context of use including patient population that we hope to study. So this really means we are measuring the right things in the right way in defined population so that at the end of the day we can really interpret the treatment benefit.

So I'd now like to go through a road map that we've developed to Patient Focused Outcome Measurement and clinical trials and I'd just like to step back a minute and say that when we describe patient focused outcome measurement, we don't necessarily always need to a Patient Reported Outcome Measure. What we mean by a Patient Focused Outcome Measurement is that we truly understand the things that are important to patients and then select or develop the most important type of outcome measure for that context of use.

So as Janet alluded to, really at the front end of this process, and we can see here summarized under column one, understanding the disease or condition interest, and this

involves understanding its natural history, the patient history, the patient sub populations involved, the health care environment and clinical practice patterns and importantly as we're discussing today, input from patients and care givers, on what is important to be measured. Once we understand these things, we then operationalize them by a process we call Conceptualized Treatment Benefit. This involves defining the measurable concept that we will be using to measure treatment benefits, defining the context of use that we will be using in the clinical trial and then once those are done, we can then turn to selecting the type of COA whether it is a PRO or clinician report or performance based measure. At that point, we go to selecting and developing the outcome measurement. And so we first look for existing measures for the particular purpose of interest and if we don't find an existing measure, we may need to modified measure for a particular concept of use or even develop a new measure.

So, as I alluded to the 2009 guidance for industry, defines a PRO as a measurement based on a report that comes from the patient about the state of that patient's health condition without amendment or interpretation by clinician or anyone else. While this guidance, while it describes the good measurement principles in patient outcome measures, many of these measurement principles are also applicable to other types of COA's. While it provides an optimal or ideal approach to development, we recognize that flexibility and judgment is needed to make practical demands and timelines of drug development that we face.

So a key consideration in determining adequacy of an outcome measure is establishing its content validity and this is defined as the evidence that the instrument measures the targeted concept of interest in the context of use and that the score represents that concept accurately. Content recorded by literature review, input and expert by the clinicians and instrument developers and also importantly the input from patients themselves. As I said before, it begins after confirmation that the concept of interest and context of use are appropriate and importantly measurement of other measurement properties such as test retest reliability, ability to detect change while very important, cannot replace or rectify problems with content validity.

This is a wheel of spoke diagrams, this was adopted from the PRO guidance and can be used, and again it can be applicable to other types of outcome assessment tools. We won't go into this in detail but it shows the iterative steps involved in the development or modification with Clinical Outcome Assessment, again identifying the context of use and concept of interest. Then developing the instrument and evaluating content validity prior to measurement of other measurement properties.

I'd like to now switch gears and describe the drug development tool qualification process that we have developed to help facilitate and make more efficient instrument development for use in clinical trials to support labelling claim. This really allows us to work collaboratively and provide us as an agency to instrument developers and consortium. Basically what it means to be qualified is that the instrument adequately measures the concept and context of use and we can rely on that instrument when used in the qualified context of use. I just wanted to emphasize that this is a completely voluntary process and in no way means that an instrument needs to have undergone this formal qualification process

to be adequate for use and deemed well defined and reliable. This slide emphasizes that point.

I will leave you with some helpful links to our website and guidance and again I would like to thank the Study Endpoints Team for their tremendous help in making this meeting today possible. So I'd like to now delve into session 1 and the purpose for session one is to really describe what we are doing currently to help facilitate instrument developments for use in instrument trials, what are some of the opportunities and challenges from our learnings.

Now I'd like to turn the podium to Dr. Katarina Halling and Katarina works as a PRO lead at Astra Zeneca and is also the industry co-chair to the Patient Reported Outcome. So at this point if panel one can join us in the front, and we can get started.

Session 1: Experiences with FDA Guidance on Patient-Reported Outcome Measures and the Clinical Outcome Assessment Tool

Qualification Process

- **Barriers and challenges**
- **Development of the proposed Clinical Outcomes Initiative Speaker presentations**

Katarina Halling: Thank you Elektra. Good morning everyone, I'm very excited to be here today. I will be providing a pharma perspective and a rather personal pharma perspective on the road that we've been travelling on Patient Reported Outcome in drug development. We will look at some of the challenges and perhaps better called opportunities lying ahead of us. I've had the opportunity of working with Patient Reported Outcome in drug development for a little more than twenty years and I do remember early on in my career I was together with my colleague at that point in time walking around the company knocking project doors and asking if you could please consider the patient perspective of the disease and of the treatment. We did manage to get some traction at the time and include at that point in time what was the most common type of clinical outcome assessment, health related quality of life. So we did include that in some of the trials but it was pretty hard effort for each included PRO in the trial. In 2009 the guidance was released which an important milestone as the FDA was laid the foundation for Patient Reported Outcomes in drug development and specifically in the context of getting labeling claims. However we did notice that it didn't increase the number of labelling claims rather as many of us know it slightly decreased the number. Which was a concern to pharma. In addition we noticed that the principles that were outlined and reviewed by Elektra about how the FDA will review PRO were slightly varying in their interpretation between different divisions. And it was also varying in how SEALD was brought into the discussion. And I think many of you have been in the room for a while it was not uncommon that we had the feedback, no the FDA does not agree. For more information please refer to the guidance and we have had a link to the guidance. So we're laughing at that today.

A lot of things have happened. As Elektra described, the best way to understand what's going on from a patient's perspective is actually to listen to the patient and incorporate a Clinical Outcome Assessment into our clinical trials. And I think we as a pharma industry have improved in doing that in an efficient way. Although we've had an approach from patients for a long time to include these endpoints, we see an increased push from multiple stakeholders including clinicians, regulators both in Europe and here as well as payers. So today, it is becoming more established that clinical benefits, treatment benefit is survival or through a clinical outcome assessment, how patients feel and function. As I'm looking back, I'm also pleased to notice that the type of feedback we receive today from the FDA has changed in character. It's been a while since I've been referred back to guidance and rather today I'm seeing more detailed responses to our submission packages from pharma. And I would like to see more suggestions for considerations that can be the

foundation for dialogue on how to improve the program. What that means is that we can spend more time considering how we include feedback from the FDA into our clinical programs, I'm thinking about what do they mean when they said no we don't agree. That's an important step.

The other thing I feel is important is openness between pharma and also an increased openness between pharma and the FDA. So right now we are not to the same extent competing with PRO instruments anymore; we are actually sharing. Most pharma companies and groups share and develop instruments with other interest groups, actually they are not our competitors and I find that to be a huge step forward. Although we had collaborated for a while within the PRO community, I also think we have a new type of collaboration between us now where we include multiple stakeholders. But we have also experienced that collaboration can be a little bit challenging and time consuming. For example, within the consortium, we've been criticized because there is still just one qualified instrument. Of course we need to and we are learning from what we went through and put that into the other working groups. It's critical that the timeframe for qualification will be increased.

However I think that a collaboration and dialogue between all the stakeholders that will be critical when we move into pushing the boundaries and pushing PRO's into the next level. Do I think that everything is perfect and seamless and we always get into a good dialogue with the FDA? We always get timely feedback? No not always. But I do think that we are on the right way and as I said, I do think we have created the foundation to be able to tackle the challenges and have a very good view of what the challenges are. And we also have a path forward to tackle them.

So Elektra referred to the Brookings meeting which was organized by the FDA and I do think that some of the key things that came out of those meeting were the many opportunities for us. One of the streams we were talking about was CDER review and communication process. While we would still like to push for the DDT process to be expedited, in terms of timelines and also for timely feedback to our packages, it was also a suggestion to create a new type of meeting in development to review early COA strategies. So currently there is no precedence yes we know, for the FDA to review our efficacy endpoints before end of phase to be and that is simply too late if we need to develop new COA endpoints or if we need to modify existing ones we would have to halt development of the new medicine to patients. So there was a suggestion to create a new meeting again that would be voluntary and up to the sponsor to define if and when they'd like to have it. And we do believe that will be very important meeting. In addition, there were suggestions for increased opportunities for follow up interactions with the FDA after formal discussions in order to clarify or have follow up conversations to more efficiently go back and update our clinical programs and move forward.

The second big thing is that also what Elektra is the list of acceptable clinical outcomes which I now understand is going into a Compendium and we'll hear more about that in the session two. But overall there was positive reaction to such a list where we will get clarity around some of the endpoints that have been accepted previously whether under the right circumstances and in the right context of use, those would be potentially acceptable

accessible. So lots of positive feedback for that. But also questions around how this list will be maintained and updated. And an important discussion that we will still need to push for improved endpoints for patients that might not so much be sold to the endpoints list but the optimal ones and we need to continue to push ethically for treatment benefits for patients.

The fourth stream was the identification of the fact that we do still have some outstanding methodological questions and again those were mentioned in the previous discussions. More specificity around the details in establishing content validity and the same for establishing clinically meaningful change, it's something has been raised several times. The proposal is to put together a list of these outstanding questions and then work collaboratively with the stakeholder community to take the mask off what continues to be hurdles for us in communication.

In addition there were specific methodological issues that I'm sure that Paul Kluetz will referred to in a little while. But specific consideration within oncology for the design of a trial, open label study in similar trials and also allowing to cross over, would be great if we could act together and put on a research agenda.

So in summary, I actually think that, we should continue to, we should actually feel proud that we have identified all the issues. There are still some issues in front of us, but I do think we now have foundations to move forward and actually accelerate what has been started, to collaborate, to identify and develop new Patient centered endpoints where they are critical to understand treatment benefits, to give clarity, to establish endpoints and how they will hold in upcoming programs. And also to establish the best way for us to communicate in the context of the DDT but also for individual drug development programs. Because patients are waiting for new medicines and specifically they will be wanting to know how they will be influenced in terms of how they feel and function. Thank you.

Elektra Papadopoulos: Thank you very much Katarina for a very nice overview of the issue. And these are certainly not easy issues to overcome and really require collaborative work. Now I'd like to introduce Dr. Bryce Reeve. He is an associate professor with the Department of Health policy Management at the Gillings School of Global Public Health, University of North Carolina in Chapel Hill. He received his doctorate in quantitative psychology in North Carolina and previously served for ten years as an Outcomes Researcher and Programs Director at the National Cancer Institute.

Bryce Reeve: Thank you Elektra. Thank you to the FDA for allowing me to be up here to talk to you. So good morning everybody. It's wonderful to see these faces around the room, a lot of people here I recognize and respect so it's great to have this meeting. And it's great for the FDA to bring us together to have this type of discussion so I'm thankful. So Katarina was focused on the industry perspective and my goal today is to talk more from an academic perspective. More specifically so because I've devoted most part of my career focused on the design and evaluation of patient reported outcome measures and their use in clinical research to understand the impact of the disease and treatment and how patients

survive. So as Katarina noted and Elektra noted, this guidance was released in 2009, but actually its first draft was released in 2006 and the guidance itself has done a lot to advance the field of health outcomes research. It's coined the phrase PRO, it has given us a standard definition where many in the room can probably cite in our head on the definition of a PRO. And it has set standards for the development of a PRO measure, the ideal principles or attributes of a PRO measure, the type of evidence one would need to use a PRO for drug labeling claims and standard for use in guidance for use of the PRO in clinical outcomes research.

In addition this guidance has launched many many meetings, conferences and hallway discussions about the guidance and implications in the industry and in research field. As Katarina noted, the Brookings meeting had a several series of meetings and I pull on a quote from the most recent summary which Katarina also emphasized, only one PRO instrument has been qualified by the FDA. And the PRO label claims approvals have declined since the publication of the guidance. In addition I was looking recently through the literature and I noticed a really nice commentary from Kate Rawson in this publication at the bottom of your screen there and she had noted several people from industry as well as academic settings. What they found is that the guidance and requirements within the PRO guidance are so onerous as to dissuade companies from pursuing PRO claims and for the census sponsored after to develop the perfect tools that we use for a COA assessment.

So this is one of the quotes I like and I teach my PRO methods class in my schools back in the University of North Carolina, it's from a German physicist Werner Heisenberg, it says 'that what we observe is not nature itself but nature subject to our questioning'. I think this quote is a great reminder for what we are doing in recognizing that we are never in our research when we've collected the information. No one ever captures the true outcome, the true concept of interest but with packaged outcome filtered through the measure or instrument we use. And no matter how well we design, our measure will never get a true indicator of what that concept and outcome is overall.

And so, as we all know, there is no perfect COA and this doesn't just reflect issues with PRO's in themselves but all the types of COA's from ClinROs, ObsROs, PerfROs, and cheerios that we use in our research today. And so recognizing that none of the outcome measures are perfect and we recognize that there is some type of measurement here and what we're trying to do is to review in the design and evaluation of the PRO method is to reduce that measurement error so our observed score is post reflective of what the true score actually is. Those that developed the PRO guidance obviously recognized this and they knew this and so in understanding they put forth in their guidance document a set of standards and attributes that would reflect a high quality PRO with minimal measurement of error. And many of those attributes are reflected in the PRO guidance, are reflected here, these are attributes put forth by the medical outcomes trust. In a really nice article published in 2002 and basically as we all know is that any quality instrument should be reliable, valid, able to detect changes over time, provide interpretable scores that is helpful for the key stakeholders who have to make a decision based on those scores, have reduced respondents and administrative burdens, be available for half a multiple modes of administration from paper work to electronic forms and phone interviews and to have

language translation and cultural adaptations in our multi-cultural multinational populations.

And so the challenge has been that some in industry and some in the FDA reviewers have in their evaluation and design of a PRO measure have thought that each instrument has to meet the highest rigor of quality of a PRO measure. And that the design of this measure has to be done within the context of a very specific population and for a very specific context of use. So this measure has not been designed as in the broad sense to be used in many different types of context of use but in very narrowly defined. Again in terms of context of use and its target population. And as what we've learnt over the past five to ten years as we develop these context specific, these specific PRO measures, the sponsors can face increased time, increased efforts and increased cost to sponsors themselves. So now, since the guidance has come out, in draft in 2006 and final in 2009, we have had the opportunity of time to look at the guidance, review the guidance, have discussions on the guidance and most importantly since its release, we've had the opportunity to conduct methodological research to look at our assumptions of what we think are the principles and guidelines for what a PRO measure specifically is.

For example a number of studies since this guidance release have looked at the issue of what is the optimal recall or retro sphere for PRO measures. In addition, the different modes of administration, how that impacts a person's response to questionnaires from paper to electronic and from electronic to phone interviews. In addition a number of organizations have released some significant guidance and recommendations that again has looked at the guidance and made their own recommendations filling in the blanks that were left in the PRO guidance. For example ISPOR has, if you go the website has a whole group of wonderful public patients and guidance document looking at different aspects of the PRO document there, so it's a wonderful website.

In addition the international society for quality of life research (ISOQOL) put out its own guidance document and specifically, instead of focusing on the most rigorous aspect, what we know is the most highly rigorous method there is, what would be the minimal level of documentation of evidence we would need to feel comfortable to use to measure in things like comparative effectiveness research studies. PCORI has put out its own guidance from its methods committee about use of designing PRO's and using research and then the COSMIN group as well has their consensus based standards for the selection of health measurement instrument. So we have that opportunity, again thankful for the FDA to give us this opportunity to go back and revisit the guidance, look at the recommendation and research to date and try to improve our understanding of what has changed since, what do we know now to move the field forward, how can we enhance the type of recommendation we give the industry for using the PRO for drug labeling claims.

So in my last slide, I had the opportunity to think back, I was asked last week thinking about things to enhance discussions not only today but over future meetings. I struggled with this picture, I thought my head looked like a big globe of an earth so I tried to reach the bottom up there. So these are my things I did, ideas, at least I think each person will have their own eight ideas to think about as well for their own research studying. Each of

these I recognize could take place in a whole session or perhaps an all-day discussion but these are things on my academic reflection of things I think we need to move forward on. And thinking about revisiting the guidance and enhancing our recommendation for PRO measures. And I'll try to be quick, recognizing my time is limited.

One is, it's wonderful to hear Dr. Janet Woodcock talk about patient focused drug development thing, and so I think we need to think carefully about better ways to engage patients as far as the instrument development and use a drug development process. And so this is moving the patient away from being a participant in study to be actively engaged in identifying what are the outcomes, what are the measures, how they use it in research and most importantly how to disseminate this information to different stakeholders including patients to maximize our ability to inform decision making in clinical practice, in clinical research. We learned a lot over the past five, ten years about the ideal use of electronic PRO's but we often need to be cautious not to leave out those people who have no access to technology.

Number three I think this is particularly important and again reflects where the recent trends or the past trends have been with the FDA guidance. I personally think, this is Bryce Reeve, that we need to move away from having disease focused PRO measures so a lung cancer fatigue measure, a breast cancer fatigue measure, a COPD fatigue measure as well and now transition over, can we have a really good measure of a concept or domain like fatigue with a well-defined measure and a comprehensive and very relievable measure of fatigue that can be used across disease populations? This would enhance our ability to reduce the number of plethora of fatigue measures or pain measures out there and have one good measure that could be used and be a valid representation in multiple populations. Again that would save us an amount of cost and savings.

In addition we need to reflect in our revised guidance on the use of modern measurement theory, is not so quite modern developed in the early 1900's but some refer to it as new measurement theory but has been around for quite a while and I think there's a lot we can learn from item response theory to understand the measurement properties of our instruments. It is certainly a better measure of the reliability or the air within the measure of what we have been capturing with things like cronbach's alpha or test retest reliability. It has a really nice information curve that understands that a PRO measure is not reliable for every single person. It depends on the level of the constructs you are measuring. However we also have to recognize that IRT is not the single tool to use for every single type of measure. So again, I look forward to that discussion on when it's appropriate or not appropriate to use IRT.

An extension of IRT is the new recently advances of the NIH's work to develop the PROMIS instrument, Patient Reported Outcome Measurement Information System which we will be talking about later this afternoon, is the issue of developing not just four or five items that measure fatigue, depression or anxiety but a full bank or library of items that have gone through extensive qualitative and quantitative evaluation to make sure they capture a valid, reliable measure of your outcome of interest. And so I think we need to take advantage of this library, item bank movement there because I think it is the metric or

system to make sure that whatever items reflect the patient's input of what fatigue is or pain is, we can go to our library in our item bank and pick those items and make sure we have a constant valid measure. But we also need to have recommendations and guidance for what represents a good item bank and not a good one. In addition computer adaptive testing is a natural extensive item banking testing where we can individually tailor instruments to a particular patient level on the concept being measured. So this will actually reduce respondent burdens by using adaptive testing.

The guidance only reflected the one paragraph, I think we need to have further discussion about PRO measures and what we know about its use in pediatric populations as recognized in the guidance is that, what a five or seven year old can do, is different from what an eight or ten year old can do which is different from an eleven to fifteen year old vs 16-20. So I think we need to base on our research there, to reflect more and have a full discussion of the appropriate use of, development of pediatric and PRO measures in the pediatric populations.

We also need to recognize that the importance of beyond just using patient reports as outcome measures in clinical studies as a measure of efficacy or treatment benefit, we also have to recommend what it stands for using patient reported data, safety or adverse event monitoring. Some key work by my colleague Ethan Bausch who works in adult cancer populations and I work in pediatric populations developing a patient reported systems for adverse event recording.

Number seven, I think we need a critical thought on how we present PRO data. We need to think about our stakeholder mind and how can we present this in a way to maximize our key decision making and stakeholder; the patient, clinicians, research and regulators, again to make informed decisions and help to inform what hopefully is the approval of the drug developers use, to disseminate its use downward stream in clinical care practice. In addition we need to think about standardization of PRO metrics. I think this will enhance understanding of PRO's if we are able to come together for a standard metric of reporting PRO's instead of having one instrument score for zero and twenty eight, zero and a hundred, zero and a thousand, it'd be nice to have a consensus on what the metric is in alignment our measures to the particular metrics.

And then my final recommendation to keep people like myself employed, I think it needs to be much more with methods research to go back, not just make assumptions about these principles and attributes but to conduct further research to make sure we're in a good situation to make recommendations about such things as recall periods and other things like that. So thank you very much for your time.

Elektra Papadopoulos: Thank you very much Bryce that was a great presentation. I think there we highlight that, we recognize that much work still needs to be done to find practical ways to implement PRO guidance principles in an imperfect world. Next I'd like to introduce Dr. Paul Kluetz. Paul is a board certified medical oncologist and internist who is currently serving as the acting Deputy Director of the Office of Hematology and Oncology Products, and he will discuss some of the ways that that office is employing to overcome

the many challenges that patient centered outcomes measurements in hematology and oncology.

Paul Kluetz: Thank you very much for having me. And Bryce you are not going to be out of a job for a very long time, that's my read on this. I have a very scary combination of situations going on today. I'm very tired because I worked at the hospital all weekend. It's my birthday number two. And number three I'm about to talk about something I'm very passionate about so God knows what's going to come out of my mouth. So we don't need the acronyms it's already seen that. There are a lot of acronyms, in the FDA and COA world. Before I start I want to give you a little story because I think we can kind of sometimes get into the weeds and not realize we're getting here. So I worked this weekend at Medstar Georgetown University Hospital, I do one weekend a month. I feel it's very important for regulators to be clinicians and maintain their contacts with patients, and I see cancer patients, in-patient cancer patients which are really struggling with their disease and very sick. And with the academic model for clinicians, a bunch of interns or students who run around from six to seven in the morning, then I roll in at 7.30 and they present me with what they found. If they go into the room, and they are doing a clinician outcome assessment, clinician related outcome, their interpretation of how patients feel and they present it to me. I have a young lady who has, {inaudible} and students talking to me "Yes she did fine overnight, no real complaints". Now I go there and talk to her and its dyspnea, its pain that's out of control, we need to titrate her meds, she has nausea, she vomited five times, she needs an NG tube and the difference between when I actually talk to a patient and the information I was getting from the clinicians as an outcome at the time is vastly different, why. We know it's different because there's plenty of public research on the adverse effects of oncology done by Dr. Bausch and others.

Well number one, the clinicians themselves have become not too asked, depending on the personality of the clinician, the clinician that comes in and sits down looks in the patient's eye and says how do you do, that kind of thing is going to get a totally different read than a student that comes running through and says 'you ok,? good,yeah bye.' So there's that one. Another thing is that, the clinician even when they hear something, interprets it. So if they say 'I'm nausea', he says 'did you vomit? No? I am not going to write that down' .So there's a need for Patient Reported Outcome because the translation of the clinician to the patient is there and I saw it this weekend. So this slide is just meant to say PRO or Clinician Outcome Assessment in general, is front and center and this is just in a meeting I went to last year. There's been many more and what I heard from all these meetings are a couple of things. Take home message number one; capturing a patient's perspective in drug development is a priority, all stakeholders are getting to that. The issue we'll hear and why Bryce will be in business for a long time is what to measure, how to measure it, how to interpret it, how to present it, are all very complicated and even more so in my therapeutic area of oncology.

Finally, I think looking at Katarina's talk and looking at Bryce's talk, and when you see my talk, they keep capturing very similar, we're a lot more the same than we are different when we are looking at what are challenges are and what are opportunities are. Everyone is

starting to align and at this this critical point where I think we can seriously get something going in the next couple of years.

So the feedback I heard is the feedback that Katarina mentioned; the 2009 PRO guidance. While it actually, I'm not a guidance basher by any means, I think this guidance was needed at the time because there was a lot of people doing a lot of different things and I think most of the people I've talked to say this was needed and it was done. But it is, very stringent, and it is the gold standard I suppose you could say for PRO development. That has led to a lack of instruments in oncology and especially that has been considered adequate by our colleagues and therefore difficult to get them in trials.

Second thing is inconsistency of advice and I'll get into that at length, I take that personally, I don't like that, I think that's part of our goal as regulators to provide some level of certainty. We're never going to be perfect but some level of consistency and certainty to the stakeholders that rely on these development programs.

Then finally, FDA Office of Hematology and Oncology doesn't put Patient Reported Outcomes in the label as much. That is true. And it's true for a reason and I'll show you next and I hope that will change over time as we improve some of these things. What's the issue in oncology, why is this more challenging than other therapeutic areas? Well number one, we treat patients who are very sick. As I mentioned in my anecdote about my experience in Georgetown, and further more we treat them with drugs that cause very significant toxicities including death. And therefore we take it , we're a little concerned to approve a drug e.g. new molecular entity based solely on a symptomatic improvement with no other evidence in one's narrow concept e.g. pain, with no other evidence that it is actually effective to the tumor itself because we have other drugs that will control pain in cancer patients and won't lead to very severe and potentially life threatening adverse events. So we have this tension, lots adverse events from our drugs, very sick patients. Our trial designs are very challenging for patient reported outcomes, if you have a very great drug in oncology, you're probably going to get approved in single arm trial because we want to get the applications. How do you interpret Patient Reported Outcomes in single arm trials? That is something we all need to get our heads around, that's something that's going to be a challenge. Even when our trials are randomized against a comparator, they are frequently either just open label to start with if you like blindly as in feasible or we try to blind them but because of the toxicities of the drugs, they are so obvious that everyone already knows what they are. If I get a huge rash from TKI, I'm going to know I'm on TKI if it's being compared to cytotoxic chemotherapy. The key here, I think moving forward, is this lack of standardization, lack of standardization I have seen all the way through, Instrument selection, the concept being measured, the analysis, the way data is captured, the way data is analyzed, the way the endpoints are structured, and the hierarchy , the lack of statistical testing, many many issues that are not standardized, that is something we can do.

And finally, something that I think I'm changing is a lack of familiarity with this concept whatsoever in oncology drug development and academia. There is still a lot of scientist who do clinical research that are very not sure where to go with PRO, we have a very good

endpoint in oncology; survival, and we can see our tumors. We can actually visualize our disease and that is not so in any other therapeutic areas. Psychiatry, say Irritable Bowel Syndrome primarily symptomatic therapeutic areas. They have all sorts of experience with Patient Reported Outcomes and that's the only endpoint they can measure. So taking, it's a heavy lift. If all the oncologist would choose their attitude on patient outcomes and make it an important thing. So what have I done, so you know that I'm not just chatting, I took that advice very seriously. I really don't like this idea of lack of consistency. What I've done over the last year is I've integrated Patient Reported Outcomes leads with each of our three clinical divisions. These are reviewers whose job it is to understand Patient Reported Outcomes, understand diseases in their division and to provide advice to all of viewers in that division. And when they have a question they kick it up to me who is trying to provide consistency across the entire office.

With respect to our interaction with SEALD, our colleagues who are the experts on instruments, I've created a combination of OHOP SEALD working group that started out like me actually and Elektra two years ago and now it's gotten very big and very interactive. Actually it's one of the things I look forward to each month, there's much to talk about, what's happened over the last month, what kind of meetings went well, which ones didn't etc and paths forward. And finally educating my higher office with Patient Outcomes and getting the oncologists to think about integrated a monthly case series where they talk about PRO cases at our offices where everyone is involved.

So in general my goals would detail more consistent, more proactive PRO advisory just like Katarina mentioned she has seen and others in industry who have heard about PROs have seen as well. So just graphically, you all know how we are doing this parallel thing where we give advice, they give advice, we consult them, and then we give our own advice. I don't know what was happening back then but today we are all talking together SEALD, the clinical review divisions, our PRO leads, we also have labelling, deputy directors in each of our clinical divisions that understand labelling and their implications and that's all going in this hybrid and hopefully that will improve our consistency.

As far as identifying PRO instruments, a big challenge, I'm not going to go into the entire topic as Elektra wraps the session but I will say, my perspective is in the long term we need better instruments and that's a priority. I don't want to dissuade people from developing new instruments and we've got to start looking at new streamlines so people can do that. In the short term, I really like this idea of looking at existing instruments that we can either say it seems reasonable or modified to be fit for purpose. In either of those, it's going to be iterative, we're going to use an instrument and see how it operates in a trial when we look at the data, when we keyed it, we may change it, and it may go around in a circle. I acknowledge that the PRO guidance is a gold standard for PRO development and the perfect is the enemy of good, I'm borrowing Steven's line, he stole it from someone probably. But I would also say that the bad is a friend of no one. We have seen the bad, and we continue to see the bad and we all can do better. So moving forward, I would like to see standardization of Patient Reported Outcomes in cancer clinical trials, I have identified what I think is the most proximal for a concept that is occurring and should be measured in every cancer patient in every cancer clinical trial, with a registration trial which includes

good use related symptoms, untreated related symptoms. And we know they overlap but to the extent possible keep them separate. And then a summation of the two being some kind of physical function; how is the patient doing, activities that they are living. The summation of those two things, how does that affect their function?

There's got to be a balance, and you know the purpose is going to be to very little patient data and label, lots of certainty, lots of data, we'd like to see if that is feasible but we know in many case it may not be. On the other hand I don't want the tangent going to whatever PRO data is low quality, you'd like to put in your trial is fine because as an oncologist I think it is particularly concerning if you have misleading Patient Reported Outcomes results that could screen patients and physicians to therapy for the wrong reasons.

So in conclusion, my office has been doing a lot, interacting with many of you in the audience and I'll continue to do so. I think we have to work towards standardization and I'll end on that. Thank you for your attention.

Elektra Papadopoulos: Thank you Paul that was a wonderful talk and really highlights a number of ways we can increase transparency, communication and standardization in this very challenging area of hematology and oncology. Next I'd like to present some forward thinking thoughts about what we do now and these are thoughts stemming from our communications from the Brookings institute meetings last year and I think it echoes what a number of speakers have already alluded to. First how can we work with internal and external stakeholders to show how PRO development and implementation can be operationalized in the real world to think of a number of activities, that are collaborative activities with the office of Hematology and Oncology can be used in other disease areas. We need to be more proactive and encourage the use of Patient Reported Outcomes. We need to enhance communications, processes and transparency. There we heard loud and clear that there is the need for earlier industry FDA, communication even before the submission of an initial IND. So we've taken some steps to begin to address the issue. And we also delved into how this compendium of qualified instruments and previous labeled potentially acceptable Clinical Outcome Assessment.

We need to continue to work to enhance the consistency of advice and also to forward the scientific agenda that others have alluded to. So here is a proposed approach, I think we can conceptualize and we recognize that the challenges that we face are multi-faceted and therefore we need a multi-faceted solution. So in session two, we'll be delving more into the compendium of Clinical Outcome Assessments and how we think that can be an important communication tool. But first I'd like to say a few words about the other major arm of this initiative which is to advance scientific standards and policy development.

So these are really our needs. We need to continue to work together towards operationalizing PRO guidance principles particularly across the stages of drug development. So what do we need to see early on in development versus following phase two and right through the NDA review and labelling process? We need to expand our communication and how we think about the measurement principle for the development of

other Clinical Outcome Assessments as well as patient clinician report and performance based measurement. Because all of these areas can benefit from the measurement principles, for standardization of procedures and methods really to ensure that people performing these assessments interpret the instruments in a way that is consistent and that is reflective of the intent of the measure.

We also need to work towards standards for analysis of PRO data so how do we aggregate our measurement into endpoints and consequently how are these displayed in labeling. And then there are many other items that we have identified and we are actively working with, prioritizing our efforts with the PRO consortium and other Consortium to address these. Last year we conducted a survey at the FDA clinical reviewers to try to identify areas where we can continue to improve the consistency and clarity of the study endpoint team advice. And what we found is that we do have more work to do in providing clear advice. Some of the feedback we got is there needs to be high input high level early in drug development rather than including all the detail about the instrument at the outset. So I think companies could really benefit from a clear direction rather than being inundated with a bunch of details. The other thing we've worked with clarity on, is what we think are, you know, what we think are very critical to the use of the instrument versus what we think are nice to have and recommendations. We need to provide practical advice, with the greater attention to concrete actionable advice and what the overall drug development strategy. And we also need to work on timeliness of our advice and we really have made a big push to it by expanding our team in the past year or so.

This is one example of concrete output that we have worked on. The Critical Path Innovation Meeting guidance was published as a draft and is now being finalized or already finalized and this provides an example our response to request for earlier communication. It's a completely voluntary process, can be used as a venue for discussion, for discussing potential approaches to developing Clinical Outcome Assessment and it is also used for a variety of other topics like your bio markers and natural history studies and others. While it does not represent is a substitute for regulatory meetings between FDA and industry on specific drug development programs such pre IND meetings or any phase two meeting.

So now I leave some questions to think about for panel one and we'd like to get your input on some of the key areas that we need improvement for scientific standards and improvements. Another one is how we can further improve the quality of an Outcome Assessment advice and with a focus on practicality and meeting drug development demands.

Now we have a break, enjoy and we'll come back and have a panel discussion and also can take questions from the floor at that point. Thank you.

Session 1: Experiences with FDA Guidance on Patient-Reported Outcome Measures and the Clinical Outcome Assessment Tool Qualification Process, cont.

• Panel discussion and question

Elektra Papadopolous: So we're going to start our panel discussion and I'd like to take a few minutes to introduce our panelist. To my right we have Dr. Gabriella Lavezza who is the Assistant Vice President, Scientific and Regulatory at PhRMA and she leads staff in a variety of strategic initiatives to establish PhRMA as a valuable source of scientific expertise and innovative bio pharmaceutical research. To her right we have Dr. Weng-Hung Chen. He is currently a reviewer in the Study Endpoints Team. He is previously the director of Psychometrics at RTI, HealthSolutions. He has also worked as a researcher at Evidera, and Bethesda, Maryland. He has expertise in psychometrics data and analysis and Clinical Outcome Assessment, and also a psychometrician by training. And then finally, we have Dr. Bob Dworkin who joins us from the University of Rochester, where he is the Director of Anesthesiology Clinical Research at the University of Rochester. He is also the Director of Analgesic and Addiction Clinical Trials Translations, Innovations, and Opportunities Network or ACTTION, which is a public- private partnership. We're very lucky to have this panel with us today. I'd like to first have an opportunity for our panelists to provide their reactions to the presentation, and then following that, we can have some questions from the floor. If you would like to provide questions on index cards, that's also an option. Thank you.

I'm going to open this up. Here again are the key questions. We can start with Gabriela. Just to provide reactions and her perspective from the pharma.

Gabriela Lavezzari: Thank you Elektra, and thank you so much for inviting me. I have to start by saying thank you all, for all of the work you have done in the past year. We started this journey a year ago, meeting just a few people. The group has grown with a lot of passion. I really appreciate the opportunity to the Brookings to really bring our issues and really share our thoughts and work with many others who are really passionate about Patient Reported Outcomes, but also passionate about the input and how this input could be integrated in drug development and that's the challenge. I think we have been working very well together. I really look forward to continue the collaboration.

With that said, one of the things that struck me with the opening remarks from Janet is the fact that she has subscribed kind of a pre area of the patient perspective element, the patient input, and then the benefit-risk on the outer end and the PRO in the middle. I just had a sense that it's still being put into buckets and silos versus I think there's an opportunity to look at that all together and really look how the patient input can be actually translated, added in space, methodology, and be integrated into

benefit-risk much earlier into the development, so that there are the important conversation between drug developer and the regulatory agency on how to carry clinical trials, so that we don't get too late in really getting the patient input and really make the patient the center drug development a reality.

The next work about, what intrigued was disease specific versus PRO specific measure. That was something that was interesting. I work also on biomarker. We similarly look at, not just looking at a biomarker for a specific disease, but can we elevate and create some sort of framework that is a baseline of what are the evidentiary standards that we need as a minimum, and then augment the base eventually off of the disease or the organ. I thought that was the interesting concept that it would be worthwhile to continue evaluating it.

I agree also about the methodology research. We need that definitely a lot more and how the patient input is actually signed for that, and how quickly we continue to develop a methodology to make this a reality. About the second question with practicality, I think Elektra has mentioned clarity, practicality, and time length. That's a tri-factor. One cannot really work without the other. Having all those together really, I think, can help us to continue making progress on this. So if I see as practical, what can really help in drug development? It's really integrating the patient's voice, the patient's perspective, making it in a way that is having a science based, evidence based to develop on many more methodology, and having that conversation much earlier in the development so we're talking in the R&D phase which Katarina has mentioned. And also having that conversation in the benefit risk conversation has assisted drug developers. Thank you.

Elektra Papadopoulos: Weng-Hung if you'd like to provide some perspectives as well. Thank you

Weng-Hung Chen: Regarding the first question, I feel the area that we need more scientific research are recall period, potential biased result in opened label trial, response shift, determination of clinically meaningful changes, and sample size.

Regarding the second question, in terms of speeding up the review process, from regulatory perspective, I would like to say that the sponsor should submit as much information as possible in your briefing package. Looking for or requesting missing information slow the review process. The sponsors may feel certain information is not important to be included. But that is because you know it by heart and you take these information for granted. However, often time we are seeing these data for the first time so that we are not as familiar as you do. More information will help us understand what you are trying to measure, how you are measuring it, and you will interpret it. I have been a consultant working on instrument development for the past 10 years, and just 2 months into my new job.

The feeling that I know very little is stronger than ever, and my fear for providing bad recommendation is stronger than ever, too. But I am also confident that we will

achieve our goals because I truly believe that this is a team work from the industry, the academic, and the agency.

From the regulatory side, I will say providing consistent recommendations to the sponsor will help speeding up the review process because so that the sponsor knows what we are looking for and what to expect. I can assure you that being consistent is our goal. However, sometimes we also need to be flexible taking into consideration of unique situation. So we have to find the balance between being consistent and being flexible; it is very challenging.

We have come a long way and accomplish a lot in term of developing guidance and sharing consensus on how to develop a well-defined and reliable clinical outcomes assessment. I feel that we have not paid enough attention to the end of the road map, that is, the end users. We have many workshops and short course on how to develop assessments, but we seldom pay attention on trainings on how to use clinical outcome assessments. I have seen enough cases of misuse or misunderstanding of the clinical outcome assessments. For example, the scoring or handling of missing item response that are not consistent with the user manual. Or use a score interpretation that was not consistent with what is described in the user manual.

The **EXA**cerbations of Chronic Pulmonary Disease **T**ool (EXACT) license agreement requires the user to using and scoring the instruments as outlined in the User Manual. I think this is a good example on the consistent use of a clinical outcome assessment to make sure that the results are accurate, interpretation, and consistent. We need to get the message out to the end users that that the use of instrument should be consistent with the user manual.

Elektra Papadopoulos: Weng- Hung has more insights than we have time to talk about unfortunately. Thank you so much.

Bob Dworkin: I just wanted to emphasize/highlight what I see. I did that qualification from an academic and public private partnership perspective. When I highlight what I see that's really the most, to me, challenging issue about qualifying a Clinical Outcome Assessment That's the question that, I think, Bryce has identified. I think Gabriela also highlighted what is the generalized ability, like a scope or the breadth of the context of use? The way I thinking about it this morning and at the start of the Dr. Woodcock is let's say I was interested in developing a COA for a fatigue as a concept of interest, and I was particularly interested in patients of Multiple Sclerosis, which many of you know report fatigue very commonly.

If my context of use or my study of fatigue and qualifying the measure of fatigue in MS, could be in patients with Relapsing Remitting MS and with such a measure, then also the applicable to patients with secondary, progressive MS. Of course, patients who have had Relapsing Remitting MS but it's now five or six or eight years later. What about if we think more broadly, patients with Rheumatoid Arthritis who have fatigue, or patients getting cancer chemotherapy or Chronic Fatigue Syndrome.

I think this issue of how do we identify the appropriate context of use in the generalized ability of that to me is in thinking about qualification are really your critical issue. I don't think I have any insight about it other than I don't know where the risk is being done. It seems to me it'd be very cool to get patients with those different conditions in the same room, with a focus group, and have them talk to each other. They can tell us whether they're fatigue is the same or more different. I have no idea. We had a meeting this afternoon of half a dozen patients with MS and fatigue and half a dozen patients with Rheumatoid Arthritis and half a dozen with Chronic Fatigue Syndrome all discussing among themselves their fatigue.

At the end of that two-hour discussion would be a conclusion that their fatigue is more similar than different, or whether there's three groups about there're are very different conditions; MS, Chronic Fatigue and RA, patients can conclude that their fatigue is different. I guess if the patients told us that their experience of fatigue and all of its consequences seem very different to me, to them. To me, I would suggest that those are different context of use, but if the patient's thought their fatigue was much more similar to convict. Right? Maybe we could develop a fatigue measure that really had the generalized ability across those neurologic, rheumatologic, auto immune conditions. That would provide, to an extent that we can have relatively generic measures rather than tightly disease-specific measures that's going to make everybody's job a whole lot easier.

Elektra Papadopoulos: Thank you. Those are very insightful comments and food for thought for all of us. We have some questions that were submitted using the cards I'd like to turn it over to Paul, to respond, to tell us what the question is and respond.

Paul Kluetz: This is a really great question. It's actually one that I hear from my reviewers sometimes. I hear from patients a lot. And that is, that is why can we not believe that Patients Reported Outcome in the open label of clinical trial. Why can you not believe that? That's a good question. Do we not believe what patients say when they're communicating, when they come into clinic and know what drug they're on? A pretty interesting question.

First of all, I would say that the more that I learn about patient reported outcome the more that I realize that there's simply no way that I'm going to tell you what your nausea is. The one truth is that's the patient is the one who can tell you with a clinician what they are feeling. You can't see it. You cannot measure that. The measurement itself is true to their perception at the time. I do believe what the patient says on that open label clinical trials, what they perceive at that time point.

What is a little more tricky is that we know through, we published literature at such a thing as the placebo effect exist where you know you're going to be taking an innovative drug, particularly in the setting of a severe life-threatening disease, like cancer, where there's a lot platform hope involved that you are likely to overestimate the benefit. You're perception maybe factored by the knowledge that you're going to be receiving the drug that's been on the news versus a placebo pill.

What we need to do and what might be applicable to the key areas of need for scientific research is to identify the extent to which this perception elevation occurs in open label cancer clinical trials. Try to understand the magnitude of what that is. It may be people overestimate their benefit. At least, early, whether the drug is working or not, what is that magnitude. Maybe we can have a responder definition that is over what we expect the response to be.

Then how could we mitigate this from happening or use this in our analysis better, to try to take it into consideration. I think it's an excellent question. I think it's an area that actually talks to some company development or some academics looking at this question because they know that this is one of the big concerns for utilizing quantitatively Patient Reported Outcome data in open label clinical trials.

Elektra Papadopoulos: We are actually at our allotted time and perhaps we can take one or two max more questions from the floor. We do have some questions on the web, if you'd like those. Perfect.

Question from Audience: If you don't mind just quickly, I think the compendium idea is really a good idea, but sort of along the lines of what Bob Dworkin was saying, is how are you going to take into account the dynamic and changing context of use in terms of more and more what we know about disease and how to treat particular diseases. Also, in terms of changing technologies. Right, it's like a danger. You can put compendiums, this had worked before and someone thinks, "Oh, this is an indication that this will work but it may not".

Elektra Papadopoulos: That's a great point. I'm very good prelude to session two. We can now take some questions from the web.

Question from the Web: Some of these also might relate to question two. I'm going to put one that I think is the base of this session. From June, "would you please provide a couple of examples of misuse of the tools?"

Paul Kluetz: One thing that's challenging in Oncology that we find could a potential misleading statement to make. Is that when a large broad based health related quality of life instrument is placed in an Oncology clinical trial that has many different aspects of how a patient feels many domains, physical functioning, social, emotional. Some symptoms of the disease, some symptoms of the treatment also have added up into a total score. There's the belief that, and some data suggestion, from what I see many times, that instrument, it is so many different things that can go in so many different places. It may or may not be related to treatment at hand, and sensitivity of that instrument, to detect the change, good or bad is more limited than if you're looking at one specific thing like pain.

Let's say you were looking at one specific thing. what we sometimes will see, and I think it's potentially somewhat of an erroneous assumption that if you have a cancer therapy and there's no difference ... what they call meaningful important difference,

between the two sets of arms in that measure, that we frequently see a comment such as, "We increase progression to survival, and there was no detriment in Patient Reported Outcome, or the patient quality of life is similar or equal to between the arms or no difference in the health or the quality of life."

To say that there's no difference, from a statistical standpoint, is a little different than saying that the investigational drug did not improve the health related quality of life, if that makes sense. From a statistical standpoint, there are two types of trials: superiority trials and there are non-inferiority trials. If you would like to show that your drug had no difference on the quality of life while they're on it, then you have to look at that differently just saying, "They were kind of about the same so there was no difference. Because that we do see and it's come about in advisory committee meetings that can be somewhat misleading.

Elektra Papadopoulos: Great points that really speak to the importance of the context of the clinical trials and the use of that instrument in the clinical trials. So we're now going to close session 1 and transition to session 2 and Ashley Slagle my colleague will be moderating that.

Session 2: Advancing Measurement Strategies for Clinical Outcome Assessment Tools

- **Use of previously labeled clinical outcome assessment tools as an adjunct to regulatory qualification**
- **Speaker Presentations**
- **Panel Discussion and Questions**

Ashley Slagle: Good morning. I'd like to ask the speakers and the panels for session two to please join me up front here. Thank you. Welcome to session two. My name is Ashley Slagle and I serve as the Clinical Outcome Assessment qualification scientific coordinator and the Study Endpoints staff in the Office of New Drugs in CDER. We're excited today to talk about a advancing measurement strategy for clinical outcome assessment tools. I'm pleased to welcome the speakers and panelists for this session. I'd like to introduce them now in order to save some time, so we can just move through the session and really get to the presentations and then get to the discussions that will follow.

I'm very pleased to welcome Dr. Ann Marie Trentacosti. She's a medical officer in the Study Endpoints and Labeling Development staff and the Office of New Drugs in CDER, Dr. Jean Paty, who is senior director and practice lead for Endpoint strategy within global market access and commercialization at Quintiles Consulting. Dr. Stephen Joel Coons, executive director of the PRO consortium at the Critical Paths Institute. Our panel discussions include Ms. Alicyn Campbell, who is the global head of patient-centered outcome research for oncology at Genentech. Ms. Bray Patrick Lakes, she supports efforts to actively engage patient advocacy organizations and other stakeholders in the Clinical Trials Transformation Initiative. She has also served as the patient representative at the FDA.

Mr. Tom Sellers is a 16-year prostate cancer survivor and serves as a Senior Director of patient advocacy and corporate philanthropy at Takeda. Dr. Dennis Turk who is professor of Anesthesiology and Pain research and Director of the Center of Pain Research on Impact Measurement and Effectiveness at the University of Washington. Dr. Ellis Unger, who is the Director of the Office of Drug Evaluation I, in CDER. In this session, we'll continue discussing the clinical outcomes initiatives that Elektra and Katarina and others have mentioned during session one. In this current session that we're going to focus more specifically on the compendium of Clinical Outcomes Assessments.

This session will be broken up into two parts, separated by a lunch break. Before lunch, our speakers will provide some formal remarks on their perspective. First, I'll share some background on qualification and previously labeled assessments, how we think about standards and accessibility of assessments. Dr. Trentacosti will then provide some details specifically about our approach to developing a Clinical Outcomes Assessments compendium. Dr. Paty will share an industry perspective on compendium and standards and Dr. Coons will provide the PRO-consortium

perspective on how qualification of those assessments and a list of other potentially acceptable assessments can go hand in hand.

Then we'll ask for some brief reflections and reactions from the panelists, especially focused on our current thinking about standards as well as our initial approach to developing stage one of the compendium. We'll then break for lunch. Lunch will be followed by a continued panel discussion and audience questions and answers. I do ask if you have questions that you please submit those questions on the cards that are found in your packets. Submit those to us before you head out to lunch.

There are two pathways for FDA to review and provide advice on Clinical Outcome Assessments. The first is the traditional way, within an individual drug development program. Assessment reviewed and found acceptable in this context have the potential to support drug approval and product labeling claims. The second pathway is a newer process, like in our drug development tool qualification program. This is outside of any individual drug development program. Assessments that are reviewed and found acceptable in this context result in qualified assessment.

This means that a notice is published in the federal register identifying the assessment and the clinical context for which it is qualified for you. Qualified assessments are intended to be made publicly available for use across multiple drug programs. As more assessment tools are qualified, we expect that there will be both tools that are qualified and in product labeling. Let's just spend just a little bit more time describing what qualification is because I think there's been a little bit of confusion about terminology.

The “qualification” is a regulatory term. It's used to describe that formal process to work with FDA outside of an individual drug development program, to develop what will be again publicly available tools for use across multiple drug programs. It's important to note that it is not necessary that an assessment be qualified for it to be used successfully support approvals and labeling claims within an individual drug development program. The term qualifications is not equivalent to validation.

Evidence of validation of an assessment tool, meaning the documentation of adequate measurement properties for a particular context is necessary during any instrument development process, whether it be within a qualification program or whether the assessment needs to be developed or evaluated within an individual drug development program. For clinical outcome assessments, there are two points that which we can qualify tools within the qualifications program. The first is a qualified assessment or exploratory use and a second to qualify the assessment for use of a primary or secondary endpoint.

What do we mean by qualification for exploratory use? This means that we agree with the content of the assessments and believe that it is measuring something important, and it measures what it set out to measure. We refer to this as content validity, and there is early evidence of cross-sectional measurement properties of the

assessment. However, we don't yet have a full understanding of the instruments ability to detect change or how to interpret what is meaningful change on that assessment.

By qualifying for exploratory use, we are making the instrument publicly available and recommending the instrument be used in exploratory studies, which is typically phase two trials, in order to learn more about the assessments and obtain the needed information to be able to plan for its use in phase three confirmatory trials. After successful evaluation of longitudinal measurement properties, and we have a good understanding of the assessment's ability to detect change and how to interpret that change, we can consider qualifying the assessment for use in adequate, well controlled studies as a primary or secondary endpoint to support approval in labeling claims.

When we think about the confidence that we have and assessment meets our regulatory requirements as being well defined and reliable, we see that assessments really fall along a continuum of confidence. For Clinical Outcome Assessments, to support approval claims we need to have adequate level of confidence in two really broad categories: One, that what is being measured is appropriate, relevant to patients and physicians, and sufficiently but comprehensive to interpret treatment benefits and support labeling claims. Two, whether the assessment is reliable and sensitive enough to detect small, but meaningful changes with information about how to interpret changes.

On the left side of the continuum, there are assessments for which we have no supporting evidence and no regulatory experience. These clearly fall below a line of adequate confidence. On the other or right end of the continuum, we will have assessments that are qualified for use as a primary or secondary endpoint. These are assessments to which we have the most evidence and therefore confidence in the assessments. Because we would be prospectively recommending these qualified assessment tools for use to multiple drug development programs, we believe we need to have the highest standards for these assessments.

Other assessments, those that are qualified for exploratory use or those that have been previously used in individual drug development programs to support labeling claims fall somewhere along this continuum. For assessments that have previously supported approval and labeling claims in the past, we have sufficient confidence at that point in what was being measured, and we could describe that in labeling. However, many of these assessments may not be optimal are our thinking may evolve over time. For example, as we gain more evidence that our previously used in labeled assessment does not adequately reflect what is meaningful to patients, we may need to move away from that assessment towards another that better captures the patient's experience.

Another consideration with previously labeled assessments is that they might not be sensitive enough to detect small, but meaningful changes across all drug development

programs. With this lower level of confidence, we might find the assessments potentially acceptable, but would not have sufficient confidence to prospectively recommend the assessment across all of our development programs. Individual drug developers would need to consider whether they wish to take on that additional risk or whether they wish to develop or modify another better, more sensitive outcome assessment.

With assessment tools that are qualified for exploratory use, we may have more confidence in what is being measured and when it really reflects what is meaningful to patients]. Then we might with some previously labeled assessments, because for this type of qualification, patients and other stakeholders, care givers or parents, clinicians have all provided input into the development or assessment of that measure, but we don't yet know how well the assessment can detect small, but meaningful and treatment effect in trials. Sometimes an instrument development or evaluation seems like really hard work, but at the end of the failed trial or null findings on important patient-centered outcome assessments, we don't want to be left wondering whether it's the drug that failed or was the outcome assessment insufficient to detect small, but meaningful and interpretable changes.

This is why, in the spirit of improving outcome measurements, we really do encourage our developers to discuss outcome assessments with us as early as possible in drug development. With that, I would like to ask Ann Marie to share her presentation.

Ann Marie Trentacosti: Thank you, Ashley. I'm actually going to be providing an overview of our proposed development of compendium of clinical outcome assessments. Why is the FDA considering this compendium at this time? Qualification is FDA's conclusion that if COA can be relied upon to have a specific interpretation application in drug development in clinical trials. We find it as a very important milestone to achieve however, as we all know, qualification takes considerable time and resources and it can take years to qualify a measure. FDA really wants to identify an additional approach, not a replacement approach to qualification, an additional approach that we can expedite our identification of Clinical Outcome Assessments that could potentially support future labeling claims.

In addition we want to provide clarity and transparency in a public forum of our thinking about COAs and a public compendium of website that can be updated periodically would be a good communication tool to achieve that. A third and very important feature of the compendium is that we want to encourage development and implementation of COAs generally, but especially those outcomes, such as Patient Report Outcomes, which measure how patients feel and function as a treatment benefit. It includes those and identifies those on the compendium. We're hoping that this will also foster patient drug development as well.

Using FDA's current approach for how we review COAs and submissions we actually we look at will help us in populating this compendium. Currently FDA has

two pathways that we look from and evaluate COAs. There's a complication pathway which Ashley eluded to and then there's the IND/NDA pathway. Currently when FDA agrees to participate in qualifications and a measure is qualified, it actually is listed on our website. However, there are many ongoing qualifications going on that the FDA has agreed to participate in and the clinical outcome assessments are under development, which would be really helpful if we could identify and list those in our website.

That would clarify our thinking about these COAs as well as encourage collaboration and development of these COAs. They're very important. Looking at the IND/NDA pathway we review many COAs, unfortunately many of them don't make it through approved labeling, for whatever reason. We do drug development program failed and it was stopped. However, there are many Clinical Outcome Assessments that in approved labelling that we could consider using in future labeling. We want to identify those and populate those on our compendiums.

Ashley presented this slide. I'm going to reiterate a little bit because I think it's important in the context of this compendium. This slide shows FDA's confidence that a COA represents a clinically meaningful and sensitive change for a patient in a clinical trial. And of course this is low evidence. We have no regulatory experience and no evidence to base that confidence. At this end, we have a very high end of evidence, highest level for qualification for primary, secondary assessments. However we have a plethora, many of our clinical outcome assessments are in here in the continuum range level. Especially when we look at previously labeled Clinical Outcome Assessments or those that need to be qualified for exploratory use.

In each case, a clinical outcome assessment would probably fall somewhere along the continuum, but our goal is to try to identify those that actually probably fall more closer to our higher level of confidence and identify a regulatory and scientific experience that we can justify putting these on our compendium. What's the difference between a previously labeled versus a qualified clinical outcome assessment? A previously labeled clinical outcome assessment may not have undergone the qualification process, but has been used to support recent drug labeling claims. Based on current scientific regulatory standards could potentially be used in the support future drug regulatory claims when used as primary or secondary endpoints

This contrast our qualification COAs, qualified COAs have undergone the rigors of the qualification program, which is identified in our guidance. We look at this compendium. There's really two major communications group we're looking at. One is a guidance and the other is the actual compendium, which will be a table that will be published and accessed through a public FDA website. The guidance is going to be a collaborative effort between the Review division and SEALD. Of course, it will be discussing the goals of the compendium as well as how we're choosing in the future Clinical Outcome Assessments to be posted on compendiums.

The dates the label you're looking at to choose those label COAs as well as the scientific regulatory standards for the deciding on the COAs. They're also discussing limitations of the compendium and this draft guidance will provide an avenue for providing public input. Of course, these regulatory and scientific standards that are something we are discussing and internally and we obviously welcome feedback today and will continue to get public feedback. The table itself, again, a collaborative effort between SEALD and reviewed teams. It will be organized by therapeutic errors and the user condition. We're really looking at this in two stages. Stage one is more of a pilot stage, which, as I mentioned before, will be populated based on currently qualified COAs, on going qualifications, and recently approved labeled COAs we've identified could potentially support future labeling claims. In order to pilot the project, we're just looking at NME's approved 2003 or later. We had to start somewhere.

In the future, we could expand the project. This is stage two, which again we're going to discuss your thoughts about stage two, how to expand throughout the program. We haven't decided that obviously, but this table, again, it will be constantly updated based upon our scientific and regulatory experience, drug approvals. It will be constantly fluid type of a document. This is an example of what we're proposing right now, it's on the website and we would like your input. Obviously it's going to be divided. The first category is going to be what the conditions disease is. In this case an example treatment of Irritable Bowel Syndrome. That would be the condition here in column one.

Column two is what's the indication or the claim. Now it could be a symptom. It could be a function. In this case, it's the overall treatment of IBS-C, which is what the target claim would be. Column three discusses the outcome of the interest. Meaning, what are we trying to measure? In this case, we're trying to measure the symptoms of IBS-C which are complete spontaneous bowel movement frequency (CSBM) and abdominal pain intensity. Column four is actually the labeled Clinical Outcome Assessment, what we're seeing in labeling. Here we do have a label clinical assessment as well as a numeric rating of abdominal pain intensity, we have a complete spontaneous bowel movement count as well as a numeric rating scale of abdominal intensity. Both these were measured by a Patient Reported Outcome diary. Column five would be any specific characteristics or any additional information that would provide the context of how we look at the Clinical Outcome Assessment. In this case we don't have much just a patient with IBS-C.

In this case, we don't have much information to provide to the FDA. Column six would be discussing any relevant guidance or ongoing qualification efforts. In this case, we have both we have a published guidance and we do have an ongoing qualifications program developing a new measure for IBS-C symptoms. We see this as a one-stop shopping approach where hopefully it's a communication tool, which is providing information on labels, Clinical Outcome Assessments, guidance information, and qualification projects. We don't provide too much detail intentionally because we don't want this to replace our ongoing communications with

our drug developers. We still want companies to come to us and talk to us about what's going on. We don't include in here primary endpoints, secondary endpoints, intentionally.

This is just another example of what we're proposing for the table. In this case, the condition is advanced Non-Small Cell Lung Cancer. The indication again is the treatment of advanced non-small cell lung cancer. The outcome of interest here or interest in symptoms of the disease, either improvement or progression, we currently don't have any labeled Patient Report Outcome measured in approved labeling of symptoms that present as Non-Small Cell Lung Cancer and when you look at column five again it talks perspective, the context here, we say for use and association of other disease specific endpoints to describe a treatment benefit in adults with non-small cell lung cancer.

Again, not specific, not very specific intentionally. Obviously, if you're wanting information on Non-Small Cell Cancer we're being not specific because we want to encourage companies to come to us, and there could be a lot of other outcome assessments, maybe functions that would be interested in it. That's why this is not going into very much detail, just a communication tool. In this case, we do have an ongoing qualification program to develop this measure. We think this may be a hyper link to the, the PRO Consortium has a website discussing it. We're hoping that this type of posting would be very useful to several areas. Number one, it would provide clarity about what FDA is thinking. We're encouraging, we want development of symptom measures in advanced Non-Small Cell Lung Cancer, and we're putting it on our website.

The other thing is it's also informant about the development of an instrument, so encouraging the collaborative approach to developing new measures such as this. What the compendium is and what it is not. Obviously we can mention several times we are trying to focus it is a communication tool where you don't want it to ... we want to be transparent with your developers in a one-stop shopping approach. What we're thinking about Clinical Outcome Assessments, we want to, this whole issue of collaboration. We see with the INDs, we think this is a great instrument in the program and we really don't have any avenues to foster development of that. We have several measurements coming in at once.

This will foster hope with collaboration with ongoing qualification programs that folks can join together and develop measures. We also want to encourage the development of these measures. With this collaboration approach and encourage identification of COAs such as Patient reported Outcomes. What this compendium is not, it couldn't possibly be all inclusive. It's not stifling innovation, we're hoping it's not. We certainly don't want to replace any of our existing communications tools with companies which we think is very key. It's not to replace any guidance or to replace qualifications. It's really an adjunct to qualifications. So obviously this is going to have limitations, like what I just mentioned. It can't possibly be all-inclusive or all exhaustive. That can't possibly be our goal.

There may be many conditions and COAs out there. We have not identified that we will maybe in the future identify an alternative could certainly be considered, again, just a starting point to discuss a dialog to the company. Of course some of these outcome assessments may be have proprietary rights. It's not any way of FDA endorsing it. It's more of a communication tool of what we have and what we know. For the purposes of discussion today, and right now we are going to be discussing stage one. I'm going to reiterate that in stage two, more this afternoon. Stage one is our pilot, which is really how we're going to populate this compendium. It's really three main things we're going to populate with, which I mentioned.

It's, number one, this identifiable labeled of COAs from recently approved labeling and we start with 2003 or later that based on our review with review divisions and SEALD could potentially support future labeling claims and future clinical development programs. Qualified COA's and ongoing qualification programs of course, would have to get the instruments developer's approval for that, but we would like to hopefully post on our website. The stage two is the future. This is our current thinking of the future, but again we would be very interested to hear your input on this. Of course, we think about maybe expanding stage one goes well and into looking at other labels, COAs through efficacy supplements or other years. This is just a thought. One thought that we have was use the compendium as a communications tool to identify or communicate unmet measurement needs. Since we really have need for pediatric tools in many conditions and diseases. If we could post that in our compendium, it would again provide clarity if FDA was interested in this is important and a collaborative approach where companies could obviously see this information, join a consortium . These are just some of our ideas of how we would obtain this information about unmet measurement needs, patient-focused drug development meetings, advisory committees, and FDA stakeholder meetings. Again, we're welcomed to think of others and we'd like your input.

Where are we? As mentioned, we did have a Brookings meeting this summer, the Compendium idea was discussed at the meeting. We got significant positive feedback that's why we're bringing it to your attention today. Obviously, we've been discussing this internally at length. Hopefully we'll get some feedback today. Our next step would be to go develop a FR notice and then get additional feedback from the public about our compendium, and that upon those, we hope we'd have a mock up similar to what I've shown but probably more extensive as what we hope the compendium will look like and the goal of the Compendium.

I just wanted to thank everybody on the Study Endpoints team for this collaborative effort and initiative, especially Nikunj Patel, who is very instrumental in the whole program.

Ashley Slagle: Thank you Ann Marie, Jean?

Jean Paty: Thank you. This is the first time that I was invited to the FDA to speak and I didn't have to make up any slides. I get to use Ann Marie's slides, thank you

Ann Marie. I'm going to pick up on Paul's theme from this morning about being nostalgic. I'm prone to be emotional. I may cry for your birthday. Actually, what I'm referring to is that, I think, it was early 2006 when the FDA held a meeting in Chantilly, which I think is somewhere around here. And started was first talking about the Patient Reported Outcome draft guidance at the time. Nine years later this is a big difference. This is a really big difference, and I appreciate folks like Ashley and Paul and Ann Marie and Elektra, folks I've known for quite some time. I real like Paul's very candid way of saying, "Gosh, we can do more, and we want to do more." Being a part of these Brookings meetings and this culminating meeting I see and feel a big difference. From an industry side, this is hard. Developing drugs is hard. Measuring whether rather doing something that you think is hard, it's hard. What does that mean?

That means to me means, that there's opportunity for us to do something in a way that I really think, as Elektra said this morning, allows the patient voice to come out in terms of what the product does and doesn't do. I've had really good fortune to live a lot of what both Ann Marie and Ashley talked about, and that is I've had the opportunity to be a part of the qualification pathway. That's hard, and that's long. That's what that is. To me, the outcome of that as I'll show in a moment, the far right side of that continuum is a high bar. In no way shape or form has that got In the way of me working with clients.

One good example is Insight with a product called Jakafi®, who got their first label on symptoms. A number of people in this room were instrumental in making that work on both FDA and on the industry side. Another product recently approved called Varithena™ for varicose veins. We work collaboratively with the FDA for both primary endpoint in symptoms. Also a part of the label are change in appearance, key outcomes of working with the FDA. This is hard, but I'm living and I've had a chance to live this regularly both on the qualification side and on the IND side so I encourage us. Part of the problem is sometimes I find that these meetings, so I think I know a lot of you, maybe most of you in the room. I know a number of my colleagues are on the phone. I'm thinking bummer. The people I want to be here are the 10-12 people that we have to work with every day that go 'do I have to do that?' It's time to really start taking these messages out. I think this continuum is one of the coolest things I've seen in quite a while because what it reflects, and to me if I had one slide to show a lot of my colleagues, who give me the deer in the headlights when I say, "You've got to invest time and effort in this, is that this is not a 0-1. There's a continuum along which we can find something acceptable." FDA didn't make that up. FDA simply is reflecting the way instrument development with works.

At some point if you're on the phone, left-hand side, the thing is not is working or if it's working, we sure as heck don't know. On the far right-hand side, we know for sure, but along the way, we can know enough to be confident and to interact with our regulatory colleagues and other key stakeholders to say, "We're over the line." To me, part of the use of the compendium is going to be that, the way that I'm going to use it is to say, "We need to see in our specific context of use, when I look at this

compendium, where do we fall on this line? I'm not going to go ask FDA where we fall on the line.

We're going to come up with that, and then we're going to go chat with FDA or EMA who've move far along in terms of the sophistication of our dialog within about instruments. We're going to say, "Here's where we think we're on the line. Here's why we think that's good enough. Let's talk about what we need to do together." If we deem that we're on the far left-hand side of this, I'm not going into that conversation. We're going to have to move over to the right. I think the key thing about the compendium, this idea came up last summer. I had two immediate strong reactions. One was "Cool. I can finally hold something out to folks to say, 'look we've got a starting place'," or "Look, don't just listen to my examples, here's a list of examples that's a good part for the discussion."

The other reaction was, "Oh, my gosh. I'm going to never get the precedent folks, the grab and go folks to move off their position. That is, "Jean. Just go and do a label search" because what the FDA is saying with the Compendium is "All I have to do is a label search and grab the last of the instruments." Right? Is that what they're saying?" No. I've actually confirmed that in multiple conversations. That's not what's being said here. This is not a grab and go list. So I like Ann Marie's point about on purpose we're not going to articulate every single detail because we don't want to communicate that.

However, it is communicating, guess what? This is hard, but it's do-able and drug development is hard. The other key thing which I really thought was key in the first sentence here, based on current scientific and regulatory standards. FDA didn't make up anything about instrument development, not one single thing. FDA is simply reflecting a long tradition of developing and testing instruments, so that you know what you are measuring is what you're measuring. Somebody said to me yesterday, like "Hey. You know what? Will FDA accept, like if you did the small bridge end study and show it with the two things are the same?"

I'm like, "Probably." Guess what? That doesn't help us. We have a key question that we we're going to need to answer. Let's answer that question. Trust me, once we get the answer to that, our FDA colleagues they're going to be cool with it because we need to do the work for ourselves to be able to move forward in our program. I really think that this compendium is a very strong starting point for productive dialog around where we are on a starting place, as a starting place in terms of a specific context of use for specific indications.

If we're not on the list or there's nothing on the list, again, that gives us a sense of where we are. I actually think that as much as what's not there, it's going to communicate something to us as much as what is there. I'm very positive about this. I really believe that we've moved a very long way in 9 years. I give a ton of credit to the early folks that launched this back far more than nine years, and here we are now. And on that, thank you.

Ashley Slagle: Thank you, Jean.

Stephen Coons: I'm very sorry I have to follow Jean. It should have been age before beauty. I do certainly want to thank the organizers of this workshop for giving me the opportunity to talk about my views and opinions. I do want to say that they don't necessarily reflect my employer the PRO Consortium or the FDA. I hope they do to some extent. Just to give you a little background on the environment, which I work. The Critical Path Institute, C-Path, as we call it, was established in 2005 by the University of Arizona and the FDA Center for Drug Evaluation and Research as a public-private partnership and we do receive funding through the public-private partnership grant program.

It's dedicated to implementing FDA's critical path initiative, which is a strategy for transforming the way FDA regulated products are developed, evaluated, and manufactured. It's an independent, non-profit organization. C-Path provides a neutral pre-competitive venue for collaboration aimed that accelerated development of safe and effective medical products. The PRO consortium was formed in late 2008 by C-Path in cooperation with CDER and the pharmaceutical industry. We have 27 members. They are all pharmaceutical firms, and then other participating stakeholders or representatives of the government agencies primarily the FDA and NIH.

And clinical consultants and academic researchers, patients, and the contract research organizations that partner with us to develop and test the PRO instruments. The mission, it stated here. I underlined and bolded qualified because it's our organization that the PRO consortium was established essentially to work on the qualification measures. One of the reasons I was asked to give this perspective is the issue about, what will this compendium do to the qualification program, so I'll talk a little more about that in my remarks.

The impetus for a consortium approach to qualification is based on what was said in the DDT qualification process guidance. Because substantial effort is involved in achieving qualification CDER encourages the formation of collaborative groups to work jointly to increase the efficiency of DDT development. Then they go on to say, "Nevertheless, CDER will consider DDT proposals from individual person or company as well." I know Cynthia Bens is on the room. She's from the Alliance for Aging Research. The Alliance, aging in motion coalition. It's working towards FDA qualification of performance measures, for people with sarcoma.

It's a situation where this is open to a number of organizations, including advocacy groups that want to advance measurement science for specific patients. I think it's important for people to know that. Qualification of the COA tool, one definition is qualification is based on CDER review in this case, evidence that supports the conclusion that a COA tool provides a well-defined and reliable assessment of a targeted concept, in a specified context of use.

The qualification of a COA tool, from my perspective, facilitates pre-competitive collaboration which includes the FDA. It's a part of the qualification process and avoid development of multiple COA tool for the same context of use and within a collaborative environment where it can be a sharing of the cost associated with development of the COA tool. I don't know how the slides got like this. I didn't necessarily set them up like this, but I must have, I guess. Facilitates FDA review by standardizing COA endpoints.

Lowers the risk and uncertainty for clinical trials sponsors and the challenges include the evidentiary hurdle. We talked about that today. It may be easier in a sense to get a PRO or a COA endpoint measure to the NDA path rather than the qualification path. That is just probably the process. The process of qualification is time and resource intensive. There's another benefit. Once qualified, the COA tools are publicly available. At that point, it's already been made a couple of times. It is an important one because it does then make it such that the FDA can point to the instrument, recommend the instrument and people will be able to get access to it, with sponsors of trials.

Compendium of the COA tools in terms of the benefits, it really will enhance transparency, Jean was hawking back to the 2006 meeting in Chantilly, where the PRO guidance, the draft guidance, was being rolled out. I remember somebody getting up. Paul Langley is a health economist, got up and said, "Why doesn't the FDA just give us a list of the instruments they'll accept." I don't know if any of you remember that. It wasn't something that was really on the FDA's radar screen at that point, as you can imagine.

We have come a long way in nine years. There will be in essence a list of what instruments have been used and what instruments will be able to be used in trials, as endpoint measures. Encourages consistency in COA endpoints, we really do need more standardization of COA endpoints. This should help that process. Again, this should lower the risk and uncertainty for sponsors of clinical trials as well. Potential challenges do include, and Ashley really mentioned this as well, out of the COA tools sufficiently patient focused, there certainly are some labels out there that have COA tools and those COA tools may not have patients involved in the development of them, and we need to re-evaluate that.

Some COA tools listed may not be publicly available. Initial focus on COA tools rather than outcomes. I think that's one of the things that has to be considered for stage 2 that it may be more important to start identifying what outcomes of interest the review divisions would like to see measured as opposed to going from the measures to what those measures are measuring in terms of the outcome. Initial focus on COA tools ill it undermine the qualification program? I really don't think it will, from my perspective. I think it's a situation where there will be COA tools that are listed on there, in the compendium, but like in depression, we have a depression working group within the PRO consortium. What I assume will be listed in the compendium are the MADRS of Montgomery Asberg Depression Rating scale, the

HAM-D, the Hamilton Rating Scale for Depression. That's fine because those have been very effective in getting drugs approved for major depressive disorder.

We're developing a Patient Report Outcome measure. We know that patients who have major depressive disorder do believe that they should be the direct reporters of the symptoms of the depression that they're experiencing. I think there will be room for further development of new tools, but maybe a different reporter or maybe working toward a more optimal measure, but the tools that are listed in the compendium may be good enough, but they may not be optimal. More work could be done. In terms of adding COA tools to the compendium, this was talked about in terms of certainly the qualification addition. There are tools that are qualified through the DDT qualification process, additional COA tools that lead in the future to improve the labeling, the INDNDA BLA path will be included, but I do hope there will other opportunities and some that relates to acceptance of legacy measures, some legacy measures. Dr. Klutz talked about the issue of there are a lot of legacy measures in oncology, but we may not want to move forward because of some of the concerns about what they're truly measuring. There are many other legacy tools that may not be appropriate to move forward, but there are some that are out there that should be considered. I would hope that there could be some clinical or scientific consensus that enables some current tools or other tools to be moved forward onto this list.

That obviously would be short of qualification, but for some of those tools, it could be the first step toward qualification. Just to give you one example, Jean also mentioned Jakafi®. Jakafi® is for Myelofibrosis. Insight was very effective in getting a label around total symptoms within Myelofibrosis. There are a number of other firms that are now using variants of that symptom diary. There is an interest on the part of both sponsors of the trial. The sponsors of the Myelofibrosis trial as well as the FDA to harmonize these variants and have one symptom diary for Myelofibrosis. That's something that the PRO consortium will be working on to bring forward a consensus to find measures for Myelofibrosis symptoms. I hope they'll be able to be added to the compendium.

The conclusions, the compendium of COA tools is an important first step, and it's just that, a first step and a valuable complement to COA tool qualifications. It will help identify COA tool gaps and facilitate identification of additional outcomes of interest. As I alluded to earlier I would hope that, in stage two, one of the things that is done with the review division would eventually be tasked with identifying concepts or outcomes that they would like to measure for which there may not be a measure in compendium.

Additions could be advanced by consortium, professional society, and advocacy organizations. There's a question mark there because there is no formal mechanism now within the FDA for that to happen. That may need to be built if indeed it is deemed an appropriate routes to add measures to the COA tools compendium. The level of evidence for a sponsor to use a COA tool in a clinical trial needs clarity. Do they need to have an evidence dossier that goes along with their submission or is the

fact that the tool is listed on the compendium and they're in that same context of use? Will that be enough?

Then I do believe it will enhance patient focused drug development. That's certainly why we're all here today. I have high hopes for this compendium. Thank you very much.

Ashley Slagle: Thank you very much, Stephen, and thank you to all the speakers. I'd like to take just a few minutes and get some reactions and reflections from our panel discussants. Very brief actions before lunch. We can do two to three minutes and focus, if we can, your comments on the standards, the way we think a standards, the continuum and stage one of the Compendium. Then remember we'll be coming back after lunch to have more discussion and there'll be more opportunities to share other thoughts. Maybe we'll start at the end of the table.

Bray Patrick-Lake: I'm Bray Patrick Lake and my work at CTTI focuses more on patient group engagement in non-clinical trials and seeking more effective partnerships between sponsors of research and patient groups. And I think just being here today, for me I've been in this space for a while and I've listened to things about PRO's and Clinical Outcomes Assessments and this has really lifted the fog for me. I think this is a great step forward in transparency and I think there can be some actionable recommendations that come out of the workshop for patient groups. We can start with check the compendium about columns 4 and 6 about what's already existing or in development. That's hugely important to patients groups to know what's already in the space. Patient groups are doing a lot around convening and forming these partnerships and collaborations. They're really good about getting multiple sponsors to the space and also investing resources and things that are going to make a difference to the patient. Out of this I would see patient groups who know what's out there, identify gaps, form precompetitive partnerships for collaborations, and then focus their resources on developing new tools or even adapting some of the existing tools which I'll be interested in engaging some discussion around how that might or might not affect the timeline if we took something like the symptom diary and tried to adapt it from another disease. This is very exciting. I look forward to the discussion after lunch very much. Thanks.

Stephen Coons: I apologize for having to make this quick correction. I said I talked about Cynthia Bens and her project and I said sarcoma. I should have said sarcopenia. So, I apologize for it because they are quite different. I want to make sure I corrected that.

Ashley Slagle: Thank you. Tom,

Tom Sellers: Good morning I'm Tom Sellers. As the head of patient advocacy at the Takeda Oncology, I'm responsibility for being the patient's voice and patient insights into the company. Also, for developing programs that go unmet need as well as helping us to represent, to walk the walk of being patient centric as a company, which

is an important part of what we do. I really appreciate having the opportunity to comment today. My major take away from the presentations so far is can we find ways to incorporate the patient perspective into, not just the addition of COAs, but into the design and implementation of stage one of the compendium.

I think that there is a real clear structure set out there to bring COAs into the compendium, but what's missing is are you bringing things into the compendium that patients care about? Are you actually measuring things that matter to patients? I think we need to find a way to incorporate that view into the ultimate design and implementation of the compendium as well as ultimately into additions that may happen in stage two. I think we need to start with stage one and also when we look over all the way on the right side of the continuum, that tells you what works, but does it tell you what matters?

We might even consider whether or not there should be another column in the compendium that reflects whether or not this particular COA represents something that matters to patients. That's where I'll stop for now.

Ashley Slagle: Thank you, Dennis

Dennis Turk: I am going to be the token curmudgeon. It's really exciting. Your comment actually bridges nicely. It's really exciting to hear all the positive things that people are talking about. We're all going to reach out. We're going to be clear. We're going to be more directed, more transparent. We're all going to send information. We're all going to grab hands and go kumbaya and things like that. I thought what I would do is say, "Let's just tweak this thing really good if I can." And I hate to do this before lunch. It was really delightful hearing Janet Woodcock talk about the involvement of the patient, the end user, in the drug development and how the FDA is thinking and also Tom Sellers talking about that.

It really makes a differentiation between what we measure and how we measure it. We have historically measured things based on what academics or investigators thought was important. Now all of a sudden, voila. Maybe we need to pay attention to the what, the patients care about. It's important. That's true. How are we going to go about measuring what they think is important? In the things that were developed by legacy have in the past for many years, it's very easy for a pharmaceutical company to say, "We have a product that we're developing for condition X which has had multiple other studies in the past. Let's go and look in the people that used outcomes in that study," and we can be sure that that's a good measure. It's now being in the compendium. It's been used in other studies.

For these newer issues that were identified, they were never done prior to 2003 or even 2003 when we're going to be moving forward. There's a dilemma between the optimism and confidence in existing legacy measure that makes the table and what's really important. But haven't we gotten that far. Now, I can understand the patient consortiums wanting to develop these kind of things in the US, but what's the

incentive for the pharmaceutical industry to try to do that when it's somewhat expensive, timely, and risky.

The importance of the compendium is very useful. I like that continuum except the devil in the details. What you have is continue to make this low confidence to high confidence. If we know we have low confidence, that's easy to get rid of those measures. We don't use them. If you got a very high confidence, that's a no-brainer. We got that one, but then we got something of used in previous trials to high confidence. Where's the criteria of the dividing point? Do you have something that's necessary and sufficient to make the grade to be included? I think Jean was talking about it at the companies have to do this, and that's a lot of work and its hard work, so I'll use his words.

I guess the last point I want to make, which is actually on a positive note, and this is to Bryce Reeve, on item banks. That becomes really important for things like function as an example. If everybody is concerned, that's a function that's important in everyday life, then we need some way of measuring. If I'm measuring function in someone who has upper extremity pain problems, Carpal Tunnel Syndrome or for somebody who has low back pain, functional activities may be very different than what's important. Therefore walking upstairs may be no problem for the person with carpal tunnel. It may be a huge problem for someone who has low back pain.

If we take some of the legacy measures and we look at the items, the Roland-Morris Low Back Pain and Disability questionnaire. Those who are not familiar with it, it was developed to be looking at low back pain patients. It has since been used for everything under the sun. If you look at the items, they're not necessarily appropriate for use. The idea of Item banks would be if you had sets of functional activities with known properties, you could select items that were appropriate for your particular population, and you would know the properties of the items you know could be comfortable in different settings. I didn't want to be too curmudgeon imagining, but it reminds me of a cartoon that I saw of two gentleman standing outside of a room getting ready to go to a meeting and they see a sign, "Meeting of skeptics tonight, 7:00." One guy says to the other person, "It'll never happen."

Ashley Slagle: Thank you. Alicyn.

Alicyn Campbell: Thanks a lot. In my role as Global Head of Patient Centered Outcome Research of Oncology at Genentech, we consistently think about how we measure what's most important to patients in innovative ways so I really appreciate the comments you just made. I think while advancing the knowledge base for the compendium is critical. I think it's also critical to continue to develop a novel endpoint for assess, what is most important for the patient in a very streamlined, rigorous, and reliable way. I think we still need new endpoints that measure concepts of interest with greater precision, accuracy, and brevity than the current tools and current instrument battery especially if you look at smaller populations and rare tumors.

I see the compendium as an excellent way to bridge the gap as the time it takes for these new endpoint and tools to be developed. For example, we sponsored or conducted a qualitative work with a hundred Breast Cancer patients and we might see that the output indicates that symptoms experienced that are most bothersome are adequately assessed by different tools with rescoring. This is evidence it should be broadly available as part of this compendium to be able to provide confidence in the target claims for an existing tool and the outcome of interest. We think about the slides the Ann Marie showed. How are we developing new tools when we you take that qualitative evidence to show the existing tools or aspects of the existing tools or aspects of existing tools are actually measuring what we think. I think we need to have this in the public domain to advance the field because I really see this as a way to bolster the concept assessed with that.

I want to really make sure that we all think about the compendium and new tool development. Not as two distinct paths, but really things that are occurring in parallel, where the evidence we're generating is going to be complementary. I also think, from the industry perspective, we need to partner closely with the agency and help perform the work compiling a list of endpoints with a process for regular and timely feedback for the agency. I might suggest something with less formality to preserve the finite resource on both sides and I see the critical paths innovations meeting guidance as a critical path forward and that was referenced today. But what I also really like about this process is the public dissemination of knowledge, something Katarina referenced earlier today.

As we gain information, we can really share it across sponsors to advance the field in a way I believe is critical in having open sourced, shared view, shared data, shared tools, shared evidence to really make decision making more streamlined. I just want to make sure that with the compendium we don't really lose sight of the long view, which is we need to continue endpoint development and qualification, creating tools that are useful, not just for regulatory approval but for the routine patient care to really monitor patient outcome. Just to put my comments in the context regarding new tools, there are base concepts of interest with patients and physicians that could be better characterized in oncology that Paul alluded to today, such as functioning, that Dennis alluded to, physical functioning and interference with activities daily living and oncology. That diagnostics to disease and treatment and we do need a way to make those comparisons for tolerability and benefit assessment across patient groups.

This is work that should continue, but that doesn't mean we might not generate evidence as part of this work showing that does not mean we will not generate evidence of physical functioning skills that exist today, and an existing trial can be included in label consideration for patients. I just want to close by kind of circling back a few points both Janet and Paul made, is that although I think the target of our discussion today is regulatory claim, I think it's really important to continue to remember that the most important audience is for the information we are collecting; Its physicians and patients. Our role in providing critical information for their

decision making when they're faced with what is arguably probably one of the most important and difficult healthcare decisions they're going to make in their lifetime, choice of treatment as a cancer patient or another life threatening illness. Thank you.

Ashley Slagle: Thank you. Ellis

Ellis Unger: Thanks, Ashley. I'm Ellis Unger from the Office of Drug Evaluation I here at the FDA. We oversee the divisions that regulate drugs for the Cardiovascular and Renal System and neurology and psychiatry, so heart, kidney, and brain. Without those organs nothing else much matters. The compendium, I have high hopes for the compendium. The Study Endpoints team has gone around to our 3 reviewing divisions and discussed with them the past approval endpoints that have been used, gaps where there are needs to develop better endpoints. I'm very optimistic this process will bring some fruit to bear in terms of accessing how patients feel function and survive, getting the patient's voice into that. I can't tell you how enthusiastic I am about getting patients voice into study endpoints as Paul Kluetz said this morning. Basically if you stand in the doorway of a patient with cancer and ask 'how are you doing Mrs. Smith, you're not hearing the patient's voice because you have to go in and say how is your nausea, how did you sleep and ask all those questions.

I will, after lunch, I will go off the grid a bit and give you my own view about how these assessments might be improved. I'll preview it, like a five-second preview. Basically, if you asked a patient six questions about how they're feeling and functioning and they only care about one, it's only one thing that's really bothering them, their chief complaint in other words, you get that information, but the five questions that you asked, they cared less about contribute noise to the assessment and not signal. And they often can drown out the noise. What I'll do in the afternoon is try to convince at least a few of you that a chief complaint oriented assessment is a much less noisy way to assess a study endpoint and that'll be this afternoon.

Ashley Slagle: Great. Thank you. I think all of the comments were really well taken and. It's now lunchtime. I just want to remind everyone if you have questions or comments to please submit those on your cards before you head out for lunch. Try to reconvene here at 1:10. We'll get started again. Thank you.

Session 2: Advancing Measurement Strategies for Clinical Outcome Assessment Tools

- **Continue panel discussion and questions**

Ashely Slagle: Hopefully everyone had a good lunch break, an opportunity to talk, reflect. We have about 30 minutes for a panel discussion now. We have some audience questions. We'll get through as much as we can in the next 30 minutes. The first question that I would like to pose to all of the panelists and speakers really relates to stage two of the compendium. We talked about stage one. We put the slide back up here for our initial thoughts about what stage two might look like. I know there's been some other thoughts from the panelists and speakers about what we might be able to include in stage two to expand the scope of this, so it may include a review of efficacy supplements in addition to the new molecular labeling, a consensus based approach to add some additional measures. We'd really like to hear more thoughts on what we can do to expand this in stage two, what can add the most to this that is also practical and realistic. I'll open it up to the panel.

Ellis Unger: On stage two, the first EG efficacy supplements. I'm not sure that's clear to all of the people in the audience what they're talking about. Basically, when a drug is approved, the NDA or BLA is for first approval for a drug. If an approved drug is given a claim for a new use. That's called a supplement. When your group met with psychiatry, it's obvious that there were a number of patients that made the claims that they ran into drugs in psychiatry that were called supplements, which not new drugs. Your initial strategy for identifying various endpoints that had been used did not do this. It's called supplement. I just wanted people to understand what this is.

Ashley Slagle: You're right. In the stage one, since we are focused on new molecular entities, it will be a subset of all of the possible clinical outcome that have been used. We limited the scope to get things done quickly and in stage 2 that certainly is an area that we expect to expand into. Are there any other thoughts? Stephen, you mentioned the consensus defines the approach.

Stephen Coons: I would like the FDA to consider what might be a path, short of qualifications consensus scientific on defined measures. Could be legacy measures as they are today, if they're good enough for a modification. That could bring a lot of people out of the woodwork and it could be overwhelming. To consider a path. The other thing I did want to mention and did mention earlier was this issue of what really would be helpful. I think, particularly, in some therapeutic areas where there are measurement gaps which is discussed here to determine what the review divisions really want measured as an indicator of treatment benefit. I don't think that's always sufficiently true.

Ashley Slagle: I've just received a request to ask the panelist to please say their name and to speak directly into the mic and that includes me.

Dennis Turk: I'm not sure if this is exactly on target, but it'll give me an opportunity, my name is Dennis Turk, I'm not sure if it's exactly on target, but I wanted to just clarify. If a measure has been used in a labeling claim for a treatment of problem X and you think that that might also be appropriate for treatment Y, which is a somewhat different condition and has a few different characteristics. How much difference, this is a generalizability question, what are the boundaries, let's assume I used Beck Depression Inventory for painful diabetic neuropathy. And it's never been used for central post stroke pain. What would be the decision process that you would use at the FDA to decide could that be extended or modified in some way? If it had to be modified in some way, how much modification request goes to the entire qualification process versus, which is it's reasonably, you can think about, some things are closer together, if I said painful diabetic neuropathy, post repetitive neuroglia, what about carpal tunnel, what about migraine. You might say they are close enough you might say well they're close enough. How far out does it get where you would start deciding that now you need something totally different? What is the thinking? If there was some guidance, some thinking about how far it would deviate from the original context of interest to say yes, but it's still close enough. How do you decide?

Ashely Sagle: Very challenging question. It's something that we struggle with a lot. Of course the devil is in the details. You've asked a very broad question. It depends on the concept what you're measuring, the different populations. There is sort of a continuum that we have to think about. I might ask Elektra and Marie, I think she has some comments to share.

Ann Marie Trentacosti: This is Ann Marie Trentacosti. I think this is very important and this could be, thinking stage two for instance do we in addition to listing things by condition or disease, do we want to list things by concept. Pain medicine for instance which you brought up, that might be applicable to the same type of measure, of course abdominal pain is that different, a plethora of myopathy, where are they similar and where could they be used across the board and that might be an interesting thought for compendium in stage two.

Elektra Papadopoulos: I agree. I envision that we could have a toolbox of measures based on input and what is important to them and we could use some of these tools and gain more information in the exploratory since, for example, first before having more confidence that indeed we are moving toward the right and in right side of our continuum.

Jean Paty: This is Jean Patty. A couple of thoughts just from my side of things from that. The first thing that I want to say Dennis is it's going to be very hard to do this. To me, part of it is constantly looking at the context of use both in terms that the patient population and also what the concepts are that are relevant for that patient population. In my simplistic thinking, this comes back to content, validity, first which we heard Elektra talked about this morning and then it is actually valuation of files. I've had conversations with folks along this line. The FDA is clearly

comfortable with the instrument used in Jakafi® therefore we can use that instrument in condition Y and Myelofibrosis have no overlap. I think it's a question of constantly looking at what are we trying to measure and in whom. I do think Dennis raised a very good point. You don't know how far away. It's sometimes difficult to answer the question. Is this a variant of the population or is this another population? I definitely don't have a good answer for that. To me, I find a constant source of good information is immediately going to the patient, doing qualitative work and getting my head wrapped around am I in the same ball park or not.

Dennis Turk: can I follow up on that. Let's take Bob Dworkin's example, he talked about rheumatoid arthritis and MS and Chronic Fatigue Syndrome. The concept that we're interested in is fatigue in those different populations. At what point, do you decide, how do you decide that those populations are sufficiently different that you need independently develop measure for the chronic fatigue different from the RA patients? And it is hard. If I was coming to the FDA, what would I have to do to convince you that the measure that we want to use has been well developed for Chronic Fatigue Syndrome? And we know fatigue we know the symptoms measure. That is then having to develop something totally new. We think that the match nicely to the patients. What else would you ask them? I know you can't be specific but in general, what kinds of things would you be looking for to make a decision, to know you've got to go up the whole development process or know there's some internal steps you might get to take?

Elektra Papadopoulos: I think this has been echoed throughout the meeting that we really need to get that patient input to see how much applicability an existing measure might have when applied across conditions. That's really something we'd consider on a case-by-case basis. It's very hard to discuss in generalities. I know, Ashley, you have a number of questions so let's go to those.

Ashley Slagle: I wanted to just give one more opportunity for the panel if there are other ways we think of expanding the compendium in stage two. We'd really like to hear that. Stephen you also mentioned the opportunity to expand to include outcomes of interest and not just measures. We've talked about that internally but I'd like to hear from the panel, but I'd like to get some comments on that, whether that would be helpful to stakeholders too. When we can't identify an instrument that's available but putting on the list something that is important. And how we might identify what important outcome exists to put on the list

Alicyn Campbell: I think it's really important to consider outcomes of interest in that instrument and I really like the way you just framed that question. I think, in thinking about patient conditions, we shouldn't be thinking about tools. We should be thinking about endpoints. An endpoints this is going to address outcomes of interest to patients. Whether that is preservation of fine motor skills if I have a brain metastasis or preservation of my ability not to have dyspnea if I'm a lung cancer patient. I do think a stage two is going to be what we need it to be for us to have a consensus approach, identifying experience of unmet measurement need and

outcomes that are most important to patients. At the end of the day, we might think a symptom is distressing but if a patient ranks another aspect of their symptom or treatment or disease burden higher we should focus on that. I definitely like the idea of having the agency and perhaps patients communicate this unmet measurement need. Perhaps we can have a timeline, because if we have a timeline for knowing what those concepts were that we at industry could then react to and influence. It takes time to address endpoints that might be able to move things forward.

Tom Sellers: Tom Sellers. I think that's really important. The stage two is also focused on communicating unmet needs. There may need to be some incentive to get folks who want pursue the unmet needs. It may take more than just communication in order to actually make it happen, particularly for a patient groups to get engaged in this kind of activity. Some of the experience I've had in working with patients, we've been talking about how we'd like to get them engaged in patient reported outcomes. They're very interested in providing input to measure and input for the instrument, helping us to define what's important, but there's not a real strong interest in creating their own instrument to report outcome because of the cost and how hard it is to do.

Bray Patrick-Lake: I think it's really a little bit just something that was provocative, as Stephen said earlier and I don't know if we can do this in stage two. He kind of mentioned there might be tools with or without developed in partnership with patients. I was wondering what's the good housekeeping seal of approval where a patient group actually says, "This is what's meaningful to our disease." It's probably a little unpractical, but how do we actually know there's a line between the patient community and whoever put forth the measure into an application?

Jean Paty: I think building on that, for people that I've done work with. If you communicate the need and it's actually that's coming through, especially patient groups that are communicating, if patient groups are helping communicate an unmet need. The one thing would motivate, I know folks that I work with is that if we can then partner with that patient group to actually get access to the patients, that would be a significant motivator because it would greatly cut down our time and potentially cost to move forward. Tom, I was thinking about something you said earlier. Again, I don't know if this is stage one or stage two, but you said how did things make it to the list? And to me again I go back to the qualitative work. There's some venue for us to reflect that in the compendium, I'm not sure what stage that indeed this is here because patients have said this is important and that aligns with the instrument that becomes the endpoint and the potential claim. You could definitely motivate a bunch of us if you say, "There's an unmet need, and by the way, here's a vehicle to get to the patients."

Ashley Slagle: I would like to ask the panel and speakers some reflections on the continuum and ask if you agree that. You can see that we have qualified as primary, secondary endpoints as the furthest, the highest confidence, all the way to the right there. I mentioned earlier that we've been approaching qualification as having really

the highest evidence, we're prospectively recommending these tools, they need to have patient input, they need to detect small but meaningful changes. I'd like to ask if there is agreement that for qualification, this highest level of evidence needed for qualification.

Bray Patrick-Lake: My primary community identifies with the patient group. I think the end of the spectrum are fine and they seem clear in the middle I don't really know what that means. If there's already nothing in critical path, it's taken 8 years, 7 years, 8, 9, 10 to develop a PRO. I'll keep going, but that's way too long and it's completely unacceptable. Not to be disrespectful of all the great work that's going on and I realize this is complex. Patients can't wait that long. I think we need to come up with some type of solution. If you come in as a white space and there's nothing for your disease yet, that it's been developed under these models, then look in the item bank. This is the nausea, the fatigue, the insomnia, the itching. Some things that we can all agree on, but I'm concerned about this middle piece because it is kind of sculpting the fog.

Stephen Coons: I am concerned about the amount of time that it takes to get qualification and the hurdles that we jump over to get there. I was talking to a woman at break about an orphan disease and the need for an endpoint in that disease to even draw pharmaceutical company interest to it because if there isn't a viable path for it in terms of getting an approval in an area. It could be very hard for that small advocacy organization to take both the time and the money that it would take to get the full qualification of a measure so I do think there has to be a viable path to bring measures forward. But again we are short of qualifications if indeed if the qualification bar is going to be as high as it is now.

Alicyn Campbell: I have some follow-up question to Stephen's point. Something I was thinking about was if we create a new endpoint that hasn't gone through the DDT process, but it's brought to an agency via type C meeting, where does that fall on the continuum? I'm thinking it's in the 3/4 quartile. If I'm thinking of this question, I know someone else is. Where along that continuum is the instruments that are developed and shown to be well reliable and valid and perhaps brought to the agency via a type C meeting of rather than through the DDT process? Where do you see that on the continuum?

Ashley Slagle: I think they could follow on the continuum. In some cases, it could certainly be as hard to the right as a qualified tool. I think you raised a good point because the previously labeled tools that were put into the compendium, some of them will not be qualified but they will have as much evidence as a qualified tool. Some will be further left on the compendium where we have some gaps in knowledge. Our thought was to describe that these tools still need to be in the guidance. They still need to be discussed with the review division in advance, as early as possible, so we can help advise on these tools where we have strong evidence or where we don't and where there may be gaps that the sponsor may consider filling just for their own individual drug development career.

Alicyn Campbell: I didn't want anyone to look at the slide and think that unless it's qualified it can't be a primary, secondary endpoint and wanted to make sure we were clear on that. Thanks a lot. I really appreciate it.

Jean Paty: Jean Paty. I'd like to build on that. To me that's a key thing, I don't want folks walking away thinking if you are not all the way to the right there's no goal. One of the things I wonder about, slight variant, is there's a number of tools that are in the qualification process. It almost seems like when they're in the qualification process, you're in a black box that we can't access. If one path to potentially a good enough for now is through IND and potentially on labeling, it seems to me if a tool is far enough along in the qualification process, let me have it. I would take it, and I would take it far enough along and work with you and the IND to get it approved. That shouldn't affect the qualification stream at all. Not right now. I feel like, "Great. I know that FDA is interested in this kind of thing. It's in the qualification path. So, I'm going to go develop something that's like that and then go through an IND." It'd be great if we could leverage that so continue to stream and then end up on here. Your thoughts on that.

Ann Marie Trentacosti: Thank you, Jean. This is Ann Marie Trentacosti. I think that was really the purpose of putting instruments on the compendium that are undergoing qualification is to encourage collaboration so that Instrument developers won't duplicate that process but contact the PRO consortium saying we've got this drug, what can we do, can we participate, where are you right now. It's certainly not duplicating effort that we're not there.

Elektra Papadopoulos: I'd just like to add to that. In fact, that could be advanced, the qualification process if the tool is at the stage where it could be used in a clinical trial. The measurement properties obtained from that could really help with the qualification process as well as that drug development program.

Ann Marie Trentacosti: Can I ask Stephen a question, because you do currently post these programs on your website, do you see that folks are taking advantage contacting you, encouraging collaboration?

Stephen Coons: Yes, that is the case. We do get a lot of inquiries about the tool, what stage of development they are within the PRO consortium to use the instrument, once it's qualified for exploratory use, then it would be available for use beyond the consortium. One way of getting access to it is to become a part of it, the consortium. We are talking to individual member firms who do want to use these instruments before we even get to the exploratory qualification step. So we do see that as a true advantage in collecting data. They'll use it only as an exploratory endpoint. But it would provide very valuable data.

Ashley Slagle: We have some more audience questions. How does one currently find Clinical Outcome Assessments that are supported product labeling? We have an online resource, drugs@fda.com where we post current product labeling as well as

reviews for approved products. It's easily accessible online ,in the labeling. This question is a little bit more complicated. The panel can comment on this. A lot of progress has been made, I think this is referring to the compendium, how are the success of these new steps being measured? A. by more thorough label claim, B. by less abuse and misuse of PRO and regulatory submissions, C by something else. I'd like to give some initial thought that we have discussed this internally. We're still discussing it how best to measure success in all of the effort that we're undertaking in particular with the compendium. We can do internal and external surveys and look at counts of the number of qualified instruments, the number of PRO's and patient centered outcomes that are in labeling going forward. But I would open it up to the panel to ask how you would think about evaluating whether the Clinical Outcome Initiative and the compendium are really successful, in moving the field forward.

Stephen Coons: I do think it gets to numbers, to really looking at the number of additional approved products that have COA endpoints in the label. I don't see any other way than to quantify it in that sort of way.

Dennis Turk: This has been a, obviously the numbers is important, but it seems like there's always two levels of numbers. There's the, how many instruments are being qualified, and then second, how many of that qualified instruments are actually being used in studies to see if they're actually coming forward. Both studies were indications but also studies in the literature I would hope, naïve academic that I am and in addition to talking so much about the FDA approval process, that there's no reason why these measures could not be adapted to other kinds of studies that are not specifically related to coming into drug indications .I would look for numbers of qualified instruments, number of times that have actually been used in FDA related, and the number of times of getting picked up and used outside the system.

Tom Sellers: I would say also because you don't want the compendium to stifle innovation. How many new instruments are being developed as you go along? That will be a measure of whether or not it's generating innovation as opposed to stifling.

Jean Paty: Tom, you and I should work together because for some reason every time you say stuff, you gives me a new idea. Something I just thought of, literally as Tom started to speak, was, there's, this touches on some sensitivities, but I'm not known to be particularly sensitive to these things. There's a number of instruments that we're developing that nobody knows about. One potential path encourages, can we find a context in which those actually get listed on the compendium? There's opportunity then to potentially enter into a collaborative effort, especially the larger group consortia for qualification is a different path than we need to get this done.

I think we need to have further discussions about how we protect potentially set that context up with folks to get comfortable. To you measurement question, and maybe I think this is what Stephen said, I just want to see all kinds of lines start to fill up this continuum. Then somewhere on the left, there's going to be a line. To the left of that would be blank. If we start filling that up, and then at some point say, this line here,

here's what that really means. It would be a very valuable measure of success and clarification points.

Ashley Slagle: We're almost at time here. I just have two quick questions. First, when will the compendium be publicly available?

Ann Marie Trentascoti: The first step is the FR notice and a mock up similar to what I had showed on the slides, but more extensive. We're really aiming for that this year, this 2015 year. The compendium will take a little longer, the actually full compendium because it will be accompanied by a draft guidance. Obviously we'll have to do those simultaneously and that takes as you can imagine a bit longer. I don't anticipate that necessarily, but the first thing obviously would be mockup and the FR notice. We'll get more comments on that which we can add to the full compendium.

Ashley Slagle: Thank you. One final question. Elektra this is to you. Is FDA going to consider guidance for other outcomes like Performance Outcomes Measures?

Elektra Papadopoulos: Yes, that's definitely on the table for us to consider. I think this has been raised by a number of people that we have the PRO guidance, but then how do we take those principles and apply them to other types of Outcome Measures. That is definitely on our list.

Ashley Slagle: Thank you. Any final parting thoughts from the rest of the panel, speakers? Let me thank you very much. I think this was a really helpful for us and hopefully for the audience as well. I appreciate your time. Thank you. If I could now ask the participants for session three to join me upfront.

Session 3: Use of Clinical Outcome Assessment Tools in Multinational Trials

- **Stakeholder Perspectives**

Ashley Slagle: Now we're going to shift gears into session three. I will be moderating this session as well. This session, we're going to talk a bit about the use of clinical outcome assessment tools in multinational trials. We're joined by five great speakers in this session, who has agreed to share different perspectives, learning, challenges, opportunities, and suggestions that are related to the development and use of clinical outcome assessment for multinational trials.

This session will not have a discussion panel, or audience question and answer, but each speaker will provide her mark for about 10 to 12 minutes. I think the information that they'd share will be really helpful to all of the stakeholders who are thinking about international collaboration and thinking about incorporating Clinical Outcome Assessment into multinational trials. I'll first introduce our speakers. We have Dr. Maria Isaac who is the Senior Scientific Officer and member of the European Medical Agency scientific advice team and she'll share her perspective on the importance of harmonization across regulatory agencies as well as share details about how FDA and EMA work together specifically within the drug development qualification process.

Dr. Andrew Mulberg, Deputy Director Division of Gastroenterology and Inborn Error Products here in CDER will share his perspective on the importance of global stakeholder engagement, sharing examples from an international collaboration in Irritable Bowel Disease.

Dr. Donald Patrick, professor of Health Services University of Washington will share some important considerations and good practices when implementing Clinical Outcome Assessments across multinational sites.

Dr. Debra Silberg, a Vice President at Shire where she has worked in GI research and development will share some challenges and suggestions in approaching the use of Clinical Outcome Assessments across multinational sites from the industry perspective.

And then Dr. Laura Lee Johnson, Associate Director, division of Biometrics III, Office of Bio Statistics here in CDER will share some practical advice about incorporating translations and cultural validation activities into an instrument development process within an individual drug development program. And with that I'll ask Maria.

Maria Isaac: First of all, thank you for inviting me to this fascinating and timely conference. I've learned a great deal already! I would like to express my gratitude to the organizers for the invitation today. Having a foot in both clinical academia and

regulatory affairs, I appreciate that each has its own perspective. I am taking part in this meeting as a senior scientific officer working in development of medicines at EMA, though of course my views are my own, whilst they are in keeping with the regulations. In this segment, I want to give you an overview of the European perspective on novel methodology qualification, pro and the key stake holders involved on it.

The European Medicines Agency (EMA) is, in essence, a networking agency involving the national competent authorities of the 28 Member States of the European Union. It facilitates cooperation and coordination of Member States' activities concerning medicinal products and its work is underpinned by the European Experts' Network, supporting the committees and working parties of the Agency. The current expert list contains 4,900 nominated experts, including patients, who are selected for their expertise in the particular area, rather than by their nationality.

The main standing committees of European Medicines Agency comprise the committees for human medicinal products (CHMP), orphan medical products (COMP), herbal medicinal products (HMPC), pediatrics (PDCO), advanced therapy medicinal products (CAT) and pharmacovigilance risk assessment (PRAC). The whole is served by the Scientific Advice Working Party (SAWP). The SAWP is a standing working party of CHMP, set up by EU Regulation 726/2004. The EMA orchestra is a large one, containing a number of scientific advice groups (SAG) and working parties. For the present purpose, the diagnostics, pharmacogenomics, modelling and simulation, statistics and methodology, SAWP and CHMP are the main actors.

How do we embrace and fund disruptive and challenging concepts? In the development of innovative medicinal products. The creation of a development road map for innovative products - can be thought of as following two parallel work streams, scientific advice or protocol assistance and qualification advice and opinion. Scientific advice and protocol assistance are product and indication specific. In contrast, qualification advice and opinion has a broader scope and may concern several indications or products fit for pharmaceutical medicine/ patients / academics/ government, where a rapid update of translational pharmaceutical science for a global medicines development can be formulated.

The data are assessed as part of the qualification advice and opinion. Finally, if the applicant agrees, the qualification advice and opinion are made public if a positive opinion is issued. Note - The term, 'qualification,' means the official regulatory opinion on the specific use of the proposed method (e.g. use of a biomarker) in a research and development (R&D) and/or clinical context after the review of the presented data. It can be a way of streamlining the marketing authorization procedure

A CHMP qualification opinion on the acceptability of specific use of, say, a clinical outcome or patient reported outcome or performance assessment outcome in a research and drug development context, is based on the assessment of data and is not specific to the individual product. The process involves a qualification team including patients, health technology assessment agencies, academics, experts, peer review, public consultation and publication. We have scientific guidelines specific to therapeutic areas where we incorporate the accepted clinical outcomes and we also as example we have A Reflection Paper on the use of patient reported outcome, (PRO) measures in oncology studies states that a PRO includes any outcome evaluated directly by the patient himself and based on patients' perception of a disease and its treatment(s). Patient reported outcome is an umbrella term covering both single dimension and multi- 'Clinical studies in oncology may include PRO measures as secondary or exploratory outcomes and rarely as primary outcomes, incorporated as part of the initial trial protocol.

The general recommendations for the incorporation of PRO measures in clinical studies include the extent to which the inclusion of PRO measures can provide added value in the clinical trial setting; crucially can the collection of PRO data make a difference to the study conclusions. PRO endpoints should be incorporated into the protocol development at the earliest stage and should be explicitly stated as a specific clinical trial objective or hypothesis. For specific therapeutic claims in Section 5.1 of the SmPC, a clear hypothesis lead strategy is required and measures should be selected based on their 'fit' with the hypothesis.

Questionnaires & instruments should be administered to study subjects at time points when there is a clear and hypothesis driven rationale for their use and when it is feasible to expect high levels of completion. PRO instruments should match the abilities of the patient population. PRO data should be treated like any other data in monitoring clinical site performance and collection methods Selection of an instrument, It is beyond the scope of this reflection paper to make specific recommendations regarding valid instrument selection, but in general, the instrument should be shown to measure the concept it is intended to measure, be appropriate for the research dimension measures of symptoms, health-related quality of life (HRQL), health status, adherence to treatment, satisfaction with treatment.

The paper also says, a major change I've noticed during my time at EMA is the emergence of parallel qualification advice between the FDA and us. We have learned so much over the last 4 years, and I especially want to thank you Elektra, Ashley, Laurie Burke, ... and everybody in the qualification endpoints team for working together and such a fruitful collaboration. Every 3 months, sometimes monthly, we have meetings that have become discussions where we can keep each other informed and can collaborate in learning, and these teleconferences help us to listen to each other and collaborate in a transparent way.

The good news is that the Agencies have agreed to use a common letter of intent for qualification procedures. This is voluntary at the sponsor's request, and involves

questions on clinical outcome tools development being put to both FDA and EMA, followed by discussions between the two Agencies and joint discussion with the sponsor. Each Agency, however, will issue separate responses to a sponsor's questions according to their individual procedures. The possible benefits of such an approach include increased dialogue between Agencies and the sponsor from the early stages of development, together with the exchange of views and sharing of expertise and best practice. What is needed to make investing in disruptive and challenging concepts attractive, particularly to private investors and society? As regulators we base our decision in a benefit/risk and again the main discussion during the qualifications opinion is around that because the label will reflect the results of the qualification data assessment, thus base in the population study and the symptoms treated. Better that is the clinical outcome clear it will be described in the label. We cannot forget that patients' representatives are involved in scientific advice and qualification procedures of clinical outcomes and to the agency these discussions are fundamental. Slide 8 &

To conclude, but can a PRO be qualified by the FDA and in EU? Here's a well-known example from respiratory disease. The next step is to translate the regulatory language to a patients language, if we are able to understand what are the benefits and risk of taking this medicines and what this mean you will improve clinical practice, patients adherence and better inform the discussions with reimbursement authorities – not as easy as it sounds!

Early engagement of FDA and EMA during the planning stage of the projects has been key in building a regulatory framework to support future PRO and clinical outcome measures development Continued FDA and EMA oversight and guidance different projects to ensure adherence to regulatory standards People have sometimes asked, Is all this just another bureaucratic burden that stifles innovation? Well, I can just say this is the regulation, but if you think about it, all I have been talking about is a transparent process to improve a quality control, which can only benefit patients and indeed all of us.

In less than 5 years, EMA has incorporated translational science in drug development in collaboration with multinational stake holders, spearheading the advancement of regulatory guidelines. We have learned so much over the last years about COA that we are in a unique moment in history. You have all stake holders working together and the more that we have learned, the more that we are beginning to understand how to incorporate the patient voice. Thank you very much.

Ashley Slegle: Thank you Maria, Andrew.

Andrew Mulberg: Thank you very much for the invitation to share in all the enthusiasm that we have for global stakeholder engagement which has both implications for adult and pediatric drug development. The efforts that were discussed today are specifically focused on pediatrics and focused on pediatric inflammatory bowel disease. I think to craft the best example that one is ongoing,

continuing in our division is referred to international inflammatory bowel disease working group. It has consisted of collaboration, teleconferences, although we all wish we could see each other face to face. We've had really only one opportunity at our great meetings to interact with our diverse leaders, to be able to come to EMA, Health Canada was represented yesterday at our meeting.

This is a broad based global regulatory collaboration of EMA Health Canada and the NDA with those us and the USFDA. We initially started this program in 2012 and has continued to this day. We initially focused on Ulcerative Colitis, which is a focus of intense global interest. An area of focus for representing many orphan if not all orphan diseases. Our programs need to be conducted in a conducive way to yield viable results. We focused on various topics, all of which are listed on the slide as efficacy data extrapolation from adult data to developmental Clinical Outcome Assessments and other aspects.

These were successful collaborations resulting in a number of manuscripts which were in published literature. Those titles are reflected here. Our ongoing efforts in Crohn's disease will be most likely published assumed that the moments are right off the data. These are efforts that again are global in terms of not directing guidance. So, I'm careful to make sure that it's understood not as guidance, but really more as talking points and a framework for drug development programs, so there can be continue progress.

I will say that this is going to be continued in a meeting in June at the EMA on specific relevant topics in pediatrics, Ulcerative Colitis, and Crohn's disease, but have implications for a very old, a rare and orphaned disease drug development, role of placebo, a trial design. We need to be able to learn on how to develop Clinical Outcome Assessments, as you talked about earlier in terms of development of toolboxes, we can learn from what we do in the other pediatric development programs. This resulted again in an annual meeting we've held since 2012, which has had international collaboration; representatives of Australia, TJ were here yesterday, Health Canada, EMA.

We're making progress with regards to outcome assessments in pediatrics or drug development. I would be happy to say that collaborations with our SEALD colleagues also have influenced us publishing in the area of Eosinophilic Esophagitis developing Outcome Assessment for another orphan disease in Gastroenterology for which we're proud to be able to continue. We think it's an important mechanism with our global development programs. I would say that Dr. Isaac and colleagues we're sharing a qualification process for a Clinical Outcome Assessment for pediatric goals for Colitis right now. I think it's a continuing success. I don't know if I'm allowed any questions, I'd be happy to answer. Thank you.

Donald Patrick: Thank you very much for inviting me. My disclaimer is I'm really channeling my colleagues and friends. We're going to talk about cultural adaptation and a tentative culture in Clinical Outcome Assessments. Context is a

really growing interest in clinical outcome success groups in the global context. For the most part, we have developed Clinical Outcome Assessments in one language. Predominantly the UK and the US and the Canadian English and we translated it to other languages and the culture adapted it.

In other cases, there have been a few instruments in Swedish and in Chinese that have gone ahead of direction. These need to be culturally adapted for use in global clinical trials and thus we are talking about translation and cultural adaptation. What are the differences in the COAs that might require us new consideration in cultural adaptation? For example, what's the appropriate adaptation process when doctors ask questions in their interview and their answer is generic trial data?

For example, is the DS5 translated sufficiently so that the questions asked by clinicians in psychiatric clinical trials are done in a language of the patients, rather than the instructions being in English and the commissioners using their judgment on how they translate the diagnostic criteria? How should patients, clinicians, and observers be involved in the translation process for a specific Clinical Outcome Assessment. Are there differences between the different types of COAs. For example, the observers and then the Observer Reported Outcome and what the actual concepts and so forth are in the translation process.

How does the process accommodate the growing migrant populations? Some populations, it's a very, very large pool of people that actually have a primary language that's different from the language and the culture in which they are living. Finally, what are the considerations needed for global use with a wide variety of electronic platforms and devices that are currently available? Why is this specialized methodology necessary? Surely, anybody can do this in another language. They can simply translate the words. In fact if you go into Google the translator, play with that because it's very, very interesting to see what comes out in when you put in your English phrase and you see it in Chinese.

Over 60% of pivotal studies have submitted to CDER in 1967 contain data from one or more foreign study sites. You can imagine that 6 out of 10 is now more 8 out of 10. It's very expensive to do the work in America and Europe itself so we're increasingly going to global clinical trials in Eastern Europe, Southern America, India or over in some cases other parts of Asia. We need some discussion of cross culture equivalence. The reason for this is that we simply pool the data. There are methods, methods about comparing the data across countries, but essentially why are we concerned about this? It's because taking this data and looking at the efficacy of a medical product as a whole.

Cultural adaptation is the first step towards achieving and testing whether we have cross cultural equivalents let alone psychometric or measurement equivalence across the different inputs. So is it important to do more than basic translation? Yes. Translation, what is it? It's an act of bilingual communication. It's a rendering from one language into another. It's the product after that rendering that's made possible

only because they have parallelisms in thoughts and situations, and the transcoding operations. I learned this big time in the 1970's in the international pilot study of schizophrenia. We found different types of words used for schizophrenia since 1970 throughout the entire world, so there have been parallelisms in actual transcoding operations.

The representation of reality may be coded differently in different languages. Cultural adaptation, we make these Clinical Outcome Assessments useful in multiple languages and multiple cultures. It involves several steps that all these translations techniques in a target population. Therefore it's more than simple translation. An example of this would be the orange campaign in the United Kingdom. Orange was a mobile network operator, an internet service provider in the UK. It was launched in 1993 and 2009.

They had a motto, "The future is bright. The future is orange." Not for the Catholics of Northern Ireland. They do not see the future as Protestants. This falls as a problem in different places. Even the simplest thing, "the future is bright" has different possibilities in different cultures. There's another example in conceptual analysis. This one is so old, and I absolutely still love it. It's trying to translate the health assessment questionnaire that I wanted to hack. The original is in US English. In the eating category there was an item "Are you able to cut your meat?"

What is the concept behind this item? It's not are you able to cut your meat. It's the patient's ability to do a micro movement of the upper extremity, whether it was take a knife and fork and cut the meat. The item and cultural adaptation to help assessment questionnaire, "Are you able to cut your meat?" we're going to Hindi in India. They do not cut their meat. To assess the patient's ability to do micro movements with their upper extremities, the problem was use of a cutlery, vegetarianism. This is the culture equivalence that goes on and we're inclined to go from one culture to another.

Another quick example before we're back with the physical item bank US English. "Are you able to push open the door after turning the knob?" Target language Dutch. I don't know how many of you have been to those tiny hotel rooms in Amsterdam. The concept here is to explore the patient's ability to use his or her hand and their functional-ability. The problem is you don't have doorknobs in the Netherlands. Many doors have latches. So, "Are you able to push open a door after pushing down the latch?" is the cross cultural equivalence.

One approach or an approach is translate an ability measure. This is the evaluation of the extent to which to which a PRO measure can be meaningfully translated into another language. This is quick a trick with lots of linguistic expertise necessary, and there is a difference of opinion on how you go about this. We're trying to work on a sort of guidance on this. Some say you have to do all the entire thing in order to figure this out, but there can be guesses at what is going on in the family. It's a meaningful translation in the context of that. Global clinical trials is one that is

conceptually equivalent in the source text and culturally and linguistically appropriate for the target country. There are some countries where this is not going to go down terribly well. There are some languages in India where the concept is quite limited. The goal of TA is to identify translation difficulties if it's just items to be modified or identified for deletion before embarking on the translation process itself. Those would be when you cannot actually translate or culturally adapt the question. You can find how good practices are in cultural adaptation to looking at the ISPOR website and principles of good practice and all these different steps which I don't have time to go through.

Some of them may look really funny to you. I can guarantee you, it's extremely important to proofread what's going on with the languages you're trying to create with a user manual in all the languages that are important. I've been most interested in proof in the pudding. How much can poor cross-cultural measurements affect all of your measurement properties in the global clinical trials? We started out with statistical power. I published a paper recently in quality of life research on the potential effect of the difference in the estimation of a PRO measure on power to compare this between treatment groups in an overall sample.

The impact of poor measurement can induce a notable drop in study power and consequently your chance of showing an actual treatment affect. This result shows the importance of the effects to optimize cultural equivalence of PRO measures and standardize the assessments when pooling data in international clinical trials. This is an example from an advisory committee of the FDA. It's a very old example. Just know this. Is this a real difference in pain or analgesic progression in these countries or is there a problem of in the cross-cultural equivalence of the concept in a way in which it was measured during these trials? It's pretty wide variability. In summary, cultural adaptations are complex and a very challenging process. It's not word for word. It's world for world. Thank you.

Ashley Slagle: Thank you Donald

Debra Silberg: Hi, I'm Debra Silberg. I'm from Shire and I love following Donald because he gives such an entertaining and informative talk. But I'm going to talk about the industry perspective. First, I want to thank you for inviting me. I'm very passionate when it comes to Clinical Outcome Assessments and I've been working in this area for a while, even though I really do my job in clinical development in general. I'm a gastroenterologist. So, the examples I'm going to give are all from GI. The statements I'm going to make also are my own, not necessarily those of Shire.

From an industry perspective, most drug development and global issues. It's unlikely that the US would be the only country in this clinical development program. Even when we're talking about multinational, I would say that even if you're doing work just in the United States, you still have to consider different cultures. The US is a big mix of different cultures. Things might not be the same, depending on where

you are. I did feel when I was looking into the sect, the guidance, the FDA guidance, has really very well guidance on how to make certain that COAs are appropriate for multiple cultures. Most of us don't have own whole group of COA experts within our company. Often we are going outside. There is difficulty knowing that the company that you're using to perform the exercise is really qualified to do this type of work. It's almost buyer beware in this case. I found that there are very little standards. I was referred to the ISPOR guidelines. I think that's a really good idea.

I've been in this field for a while. Maybe I should have known that. I know that I've contracted companies. I really almost just assumed that people knew what they were doing. One of the things from an industry perspective it would be good to have some kind of certifications for the companies that are doing this work. Maybe that's too much to ask for but something that concerns me, one of the things that is very important, it's mentioned before, it's that forward and back translations are not enough.

That cognitive debriefing is very important to make sure the concepts are understood. I'm going to give you two examples. One translation is not enough. We wanted to study gastro-esophageal reflux disease in China. We did a very large survey. What we found was that it didn't exist, it was rare. As a gastroenterologist, I'm thinking is that really possible. It's so common here. It's so common in other countries. I don't really know. I'm sure that the group I was working with has done more work there, but to me, I think it's just how it was asked. If the concept of heartburn or even burning behind your breastbone or however we said it, it's not a concept that's understood by that culture, by that community. You're never going to get the understanding of that disease. You really have to go in and talk to the people who know how it's expressed to understand the disease that you're talking about. We recently developed an ulcer colitis questionnaire for pediatrics. There is no issue with it, but one thing that I did see when I looked at the cultural adaptation is what I'd like to see when you're doing this kind of work.

The kind of questions that they asked to the participants, it was either a caregiver or it was the child themselves is "Do you understand this question? What does this mean to you? Can you explain it in your own words?" That's really key is that someone has to then tell you what it means. "Can you suggest any alternative wording?" it was a little difficult for me because I don't, unfortunately, speak any of the languages, and a lot of it was in other languages. One of the things that came out is that when they were asking them about something that happened the day before, that concept, especially to a lot of kids, they didn't really understand it. We had done it initially in English and then translating it, we were trying to figure out how that expression would translate for these children. One of the things that came out is if you need to change something, make sure you change it, but that it doesn't actually change the question you're trying to answer because you have to make sure it applies across the board.

In one culture, if you say you've made a change that they're asking not for the night before, but for the day before, that would be a problem because everybody else is asking for the night before. That's another issue. It's making sure that if you do change something in another language or another culture, that it means the same thing.

Those are the kind of things that we have to consider. We have to make sure that we're doing our study and because we're doing it in many different cultures and many different nationalities is that we can combine the data. I thought that Donald's example was great. I've seen this too. It's where you see a big difference in a particular country and you don't know if it's the disease or the way you ask the question. I was in an unfortunate situation where, and I don't know if this is a cultural issue. The physicians didn't like the idea of the patient answering the questions. He said it was his obligation to ask the question. That goes against the whole concept of Patient Reported Outcome. It's also a site selection issue as well. These are the things though that we deal with, and they're not uncommon. We, as an industry, have to be cognizant that there are going to be differences. We have to make sure that we are thinking about these differences and we're doing it from a development program. Thank you.

Laura Johnson: Thank you all for inviting me today. It's been a pleasure to join the FDA group. I'm going to talk to you today to get some practical advice. I'm going to talk across a wide spectrum not just qualification, but also about the entire medical product development standpoint. Many times, we think about starting in this realm. A lot of times people talk about modifying current instruments when they're talking about multi retail trials. They're talking about translation and adaptation. That's really late in this whole big process. What I'm here today to remind folks about is start at step one if you can.

When you're identifying that context of use that concept as interest. I say this not just for myself, but because I'm hearing this repeatedly from sponsors. The symptoms are just different when we're in different countries. The expression, how we want to do our development is different. This is true regardless. If you've done all of your development work, you're at the end of phase two, and now you want to change your study endpoint, as a statistician, my heart starts beating a lot harder because I know how to justify, sample size without really having any data behind it. Not that much evidence.

The same thing which is important in fact to think about your entire drug development timeline, you've got to think about the risks and benefits. That's one reason, as you've heard this morning, we're working so hard in order to try to make sure that we can actually meet early and often, because if you back in to thinking about your pediatric population, people that may have cognitive issues, perhaps everything you're developing is on paper, but folks can't read. You back into multiregional issues that can be very costly.

But I'm a pragmatic person at heart. I'm the daughter of an engineer. I'm all about how it's going to actually work. Development work early on is also really costly. We understand this. We get that. It is important to be thinking just like as you're thinking about how is this product going to be ingested, how is it going to be used? How are we going to manufacture it? What are the tools? You have to think about it all the way from the very beginning of how you're going to be implementing everything at the end. When we talk about developing tools, as a statistician, I'm thinking two different ways. I'm also thinking how am I going to be evaluating this information when I see the statistical analysis plan for a phase two trial, for a phase three trial, and I'm looking at this post marketing information. When I go with my father to the doctor, and he's being evaluated. How is this going to be used?

Practical advice, I actually, as the last two speakers said, folks come up to me, and they're like, "Hey, all my data is 0-10. What's the big deal?" I love my numbers, but I also know that 0-10 does not always match up to 0-10. On top of that, you do have this issue with cross-multiple regions, and it's not just for COAs. It's not just for Patient Reported Outcomes. This is an issue. It's in what's called E5. We're going to link to that at the end. As a statistician and we have to look at data for each region. You want to not just do subgroup analysis. You have to do, and we all want to do, analyses of the whole. How are we going to do that? Data collection issues, it's great to use electronic methods. I like using computer methods to collect data. I hear from patients all the time. Like for example, my father. In fact, if it has a big enough button, it's easier for him to push than to shake and try to write. He likes that, but doesn't mean when I go to Nigeria and I do my research there also, that I can always plug my data that way. However, sometimes it's actually easier to do electronic collection than to have paper scattered all around that you can't have input.

You have to think, "Where am I going to go? What do I need to do?" However, that again is particular of our drug development timeline. We're used to thinking in that way. Many times, we're planning out. Even though you're in phase one, if things are going to move forward, what countries are we going into? Especially if you're working with a very defined disease population. Many times you know where you're going to be going. So, this can be worked in to our entire development paradox, because again it's really difficult and I have the quote 'it's a review issue'. This can mean different things and people are laughing about it but this is something that comes up. It's not that we want evidence to be ignored because it's very important. They're working on their tool.

They know that there's not really good endpoints. There's not really a good primary endpoint. So they're developing it. They're doing a good job. They get into their phase two study. They're collecting more data. They realize they're going to go into other countries. They start looking at the adaptability. They start doing additional qualitative work. What they realize is they need to change the tool. They need to change the PRO. They need to change maybe the electronics versus paper aspects of a diary. They may need to change the number of items, the wording etc. We have all this phase two data.

Well, you're actually at risk. We want to use now this new and improved Patient Reported Outcome, a Clinician Reported Outcome. We want to use it in your phase three trial as your primary input. This is a problem. It's a risk, but that's part of this. It's that there's a risk and there's a benefit because there's also a risk for waiting and doing additional study. That's one of the, I believe I heard somebody yesterday call it the theoretic or the noble aspect. I believe it was of qualification, was that when we do have these multiple paths that we can collect it to show information and gather that part, so in fact you're not sitting at a end of phase two meeting and everyone has heartburn, but realize it was the way forward.

Again, there's risks. There's benefits. Not necessarily saying yes, but no. Again, this isn't just COAs. This happens in a lot of places. Sometimes you're going to see differences, but they may or may not be meaningful. That's something else we have to consider too. So speak early. When it comes to translatability, I cannot emphasize enough. Everyone says it's hard. I agree. Every single aspect of clinical research is hard, but if you're not going to be able to do the translation early. If you're not going to be able to do full adaptability of the adaptation early, think at least about trying to do translatability earlier in your development because, again, we want to have a follow-up measure.

There's some tricks. Literacy is a huge issue. One of the first studies I worked on, it's like a study. I was doing it as an undergrad helping out to get extra spending money. I'll be honest, but it led me into biostatistics. It was in Virginia. Most of the women in that study could not read the patient reported outcomes that they were required to use. Therefore the psychiatric nurses would read them to them. It was incredibly burdensome, and there were huge issues. If you're going to do your early development and you're only going to do it in one country, I call this my Sesame Street.

Go into pediatrics and go into literacy. Use those little literacy groups. One because they will be in your studies. Therefore it is our obligation to make sure that they understand what we are asking about. On top of that, when you start talking to young children early, one, people at the FDA will be happy because you're going to have children eventually. So, don't just do adults. Prep first and then say, "We'll deal with the kids later." You're going to get simpler questions. You're going to get more understandable responses. It will help you have an overall better instrument.

It also might help you moving into those multiple regional studies. It is difficult to put together an episode of Sesame Street, but it is something that a 3-year-old and a 90-year-old all understand and you can get some pretty difficult concepts across because, while a 3-year-old may laugh at the question, if they get it, that's what's important. If you bring the evidence that they all got it, the FDA will say, "All right. You've got an instrument. You've got a measure." So think about how using different groups will help you get to that end, especially because those groups are going to be in your study.

This is one of the various others, so that first little wheel, I did not invent it, it's on our website. The very first thing we say, in this road map for Patient Reported Outcome measurement, understand the disease or condition, the number one thing. When you start looking through all the developments and when you look through all of these, the multi-regional trials, you could see different natural histories. You could see different patient subpopulations fight severity or onset. You will see very different healthcare environments. You're going to possibly see also very different patient and caregiver perspectives. If that's your first step, how do you not start with a multi-regional focus? Even if it's a little one, try to keep it in there first. Everybody has talked about today; a lot of different good practice guidelines. There are plenty of them that are available. I'll be honest. They don't account for that much. You'll see different groups that have published different standards. Using them and fighting them goes a long way. What were they following? Can we look at that? Can we see what actually happened?

I want to echo a comment that Wen-Hung made earlier saying, "If I can't see it in front of me, it is very hard for me to know that it was done." So, really one consistent package. I can read all the way through it and have what I need to know. There are costs to not attending to issues early. Here, I know. I sat on the side that had to give money for development. I know it costs money, and sometimes we don't do early translation, early inclusion of multiple cultures. Sometimes you can try to include them in ways that are cost effective.

You have to sow away the cost of not acting when you're looking early on, because if you're moving into phase three and you have never tried to use that outcome instrument in a group you're working in, I don't care what that outcome instrument, what that endpoint is, there's always going to be a ton of worry. If you want additional information, there's E5, there's also a Q&A session up there that could be useful. I gave you a link up there. It talks a lot about multi-regional clinical trials. It is COA specific, but on slide 8, she actually does talk quite a bit about the cultural sensitivity and endpoints in general. On slide 9, she says, "Okay, is your overall assessment meaningful and interpretable for everyone in all these different regions?" It's a nice slide that I say for people to look at and get a more global perspective of our global process. Thank you.

Ashley Slagle: Thank you, I really appreciate the presentation. It was helpful. I think at this point, we're now up for another break. We have about 10 minutes, if you can please be back for session four to start at 2:50. Thank you.

Session 4: Strategies Going Forward

- **Key learnings from the PDUFA: Where Do We Go From Here?**
- **Regulatory Perspective**
- **PROMIS (Patient Reported Outcomes Measurement Information System)**
- **Patient Perspectives**
- **Industry Perspective**
- **Researcher/Academia Perspective**
- **Panel discussion and questions**
- **Open Public Comment**
- **Closing Remarks**

Theresa Mullin: Well maybe a few more people will re-join that may still be out there in the common, I guess, I don't know what you call the area ... The area out there by the windows. We'll go ahead and get started on this.

Again, I'm Theresa Mullin. I direct the Office of Strategic Programs in the Center for Drugs Evaluation and Research. I've been, in addition to leading the FDA PDUFA V negotiations with industry on those user fees that were re-authorized in 2012, I've been leading this patient focused drug development effort that was described a little bit earlier. I'm going to really quickly review some aspects of that and get into key learnings from our perspective of what we've heard to date to help to sort of kick off the that's a perspective in addition to everything else you've heard today about the "what's next" piece, which is what we're going to cover in this meeting. I'm going to ask people when they get up to talk, they will introduce themselves and give you their views.

Just to recap, we're convening twenty meetings ... Actually, we'll be doing more than twenty meetings by the end of that 5 year period to obtain patients' perspectives on specific disease areas on the things that matter most to them in terms of what they're experiencing and actually questions such as the following that we ask. This is a sampling of some of the questions we ask in the course of these meetings. We actually have one tomorrow on breast cancer if you're able to join me and you may want to attend it if you can. What symptoms have had most significant impact on your daily life and on your ability to do specific activities?

We have an open discussion of that where the patients build on each other's comments as well, and it's very rich. We ask how well does your current treatment regimen treat the most significant aspects of your disease? What specific things would you look for in an ideal treatment? Assuming it couldn't cure, what would be an ideal treatment for you? What would it do for you? We often probe questions around study and whether patients would participate in studies and ask what factors would you take into account deciding whether to use a treatment that would be

available? Another question is what do you consider when you're thinking about participating in a trial? This is all extremely important for FDA to understand.

This is to give you a snapshot of what we're covering this year, and in the past two years we have an additional set of diseases that we're going to be doing in 16 and 17 that we're putting through the process of getting it cleared and published, and so it will be out within a few months. We've had a meeting on chronic fatigue syndrome. That was the first meeting we've had. We had a few speakers on the panel to talk to the chronic fatigue syndrome concerns and issues that came up and their insights. We had a meeting on HIV, non-small cell lung cancer, a meeting on narcolepsy, sickle cell, fibromyalgia. As you can see the list ... We've had one in this fiscal year so far, and that was on female sexual dysfunction. You can see we have, in addition to the one tomorrow, several more planned through September of this year.

We've had a pretty sizable attendance. We've had a large number of registered for the meetings. There's been a range, and the disease participants in these meetings have been in a range as you can see. But there've been a pretty fair number of people who've attended in person which is impressive considering that these conditions that people have been living with are in some cases quite debilitating. We've had a very good attendance, and we've had a very large attendance draw with the webcast. That's been a pretty good amount of input we've gotten, so I want to show you that to see that's basis of what we've learned to date.

Dr. Woodcock mentioned at the beginning of the meeting, this is one of our key learnings we feel from what we've heard, is that patients with chronic conditions really are experts in what they're living with. They can articulate very consistently and clearly, and they want to describe in their own words what they consider to be what it's like to live with the disease. I say that because the occasionally in facilitating these meetings and in talking to patients with follow up, they have inadvertently paraphrased what they said, and in the process we've changed the meaning and they've come back and very quickly correct what we've said to make sure that it's actually an accurate reflection. Not only does the one person typically do that but others concur with that person in terms of correcting us. This is an important thing for us to understand in terms of how we word things and ask questions of patients.

We have found that in patients with these chronic conditions most of what they're telling us about is physiological. It's observable to them and to their family members, and so it's a pretty straightforward report in many cases of what's happening to them. For chronic, degenerative, and progressive diseases we've heard from patients and from parents who are caring for children with such diseases that an ideal treatment would at least stop progression. We're not even talking about reversing or curing, but just stopping progression would be very, very valuable to them. How do we measure that? Patients tell us that the things they care about most are usually not even in the label. We can tell these things are not factored explicitly into the product

element programs by and large, and that includes the measures of benefits sponsors are collecting in trials. That's sort of a call to all of us to do something about that.

Patients indicate things they want to be as active as possible in helping to develop new treatments. They are clearly very willing to engage a whole variety of mechanisms, and we say that based on what we have seen through the docket submissions we have a very large response we get from the webcasts and other information. That's something that we think is very important going forward. They're not expecting the FDA to address all the gaps in our current treatment in these issues with getting drugs developed. They do want us to be providing effective pathways and helping to identify what sponsors and patients and other groups need to do, so provide clarity wherever we can and should, and we would agree with that. Some potential next steps for us that we've been talking about here and other meetings, it's really advancing what some are calling the science of patient input.

This has been a theme I think in today's meeting, you know, really methodologically sound approaches that are good enough, fit for purpose, maybe not seeking perfection but really taking that approach, and looking for bridging from these meetings that we have that are so rich to something that can be collected systematically to capture the patient's experience within the disease. How do we proceed with this in terms of getting patients' reports, patient preferences? How do we capture and explain to them the uncertainty about what they're experience could be. We get a lot of questions about are you going to use benefit/risk trade-offs? How do we even articulate what the perspective benefit or risk might be or the uncertainty about what the individual would experience using a drug that isn't on the market yet? These are important as methodological questions and logistical questions that we're going to need to deal with, and we need to provide guidance, as I said, to provide as much clarity as we can to not be ambiguous or create uncertainty that we don't need to create.

With that, we have questions for our panelists who are very extremely smart, experienced, thoughtful bunch. We're going to start by asking each of them to come up, and we're going to call them in the order as they appear in on the agenda to address questions of what are the key elements from your perspectives and strategy going forward to try to build on what we've been learning from the COA experiences, through this patient focused experiences. What actionable steps do they think can be taken within the next two to five years? After that you can just build on the ideas that our panelists provide us. With that I will leave the podium and let Paul come up and talk.

Paul Kluetz: Thought I was next; I wasn't sure. I've jotted down so many notes today. I think it's been a very good meeting. I think, as I've said before, these meetings can tend to be very optimistic and yet somewhat vague, and in this meeting I think there was a lot of actually clear steps about what we have to do, and the work we have to do to move forward.

I want to make it clear that in oncology the way I see it is that, and I think this is probably true for all disease areas, there's really two questions that one can ask when looking at patient reported outcome data. You hear a lot about endpoints, and that is one question to ask, the efficacy question. Does the drug improve some kind of symptom? That's one type of question that's probably the highest bar. Do we have examples of where Patient's Reported Outcomes in oncology have been sold endpoints for approval? Yeah, sure we have, but not very many. Pain has been used for radio- seeking isotopes for prostate cancer. Have we used secondary endpoints to add key support for regular approval rather than accelerated approval? Yes, the Jakafi® application showed a dramatic reduction spleen and objective endpoints oncologists are comfortable with while also showing that the symptoms related to that disease were improved, therefore meaning this fields functions or survives bar and that drug was given regular approval.

I would say, for one tip I would say moving forward in the oncology realm, if you want to use a PRO as a very important part of the efficacy of your drug, you have to be very, very thoughtful on how to use that endpoint and what we see frequently is that everyone tries to put everything into one trial. You have your PFS primary endpoint, let's say, but there's also looking to find this PRO endpoint and several others and several others. Typically that's not a good way to optimize the patient-reported outcomes. What might be a better strategy is to look for a smaller, second trial that is enriched to those who have symptoms of the disease, and therefore you can look for symptom palliation type endpoint rather than a time-to-symptom progression endpoint, which is harder to show and requires a lot more sensitivity. It's something to think about moving forward if you'd like to use that.

The second question to answer is something I think we do in all cancer clinical trials and that is more of a distinctive question. It's not is my drug effective? It's what's the patient is feeling while they're taking my drug and that actually can add value to your proposition as a drug developer because you can show for a clear picture of not only the anti-tumor activity of the drug but also how it's affecting the symptoms and function of the patient. I think we have some work to do regarding how we analyze and utilize the more descriptive patient-reported outcomes, exploratory type data and trials. We do have descriptive data that we use all the time in oncology to describe the patient's perspective and label it. It's called adverse events. They're clinician reported right now. Some low-hanging fruit we'd like to mention in oncology is that the very same criteria we use for adverse events, we can use from the patient perspective. There is a tool out there called PRO-CTCAE that's being developed. That's something that we could consider as a possibility for measuring from the patient's perspective.

In conclusion, while oncology has all sorts of unique challenges that I hope I was able to articulate to you, I think that it's important for you to know that the oncology office belief right now is that regardless of which question you want to answer, an efficacy question or a descriptive question, the data needs to be as sound as possible for either of those because they're both critically important. All of that PRO data that

comes in with your registration trial we're going to look at very carefully, and we're currently looking ways to best analyze that data and inform our overall risk/benefit calculation on whether that drug would be the type of drug we would take regulatory action with and what type of regulatory action we would take with that drug. I'll end there.

Theresa Mullin: Thank you, Paul. Janet Maynard, get up and introduce yourself please

Janet Maynard: Hello, my name is Janet Maynard. I am a clinical team leader in the division of Pulmonary, Allergy, and Rheumatology Products or DPARP. My overall vision is that safe and effective drugs are available for patients. In my role at FDA, I've really focused on some disease areas for the significant unmet medical needs.

One example that I wanted to talk about was chronic fatigue syndrome, myalgic encephalomyelitis which is also referred to as CFS/ME. In April 2013, the FDA held a two-day workshop regarding drug development for CFS/ME. The first day of this workshop was conducted in accordance with the patient focused drug development initiative. I think that there are multiple outcomes that we can see from that CFS/ME, which I think are very helpful as we talk generally about these issues.

From that CFS/ME meeting and that workshop, we had summaries published, we had "Voice of the Patient" report, a draft guidance for industry regarding drug development for CFS/ME was published, and we've also formed a working group discussing PROs or Patient Reported Outcomes for CFS/ME. As I think of moving forward, I really hope that we can build on these outcomes that we've had so far and specifically, we will work with stakeholders in drug development, such as pharmaceutical companies, so that they clearly understand the steps that are needed in their drug development process to support regulatory requirements. We hope that looking at this specific example of CFS/ME, we hope that the guidance really articulates FDA's expectations for drug approval for this indication and also emphasizes the importance of assessing patient symptoms. This is one example of the importance of incorporating patient's voices into drug development.

In addition, it emphasizes FDA's flexibility and our desire to work with stakeholders because we know that really it takes many different stakeholders to effectively get a drug developed. Thank you.

Theresa Mullin: Thank you, Janet. I'd like to ask Jim Witter to come up and tell us what he thinks part of our strategy should be.

Jim Witter: Thank you, Theresa, and thank you to colleagues. Good afternoon, everybody. I have some written comments here so forgive me if I'm looking down. I have three to five minutes to talk to you about PROMIS which has been going on for the last 10 plus years has invested well over \$100 million so good luck to me.

I just wanted to thank you again for the opportunity to talk about the value of the NIH PROMIS as it continues to bring the person and patient voice forward, including now in the development, as we're discussing today, in maturation of therapeutics throughout their life cycle. Theresa said we should say a word about ourselves. I'll take that, and I will. I'm a medical officer in the Division of Skin and Rheumatic Diseases at the National Institute of Arthritis and Musculoskeletal Diseases where I'm involved in Rheumatic Diseases Clinical Program. I had the good fortune for the past 7 years to be involved in PROMIS as the Chief Science Officer and Chair of the outreach community. I'm a board certified adult rheumatologist, currently an attending, at NIAMS clinic care centers and I'm a former FDA employee, working in the same division where Janet used to work. After 13 years I have a little bit of understanding of what goes on behind the curtain.

I'm also a patient since 1976 where I had very severe reaction to the swine flu vaccine. Today I now have at least 4 ICD-9 or 10 codes whichever you decide to use after my name. I'll bring that point back in a second.

Over the years, NIH has engaged the FDA in multiple efforts in the education and advancement of PROs. This has ranged from meetings with divisions and FDA leadership; it's involved a CPAP co-consortium launch, Stephen Coons, standing in the back there when he first started his role there I was also there and gave a presentation. Lori Burke who's sitting in the crowd, was a member of our scientific advisory board on PROMIS I. Dr. Janet Woodcock you heard from this morning, she gave a presentation at our retreat when we launched PROMIS 2 has been a big fan ever since and now we have this thing called the ICOAWG, Inter-Agency Clinical Outcome Assessing Working Group. In that effort, which is ongoing now, we are looking at CFS/ME ending you'll probably learn more about that in a second, FTM, I'm happy to say that Ashley is really leading that effort, so thank you, Ashley. We also have a Rheumatoid Arthritis working group. These are both focusing in on fatigue and sort of a question that was asked before about how many diseases do we need to qualify PROMIS in before we've done enough.

Anyway, it's important to remember that since its inception back in 2003, PROMIS and we have Bryce Reeve here who is the godfather of PROMIS and we need to thank him for it not being called APRON, but it's called PROMIS. Was always looking to the future and that continues today. The dream, really, back in 2003 I'm just going to read a quote from back then. It says: "the clinical outcomes research enterprise would be greatly enhanced by the availability of the psychometrically validated dynamic system. The measure PRO was efficiently in study participants for the wide range of chronic diseases and demographic characteristics.

What you have, in a nutshell, is PROMIS and it's loaded on our website I'm reading again here is "a system of highly reliable precise measures of patient reported health status for physical, mental, and social well-being. PROMIS measures what patients are able to do and how they feel about asking questions. PROMIS measures can be

used as primary, secondary or exploratory endpoints for the effectiveness in treatment." Just to point out, PROMIS has been embraced and funded by PCORI.

The FDA certainly should be applauded for their efforts to include the patient's perspective in the development and labeling of therapeutics but why the 20 selected that we heard today? It's estimated for example, that and I gave a presentation back in March 2013 on Rare Diseases Day that there are 7,000 rare diseases. If the current PRO development process which you've heard is a little bit ... takes a while, you can imagine who are trying to develop PROs for all of those patients. It just wouldn't be possible. 6 years x 7,000 patients; you do the math. There are and will continue to be in the foreseeable future, what I think are huge gaps in PRO assessment across human diseases. This is why I think PROMIS can really help today. Perhaps FDA then needs to consider an alternative approach to PRO development and subsequent labeling in order to advance the inclusion of patient perspective and preference. The alternative approach language is actually ... noticed this but in the box section the guidance box not only the PRO guidance but in every guidance document.

Therefore, I'm going to make the argument that PROMIS represents an alternate approach, in other words: it's a new and exciting science so really PROMIS allows you to personalize and population based assessments and comparison. PROMIS represents a mature and maturing collection of standardized universally applicable tools to measure health and disease, (meaning someone's quality of life). PROMIS assesses domains such as pain, fatigue, physical function, depression. These are all these domains are important in many if not most diseases. With a domain approach then PROMIS offers the potential to understand diseases in the premise in a uniquely different way. Potentially complementing the mechanistic based approaches that we see today with all the omics. Oh by the way, we might start to think of pro-omics adding to that lingo. PROMIS also offers the ability to assess outcomes with of patients with multiple diseases such as myself. Thus eliminating the burden on patients to try and attribute their symptoms or impact on the quality of life to one disease and I think this would be especially important as our population ages and people accumulate different diseases and conditions.

I think it's important to note that no biomarker is perfect today and no PRO is perfect and PROMIS is no exception. However, PROMIS is designed from the get go to be improved as it continues and be validated and implemented. In contrast to the very key specific measures it only addresses certain aspect disease, PROMIS offers the option to understand a much bigger piece of the clinical pie. This is especially true since it's responsive to a pharmacologic, non-pharmacologic and both in their combinations.

Some final words on key elements moving forward PROMIS is that it doesn't really matter. In other words, it's agnostic the setting or to disease condition words administered and because of the same standardized metrics it's employed, which by the way is developed with state of the art psychometrics that are completely in line with the PRO guidance, PROMIS represents a meaningful way to compare across

settings clinical trials, clinical care or internet based surveys across the common and rare diseases. In ways yet to be determined by more empiric data as we collect this. PROMIS facilitates comparative effectiveness research of both the individual and the population level.

Here are my suggestions for some actionable next steps for the next 2-5 years: I'm dreaming big here and these are sort of high level goals. The FDA we hope will embrace the new measurements that we heard about today to better understand how it fits into the future of not only therapeutics but really this is where we're heading in personalized precision medicine. FDA should be applauded as they have always be open to innovative science and thinking and CAT, computer adaptive testing, is arguably the future of patient assessment of PROs. Both decreasing patient burden, its improved decision but also because it can be automatically incorporated into electronic health records and other databases.

Alternate approaches would also include things such as context of use. We may need to define that more broadly. In terms of, for example, clinical trials, clinical care and fit for purpose: what's not fit for purpose? Maybe we should define more broadly again to really encompass the assessment of symptoms functioning quality of life at both the individual and population level. FDA should encourage, we would like to see, as strong as possible not only verbally but in writing, the use of PROMIS measure of exploratory endpoints in industry sponsored adult and pediatric trials.

This implementation will help to adapt without the adept PROMIS measures going into the future will help create a robust prospective future longitudinal database that will facilitate ongoing clinical validation of these measures in national and international settings. The FDA and industry play a key role and this is a critical need for PROMIS at this time.

In terms of labeling, again looking perhaps at more dreaming here and some innovations just imagine for a bit being able to directly compare results from an industry sponsored clinical trial to one sponsored by NIH or other funders. Or when you interact with your healthcare provider or when you participate in an internet-based survey such as might be by some of the patient organizations that are here today.

So perhaps we should consider some new ways in terms of language labelling. For example, should there be an exploratory endpoint section in the label? Should there be precision personalized medicine section in the label? Or should there maybe be a clinical care section? All of these are where things PROMIS for example could come easily populate and help with the science of PROs forward. Finally, let me just mention one thing: it's a new exciting initiative at the NIH it's called PEPPER. We like acronyms. What PEPPER stands for it is: Validation of Pediatric Patient Reported Outcomes in Chronic Diseases. It's a consortium that's being put together it's under a U19 mechanism, there's \$12 million that's going to be spent on this. There's going to be obligated this fiscal year. This really represents the again in a

nutshell is the new initiative this is from reallocated funds to address questions at the intersection of pediatric health and environment and is focused on engaging underrepresented communities. Thank you for your time.

Theresa Mullin: Thank you Jim. Jeff Allen from Friends of Cancer Research

Jeff Allen: I don't have a great program to describe to you like that so I'll just cut to the chase with a couple of ideas that I think some are probably going to bounce around a little bit throughout the day. As they came to mind I jot them down as to what are some key elements that moving forward to build on the current patient focused drug development program.

Number one: methodology and I raise that because I think it would be extremely helpful building on some of the things that have been learned from the meeting. Develop methodology that could be provided to different patient service organizations on how to collect this data better. We haven't heard from our team colleagues in industry and academia but I suspect that they have sort of started to figure it out but the organizations that have direct services and are trusted enough most cases interactions with patients don't necessarily have the bandwidth to develop these methodologies themselves so having some sort of blueprint on how they might collect the data in a rigorous way so that it's more useful for the regulatory bodies, for industry, for the research community it is only a positive. I think those organizations would really start to channel resources into doing that if it was a little bit more predictable in knowing what would come out of it at the end.

Number two: Jim was much more articulate with this than I can be but labeling alternatives. A number of people have mentioned today the idea of this continuum but I think that one artifact of having the gold standard being laid out in terms of FDA guidance through PRO. A lot of people think that using a PRO was only available as a secondary or a primary endpoint and that was the only way that it would be included in the label. I think that perhaps it led to in some regards, undervalue isn't maybe the right word because obviously when you're at that side of the continuum it's the most valuable but it doesn't mean it's not important to look at things like experience versus just looking at endpoint and if there's a way to look at other ways for including that in the drug label as has been mentioned for the potential like PROCTCAE that conveying the patient's experience for using the drugs is important and I suspect that many patients and potentially a lot of physicians would be interested in that information even if it isn't to the p-value of less than .05 significance.

Number three is the study design. I think the changes that we're seeing in some cases in oncology to study design because the drugs are showing a differential effect early on is stressing the importance of finding ways to collect this information earlier and better. In some cases and it's a good thing the opportunity to do so is becoming more and more limited so we need to prioritize and being pulled against us is policies that some major funders in research have not to fund PROs earlier on in development

makes this very difficult. I understand why those decisions have historically been made because you don't know if those drugs are going to make it toward a later stage developments and maybe devoting resources early to a product that may not make it the whole way and so collecting the PRO's things just kind of fall by wayside but if we don't figure out how to translate the development and utilization of PRO's in early stage clinical research and let that inform later stage clinical research then we're really going to keep taking baby steps rather than larger leaps.

Theresa Mullin: Thanks Jeff. Kim McCleary, from Faster Cures

Kim McCleary: I'm not going to the podium. I was sitting in the audience earlier today thinking of 31 days ago we had a meeting on a similar topic up here at FDA that was hosted by the National Health Council and Genetic Alliance it sort of kicked off a series of six meetings over the last 31 days on this topic. Issues like drug development, risk assessment, and patient centricity in general. It's really been an intense progression of the dialogue marked by subsequent conversation today and I Tweeted out from the first two meetings that Eleanor Perfetto organized three weeks ago, that we're still preaching to the choir but the choir's getting bigger and we're singing in better unison. I think that is kind of a theme that's also marked by today's conversation.

Like Jeff, I'll take the prerogative to offer three observations that are not only a result of today's discussion but this conversation that's been building and reaching a crescendo over the last month. The first one I had written down several days ago that was made by the panelists of the first two sessions very regularly that it almost doesn't bare repeating but I'm going to do it anyway. Is the real need to clarify the patient's reported doesn't always mean patient centered, and again we've heard that a lot today but Tom Sellers I think suggested and Stephen actually did say let's make that a criteria if we're going to rethink this whole PRO process. Let's make sure that patients are reporting and measuring something that is of benefit to them. I think that would change the dialogue and maybe the unmet need that's out there, the new medicine, more than anything else could. The key word that hasn't come up today but has over the last few weeks more often than in this setting, are the payers. Payers are looking for that evidence as well and the patient centricity has an opportunity to bridge the drug development and delivery system and ultimately who's going to pay for all of this once this gets out to post approval.

The second point is about capacity and sustainability that Jeff mentioned as well, the need for some sort of public/private partnership whether that's formal or informal to help establish what the methods are, do the training that will be necessary, identify the partners who have the trusted relationships back to patients to bring this evidence forward in a rigorous way that can be updated frequently. And that reflects the differences within populations and the differences in patient preferences and needs over time particularly with chronic conditions where you're looking at something over the life span and their priorities may shift according to the stage of the disease or other factors in their life such as economic factors, vocational issues, patient

family dynamics that aren't always considered in the medical system and are part of the real world of how the patient lives his or her life.

The third point is this issue of representativeness for which I feel like I have become the poster child for this topic because it's really one that we grapple with and I know that after today has seen this in meetings and Theresa showed the numbers of how many people were participating in the patient focused drug development meeting and certainly it's hard to know whether the voices heard in this room tomorrow there will be representative of entire breast cancer population or whether it will reflect the most engaged segment of that community and how do we understand particularly in communities that are not easy to mobilize and have different segments that are underrepresented or underserved and how do we know what the needs are, what the measurements are, what their preferences are across the entire community so that we understand patient journey and the breathe of experience within the community as a whole. That answer might be different depending on the disease itself, whether it's chronic or acute, whether it's a pediatric or adult condition, or something that begins in early childhood, or might be experienced later in life, whether it's self-reporting or surrogate for that effected individual or whether it's rare or prevalent, so I think it goes back to the methodology issues which is something very important that we're still grappling with and haven't yet come to good answers for but I think this continued dialogue is really important step forward and I see tremendous energy from all the stakeholder organizations to get involved with how do we do this, and the consensus around these issues is really gelling in an important way that will propel us to having better answers. Maybe if we just keep meeting five times over 30 days we'll get there faster than we would otherwise. Thank you.

Theresa Mullin: Thank you Kim. Can we here now from Marc Boutin from the National Health Council?

Marc Boutin: Thank you Theresa. I'm going to buck the trend partially because I like to talk with my hands and I don't want to be sitting down for the entire time here.

How many of you in the room consider yourself to be with industry? Raise your hands. How many of you consider yourself to be with a patient organization? How many are with the FDA? Okay so we have a really good blending.

I want and I know there are others with academics and researchers but I want to turn this on its head a little bit. We can focus on a very narrow site then and I actually think we need to broaden this up because we have left the low hanging fruit on the tree and I think that's a real problem.

I'll come to my two recommendations for what we can do in just a moment but how many of you in the room have a Samsung? How many of you have an iPhone? How many, I know all the people from the FDA have Blackberries, right? You guys have to put your hands above your heads because this doesn't count for you. But for those

of you with a Samsung and Apple, the companies that make those products would not even consider making a change to the color without doing extensive consumer research to understand how it would impact the consumer and their sale. Yet, when we look at the development of treatments that does not happen.

There's engagement of researchers, there's engagement of doctors but the engagement of the patient doesn't happen. In fact, when you speak with researchers in companies they say, "We did engage; we did clinical trials". You're kind of late at that point. Imagine if you were to engage with the patient community at the frontend when you wanted to decide what asset you were going to develop. For those of you that represent industry, every major company has spent more than a billion dollars bringing a product to market that is safe and effective but doesn't answer a problem that was important to the patient and have simply withdrawn it from the market. That's a billion dollars that could've been used to address a problem that was actually important to the patient.

We can help you design your research questions and the questions will be different if you can engage with us. We can help you determine what those reported outcomes ought to be so that you're asking the questions that are actually important to us. We can help you design your clinical trials, which by the way, if we help you design, they'll be far more accessible for us and you'd be able to fill them faster and keep people participating longer and bring your product to market a lot faster. We can help you with the benefit/risk assessments.

We can help you even with little things and this is a real story, a company brought a product to market in Japan, highly effective, very safe product, nobody in Japan would take the product. The pill was too large. Somebody who's lived in Japan and you look at the sushi that you actually get in Japan, it's about the quarter of the size of the sushi you get in the United States. Culturally, they don't ingest large items. Had they simply engaged with the end audience, they would have known that upfront. Whether than having to reformulate the pill after it was already on the market. Simply looking at the patient reported outcome is critically important but we've got to look at how we engage throughout the paradigm of the drug development, not just at that sliver of time when it's at the FDA.

I think there's a lot of opportunity to get this information into the hands of patients. A lot of the comments about labeling I think are true but here are my two solutions. One, we need to look at this in a pre-competitive space. You need some sort entity whether it's a public/private consortium or some entity that brings the parties together that starts to look at what are the best practices? How do we do this in a transparent way? How do we look at communication dissemination? What are the right methods and when do we employ them? Using in depth interviews, focus groups, outsourcing may be very helpful on the front end of development, but maybe insufficient for your patient reported outcomes. We need to align these solutions with the methods of the questions you're trying to ask and answer. You need to look at who you're engaging. As we just said, the representational aspect is critically

important. An individual patient gives you a very granule perspective. You may need to go to big David to really understand sub-populations that even a very sophisticated patient organization may not actually know themselves.

The second thing we need to do, and I think this is critically important, we need to set the guardrails. We need to understand what is insufficient and what is sufficient without defining and mandating what exactly we need to be. This is a relatively new area. The methods of engagement have been around for a long time and have been validated for many purposes. We're just beginning to employ them in drug development. We need to set the guardrails so that people know where they can operate and some guidance or direction on that would be really helpful to help push companies in this direction.

After all we'd like to say, "Why aren't we doing this?" In fact, if you ask patients they think this is already happening. There are a lot of reasons: culture, costs, regulatory predictability, issues with legal and potential fines. How do we address those? We need to look at creating a safe place for this. Companies if they want to go into this space and use these methods that are largely similar to many of the methods we use in marketing, are afraid of being fined for marketing an unapproved product. If we can define where it's safe to operate in this space, we take a lot of the risk away from the companies who are unwilling to invest money in this very important work for fear of getting a \$100 million fine.

We can fix that by giving them some guidance. We also need to look at how we I include this data into the benefit/risk framework the FDA has been working. There's a lot of opportunity even if the answer is that the information was not sufficient to impact our decision, let's begin to integrate it into the work of the regulator in a way that says, "You have to consider with the other data when you make decisions". That's how you start to shape the culture. I'm going to stop there but I also wanted to thank the FDA for being really open to working with the patient community on this issue over the course of the last several years. We worked with PDUFA V on this, it's really taking off, there's still a lot of work left to do but it is a really an exciting time to be in this business. Thank you.

Theresa Mullin: Thank you Marc. Now we'd like to hear from Jennie Spotila who's a patient and she's a part of a CFS/ME Working group and as you can see, Jennie, hi so glad you can join us. Take it away.

Jennie Spotilla: I'm a patient with MECFS and I've been largely house bound, sometimes bed bound for the last 20 years so I really appreciate the FDA making it possible for me to join you from my home and I'm going to try really hard not to think about how big my head must look on that screen. As Theresa mentioned I am part of the MECFS working group trying to validate an outcome measure for MECFS. I've been a part of the FDA patient representatives program for the last two years. I've participated in that first PFDD meeting on Chronic Fatigue Syndrome. I think the working group is actually is a really nice case study of bridging from that

collection of patient experiences with PFDD and trying to acquire more systematically in the context of instrument development or drug development.

There are three lessons that I'd like to share that apply to both patient, and the industry regulatory side. The first one is we need to speak each other's language and as Mark just said so eloquently, if we bring patients to the table and you listen to us as equals, we can make your process more efficient and more effective because we can help you short cut what's going to work best, what matters most, and the problems that come up throughout the process of development. On the flip side of that, patients have to learn how to speak your language. The language of sponsors, the language of regulators, and of researchers, so that we can come in and communicate effectively, at least from our side, and anticipate some of the concerns and issues that are important to you.

The second lesson is that of diversity to which several people have alluded to already, because not every patient can be in the room. So the challenge to me as the one patient representative on the working group is to find and speak to the diversity of experiences and views for our whole patient population, which is a real challenge. For example, chronic pain is a really big part of my disease experience but that is not true for everyone who has CFSME. And cognitive dysfunction is not the same level of problem for me as it is for other patients. And even though I've been house bound for nearly 20 years, there are patients who have been bedridden for a number of years. And they have a completely different set of concerns than I do in terms of developing a measure they can use, and understand, and then relay that information back to a clinician or to a drug trial. Trying to represent that diversity whether it's one patient or a group of patients who are speaking is a real challenge.

The final lesson is breaking down our code because we all have shorthand and we all have insider language. We heard a great presentation on multicultural issues in drug trials. I think that applies to the different stakeholder groups just as easily as it does to different cultures or nations. Because as a patient I have a different set of language that I use with other patients and they can understand me but researchers, regulators may not. To illustrate, I might say to a fellow patient, "I'm really tired" or "I'm stressed" and they will know that what I'm actually saying to them is "my pain is at a seven out of 10 on the pain scale even when I've taken all my medication. I'm too weak to sit up and support my head. I'm having trouble putting words together and I'm too exhausted to eat. That's actually what I mean when I say I'm tired but if I say I'm tired to the members of my working group, they're probably hearing it in the context of what I would have said before I got sick, after billing 80 hours at a law firm, but with a couple hours of sleep I'll be white as rain. It's a completely different set of code. I think that's important for those of you when you're listening to patients to anticipate that you might be hearing shorthand or you might be hearing code you might want to actually ask us to explain, or give examples or give more detail so you can be sure you're understanding what we think you already understand. So these all come under the roof of communication but if we can do this

effectively then ultimately the end product is going to be better which is what we all want to begin with and which is why we are all here

Theresa Mullin: Thank you very much Jennie so now I'd like turn to Roslyn Schneider from Pfizer.

Roslyn Schneider: Thanks Theresa. Hello, I am Roslyn Schneider and I'm a physician and I'm the global patient affairs lead at Pfizer and this is a role that was created about 6 months ago and it's all about driving, putting the patient at the center of everything that we do at Pfizer in a more systematic way so I'm in career heaven right now. What you'll see is that there are a few other companies that have similar names and they're organized slightly differently but really a large part of what's going on with these roles is about embedding the experience of people living with disease into our medicine development program from the very earliest time in research before a medicine is ever used in a patient in a clinical trial and then at key points in an iterative fashion all the way out until the last time the medicine is ever used for a patient anywhere in the world.

That idea is what drives the key strategies that we have in these positions which is to include the actual experience, the patient voice and the preferences of patients at each of those points in time so that the strategies though are first internal and then external going back to the choir and the people who aren't in the room today the internal engagement group is very important and huge especially in some of our large companies to make sure that we're shifting the culture. It isn't going to happen overnight and it's converting the passion and the energy that we all have in this industry and in healthcare to be able to make this operational. To say we are actually going to do this not because it's nice to do and it's altruistic and we want to listen but that we actually know that it's the right thing to do for us to be able to deliver medicines that are what patients want, what they need and that fit in with the way they live their lives.

The external part though is equally important because we need to all be as Jennie just said, speaking the same language and we need to know, we've come a long way I think in the why we should be doing this, reached much more alignment in what it is we're talking about, but we still have a greater struggle in the how and we've heard from Jean Paty and others before that this is hard as most things are it's hard partly because we don't know and we have to agree on the how. That external connection and collaboration as we're doing today in all of these Monday meetings we've been having recently is extraordinarily important so that we're not each deciding how on our own because that just isn't going to work. We know that.

Thinking about Theresa's original questions with the couple of next steps that we could potentially take to get us to that next horizon in this whole process is perhaps the FDA could hold follow up meetings after the really intense listening conversations that we're going to hear another one tomorrow at the FTB meeting we are at those follow up sessions we could have the new divisions, patients, and patient

advocates, industry members and then together put our heads together and say exactly again, "how do we take this and translate it into what we all need to be able to develop medicine that are going to be more meaningful for patients and are going to be appreciated by all of our stakeholders?" That is meaningful and acceptable the way that we're doing this.

Secondly, this system said a couple of times today but we do need clear guidance from the FDA as sponsors and other stakeholders who want to engage with patients outside of these public meetings and related to specific medicine development programs. Without that concern that that's going to be construed as promotions of our medicine before they're approved for particular indication. With those suggestions of things we could do better and there are always things that we can do better, I don't want to lose sight of how successful PDUFA has been to date in accelerating new drug approvals. I think we can't take these suggestions as criticisms without noticing how much has already been done today and we couldn't have the conversation that we're having here today without these changes in these process. It really has become much smoother, much more predictable, and better funded than 20 years of experience and we've also heard today that it's personal. Paul said it was personal for him and others have said that it's personal for them. I think everybody on each of these panels can say that it's very personal for each of us, but it's no more personal and it never gets more personal than the person who's living with the illness. When I say that I mean the patient, the caregiver, and other members of the patient's support community. We have to keep that front and center as we're developing medicines to say that it's essential to include patients along the way and again in an iterative fashion. Not just something that's nice to do but something we've all committed to do and we just have to find out how together. Thank you.

Theresa Mullin: Thank you very much Rosylyn. Now I'd like to ask Daniel Mullins to give us his perspective.

Daniel Mullins: My name is Daniel Mullins I'm a Professor University of Maryland School of Pharmacy where I run the PATIENTS program. The PATIENTS Program is a collaborative partnership between the seven professional schools in the University of Maryland system and six unique and diverse communities of patients and healthcare providers.

We work with patients to help figure out how to frame questions and then how these patients actively participated with these questions that they found meaningful. The way in which we do this is we follow 10 step framework that we published in 2012 in JAMA and we recognize that research is a continuous process. Continuity of research means bringing back individuals that participated in talking about what's next? What are the unanswered questions that are most important to you? Among those: how do we prioritize what is most important to study? Finally, when we agree upon what we're going to study, how do we frame the questions in the voice of the patient? The patient understands the question, they are motivated to answer that question and they're able to understand what that answer means.

If you think about the way we do traditional clinical research, blood pressure measurement is something that we all take for granted. It happens every day in clinical care, it happens frequently in research as well. If we ask how come we measure blood pressure? Over time we've learned how to measure blood pressure. We understand there are two numbers, we understand what those numbers mean. I'm not sure that patients always understand what those numbers mean, I'm not always sure that we communicate to them what those numbers mean. But even the process of measuring blood pressure, we can talk about making sure that we use the same instruments, we can talk about making sure that we measure twice. Over time we've learned that the way in which we engage patients' matters. Many of us understand the concept of sitting down while we're getting a blood pressure reading taken. The way in which that patient was engaged influenced what outcome was reported. There are some studies that have reported that if you put on a white coat when you're measuring the blood pressure and that that means of engaging a patient matters and it may change the result.

If this is a rather passive role that a patient participate in measurements and that engagement has a big impact. Imagine how active engagement could impact positively or negatively in the way in which we generate information and use that to report information out. I think it's wonderful that we are engaging patients. I think it's important to use the right measures for our instruments and in developing our instruments. We also have to remember there are methods that exist and which are advancing for how we engage patients in helping us to figure out how to do research. I think it's wonderful that the FDA's engaging patients more and more. I want to make sure that all of us remember it's not just about bringing people into a room and asking them questions but engaging them and figuring out we really need to know and how should we be engaging patients who participate.

That's on a higher level when you think not just that we need to engage patients but that we need to start that process much earlier on. It's not about just developing that instrument, but how did we get to the point where we decided that was the right instrument to measure? How did we engage patients in the process of helping us think through what it is we need to learn, as well as how we learn and we disseminate. So when you ask what the strategy for moving forward is, I think it's continuing to engage patients. But thinking about how we engage them and making sure that we do that meaningfully so that they don't just help us simply measure what we want to measure, but how we measure what they want us to measure.

Theresa Mullin: Thank you very much, Daniel.

What I'd like to propose that we do now is that go again through the panel and give each of the panelist, stating with myself, an opportunity to reflect on what you've heard or ask follow up questions of your fellow panelists based on the collection of what we've heard that would be a good place to start and then I'd like to open it up for questions that everyone else may have as well.

There's just so much very rich material here and I'm looking forward getting ready for PDUFA VI, starting later this year so I know we're going to have plenty of follow up conversations but I do have two questions of my own.

My first question is for Jim and thank you, Jim for really kind of giving us a quick, I realize it was quick, exposition of PROMIS and one of the things I wonder and I think and we see incorporating it into how a process as we proceed and look at that as a huge resource but what would you say about the issue of ... you mentioned that you thought one advantage is that it could be agnostic to the disease condition. Could you reflect on your view of the generalizability versus context abuse which was talked about earlier today and some of the observations that Jennie has made based on her work in the MECFS about the need for that diversity and the differences in understanding of the meaning of words for different diseases? Your thoughts how we might address that as we look at PROMIS and use PROMIS as a resource.

Jim Witter: Thank you for that question. I'll pick up and talk about fatigue and the adult fatigue bank that we have consists of 95 items or questions and the process that I mentioned very briefly in terms of engaging FDA through the ICAOWG with CFSME working group and RA. I'm trying to address the question posed earlier by, I think, Dennis Turk, when is enough information enough particularly from a qualitative perspective. From a patient perspective, when is there enough when we can comfortably say from FDA perspective for example, or from the patient perspective, that the PROMIS item bank, the questions in there cover what's important to them. So for example with patients with CFSME, post exertional malaise, is that really covered adequately in the questions that already exist currently in the bank or through the process of focus groups and cognitive interviews, would we find that there are additional questions that we need or we need to change the ones that are there. So we from the start have engaged patients, we've also engaged people, for their patients to make sure that we have something to compare against. We're all about getting it right and improving. So whatever process we can help with, we're than happy to do that.

Theresa Mullin: Thank you; sounds like a place to start with the measures that are in the bank.

My other question is for Marc my follow up question. Marc, to what extent, your first point is that we should try to proceed and do much of this work perhaps in a pre-competitive space and to the extent that we can figure out how to do that effectively, how well does that maybe address other concern that you raised about the promotion when you're engaging patients. Would it really help obviate that concern or what are your thoughts about that?

Marc Boutin: Thank you for the question. I think the pre-competitive space addresses an issue that I've seen as a patient advocate working with a number of different companies and that is that companies are looking at this issue. I think it's

been brought to the forefront for the past number of years and they're all coming up with different approaches and they're treating it as proprietary information. That's where there is a challenge. It's not just here in the United States, it's global. Because you have multiple companies going about this in different ways, the developing of different tools using different methods for understanding the patient perspective and to use it at various points along the continuum of drug development. The challenge is if you have 20 or 40 companies coming to the FDA or EMA with data on patient preference all gathered in different ways, using different methods, and different processes; EMA and FDA are going to be hard pressed to process that information. It becomes a one-off for every company and as a result it makes it very difficult for companies to move forward. It ends up delaying the progress, there timeline for bringing a product to market. It ends up costing more money and there's very little regulatory predictability. The incentives to it are not great.

If we can in a pre-competitive space bring the companies together and start to identify best practices, when methods work best for which questions, how we communicate and disseminate that, how we engage with patients. You have an opportunity to move this into a pre-competitive space and start to create a mechanism where people are doing things in a relatively similar way without stymying or stopping the innovation. It's always been my goal as a patient advocate that the companies would get to a place where this was routine or some level of standardization but at the end of the day, they would compete on who does it best, not who does it first or who does it differently. Because it does not actually bring the product to market in a way that's meaningful for a patient. The issue of ambiguity and risk on the legal side from my perspective, I actually think a company can do this. There's an element of when you use these methods to understand patient preference and inform decision making along different points along the continuum of drug development, is very different than actually going out and marketing a product that is not approved. But again, lawyers are hired to litigate risk and for this business, the risk is high. There are companies that have been fined \$100 million, in some cases, up to half a billion dollars for marketing an unapproved product. With that kind of risk, the company attorney is going to put up a lot of barriers when it comes to patient engagement. When we work with companies on setting up mechanisms to do this, the lawyers continuously come in and say, "You cannot do this."

To the extent, we get some pre-competitive standards that will help alleviate the risk but also to the extent we get some either guidance or direction from the FDA that this is appropriate within these parameters. It will also move the pre-competitive space quicker and it will relieve the pressure on those like Roz and her counterparts, which are working in the companies to try and change the culture within their organization. There's a legal component, there's a predictability component; both of which get addressed by pre-competitive work and this sort of guidance. There's also an opportunity to change the culture within the companies and I think that's key. We often talk about trying to change the culture within FDA and we have folks here at this meeting from the FDA that are working on that issue. It is part of the reason why

I indicated linking patient preference information to the benefit/risk framework before would be very useful in shifting culture among reviewers because it forces them to be accountable for looking at the data and seeing how it applies in the benefit/risk context.

Similarly, when you speak to companies, they have PhDs running their R&D departments and Elias Zerhouni who used to run NIH and is now at Centipede has been very eloquent in saying the researchers they used to have 30 years ago were clinicians but now they're all PhDs. Their distance from the end user has become very distant and they're not engaged with the patient. They view patient preference data as either non-science or very soft science. They don't understand its relevance in their context. There's no requirement to do this so a simple indication from the FDA that this is information we would find valuable and that we might use in certain ways would be a huge lightning bolt into the R&D departments of companies that would start to shift their cultures. We'd start to see how the barriers sort to come together with these two issues.

Theresa Mullin: Thank you Marc. I'd like to turn now to Paul and ask him does he have any comments? Paul has questions for the panel.

Paul Kluetz: Just first, about that last point: Marc, I completely agree and I tried to make that clear in my statements that regardless of how PRO's use with the respect to the label and with respect to the endpoints in trial. We use PRO data to inform us on risk/benefits and that's in an environment and culture that I'm trying to adhere to in our office and that I think is only going to get more real. Now, to the extent that we can add a PRO exception within the FDA clinical template that's an interesting idea and certainly low hanging fruit that would be reasonable. Perhaps that would be significant for when you read a review that's posted online that says patient reported outcome data was not at all in this clinical trial. That would say something or perhaps you'd say patient reported outcome data was collected such that it was uninterpretable because there was greater than 50% missing data. That's also something that is very important within the review.

The leap to go then to the label is a heavier lift, but we are all looking at that trying to figure out what's the most possible way to get more pterion labels that is doable and again in my opinion, I don't want the pendulum going all the way in the other direction where we end up getting some potentially inferior and possibly misleading data. I believe that is going to be to the detriment of patients and physicians. To the extent that we can improve the data we can use it better in our risk/benefits, and our review and depending on how good that data looks from the missing data sampling, from an analysis standpoint, potentially that would end up in the label.

I think that segue ways into my key mantra right now which is standardization. Imagine that you are an FDA reviewer and your analysis of the primary endpoint of a clinical trial in a disease is different every single time you get an application. It's just so challenging for my reviewers and myself because I still review; I'm a primary

reviewer. To try to understand what this specific instrument and the same disease, where I just saw the same disease with a different instrument with a different assessment period, with a different recall period, with a different minimum reporting difference. All of this lack of standardization leads to a very challenging situation on how to interpret it in the big picture. So I think we can standardize our concept.

That leads me to my last point which is to riff a little bit off of Jennie over the challenge of what Jennie says, which is absolutely true. The heterogeneity of individual patients and what it means to them, what fatigue means to one person versus another person and another. Yet this very critical thing that needs to happen which is to find an instrument that we can generalize across different therapeutic areas is clearly the tension that everyone is feeling, I can feel it from you right now. I think we have to figure out what the reasonable threshold is for that. I don't think it's reasonable to set up a new instrument for every single, very narrow context of use. It's infeasible. At the same time, I think were you clearly have developed an instrument for a population is just simply too different than the other population than you're using.

Where that line is I don't know but I would say for things like in cancer clinical trials I was talking a little bit with our PROMIS colleagues about physical function. A PRO performance status type of thing. This is a fairly ... this concept at least to me seems like it's something that could be transportable throughout cancer clinical trials and when you think about the PROMIS measurements, is there a way that we can look at items in PROMIS and somehow do a bridging study say in bio-markers and say, look at these, these are a bunch of breast cancer patients that ask this question and I want to use this in prostate cancer. What's the process to where we can talk to the prostate cancer patient and see whether or not it is also important to them? Could we try to figure out some kind of process for doing that sort of work?

Theresa Mullin: Thank you Paul. So Janet?

Janet Maynard: This is both a comment and a question mainly directed at Roslyn. I really enjoy hearing about the experiences at your company regarding how patients are being incorporated and it's more of an integrative process where patients seem to be incorporated into various stages of drug development. A key message that you communicated was that it was very important for all to collaborate and communicate. You had the interesting idea to have follow up meetings after the PDUFA meeting to focus on where do we go from here? What are the next steps? One thing mentioned was that really industry needs very clear guidance from FDA which I totally agree with but I think it's one of those things where frequently everyone thinks they're being clear from their own perspective so I didn't know if there was some specific thing that would be helpful for drug development especially when we have areas of significant unmet medical needs or we have rare diseases where endpoint collection and development have really unique challenges that we talked about today. So when you say clear guidance is there something else that you think would be helpful to facilitate drug development in your area?

Roslyn Schneider: I think that those conversations with others and we have talked about throughout the day the earlier you have the conversations with the FDA about what it is we can think about, talk about, and what we're planning and how we plan to do that we would have better guidance about whether or not we're allowed to do this, whether it's a good idea and I think that would go a long way. I also think there a multiple segments of that risk that we perceive that is real and imagined.

It's not that we can't speak with patients ever and we know that when we do speak with patients in many settings you have lots of best practices that we need to do a better job of sharing and what the context is extremely important and again I think that there is for the longest time that there is an understanding that in rare disease it was the only way to develop medicines and nobody would even think about the distant preapproval promotion. Particularly because we're often talking so far away from when there's even the potential for there to be a medicine.

In other areas it's not that clear. So in cardiovascular disease for example where you have lots of medicines or we can pick another area, I think that context is something where we may need more guidance and where in looking at a clinical trial protocol we're ... I don't know how you make that not specific to a drug program unless you cut out all the things you're actually really interested in having patient input on. That's an example of understanding how in those specific contexts you could put the guidance around ... when I say guidance I mean a formal guidance that takes years to develop, but I think the other side of this is outside of the specific, discrete points in medicine development but after approval, closer to approval, or when you know something is not going to be in the labels because it did not meet those specific needs that would have to be in place for it to be in a label, does that mean that it should never be discussed? When we know it is discussed among patients, among healthcare providers, and we're then left out of that conversation that could be very meaningful to the FDA, to us as sponsors, to us in thinking about how we want to move forward as far as development. It's on both sides of discrete points in medicine development but also in understanding how our medicines are actually used in real life.

Theresa Mullin: Jim, your thoughts or observations or questions?

Jim Witter: I do have one final point, I applaud again the FDA for putting out the compendium of COAs. When you look at that as you go from left to right it's sort of the little sweet spot. It's my understanding that PROMIS measures will not be included in that initial listing and to me that's really a missed opportunity. Because if we want to facilitate, enhance, speedup or whatever, the development of outcome measures starting with something that arguably has taken from the best already and has improved it, and we want to improve it more, it seems like that would be a good starting point. So if that decision is not written in stone, maybe it could be reconsidered.

Theresa Mullin: Thank you. Jeff do you have some observations or questions?

Jeff Allen: It's striking how many elements of the discussion that I'm hearing are similar to other conversations that are going on in other areas of drug development. Since Paul opened the door, I think I'll walk through. With the idea that there are a lot of similar things here in terms of things being discussed with bio-marker development, you know it's really not that different. And the idea that there needs to be different processes, for different types of markers. That markers need to have some type of pre-competitive space, yes, that would be a very good idea for a number of markers and PROs that could be used widespread across many development programs. But there are also a need for, what Roz just mentioned, a confidential type process for companies to discuss with FDA how to utilize a PRO or a bio-marker in the context of their development program which is going to be predominately where the data is being generated, at a high quality, in the context of the clinical trial which may be proprietary to the company. So there needs to be these two options to pursue development. Because if there's not and there's an over-reliance on one, in terms of bio-markers. Can you imagine having to have a pre-qualification for everything that constitutes a bio-marker? It's not to say that it didn't end up being a bit of a mess, but can you imagine having to have qualified HER2 as a drug target before Herceptin ever went on the market, or anti-EGFR therapy? You know that was done in the context of a specific development program to make sure that it was providing benefit. The methods for doing so had to be worked out later and it's a bit of the chicken and the egg on how this is done. So it's important to have both of those processes as ways to sort out complex information.

Just again a clarifying point to response, this is something that's misinterpreted many times. There's still is a way to do PRO in an individual drug development context. In fact, that's kind of the most common way that it's being done right now. Similar to how co-development of companion diagnostic tests are done, in a very specific drug and disease context because it's very hard to go through the qualifications and it takes a longer time.

As you mentioned Jeff, it's critical, at least in my opinion, that drug development compression that has happened over the last five years is unprecedented. We're talking about going from 10 years to like 4 years from soup to nuts. And we're approving drugs on single arm clinical trials where how much earlier in development can you start your PRO then? I agree that PRO should be looked at very early, but that begs the question: how do you interpret a PRO in a single arm trial? That's back to one of my biggest challenges in oncology. The bottom line is you do not have to have a qualified patient reported outcome in a clinical trial, you just need to provide evidence and a strong rationale for why in your very specific drug disease context this patient reported outcome makes sense.

Theresa Mullin: Kim?

Kim McCleary: Thanks Theresa. I'm going to have three points. The first is just to echo what others have said and thanking FDA not only for this forum but for really creating a venue to sort of pilot how to get this patient focused drug development off

the ground. Having been a participant in the consultation process that was set up and also working with the MECFS community to establish a practice which others have used in subsequent meetings to mobilize the patient community around that opportunity. It's been very rewarding to see how that has translated over the last couple of years to communities and companies and programs throughout a variety of venues.

The second one is on a point that Marc made about the rationale for some sort of public/private partnership so that FDA/ EMFA aren't getting a hundred different ways for documenting patient perspective. I think the capacity of the patient organization is also an important thing to take into consideration. Because if you have Pfizer and Santé Fe and UCB, coming to the same patient organization and saying, "Hey can you help us put this instrument out to the community?" We're rapidly going to strip what those patient organizations can deliver in terms of their own capacity. So that's another reason to collectivize that process.

The last is just about this is a new area where we are all co-learning together as to how to do it, and I get a little nervous when I hear about best practices. I feel that if we were to jump to best practices right now, we might calcify some things that right now that are good, but not maybe the best. I encourage all of us to keep that spirit of experimentation and exploration very much alive as we figure out how different ways to do this. They might be disease specific or condition specific or population specific so that we don't kill innovation in the spirit of trying to figure out how we can all gain this perspective forward in a meaningful way that advances outcomes that patients want.

Theresa Mullin: Thank you Kim. Marc, do you have any observations?

Marc Boutin: I have a few thoughts. One, I think I'm hearing a lot of agreement among the panelist on a lot of high level topics that is really exciting and I think that gives us great opportunity. I want to pick up on something Jeff said and that was the chicken and the egg. I think that is a key challenge that we have as to what comes first? On patient reported outcomes, there's a lot more information out there. Companies are in that arena. My primary takeaway is if you're just beginning to engage then you probably engaged too late. You should've started to engage with the patient community well before you got to that point and most companies are unwilling to do that for fear that it would be considered or deemed inappropriate. Some sort of indication that it is not only appropriate but that it could be used or incorporated into the work that they're doing in appropriate ways, that signal will help perpetuate this movement quicker. I think that is key.

The last thing that I would say is the context of people with conditions, and as Janet said what is your chief complaint? At the end of the day we have medicalized our entire healthcare system whether it's research, drug development, and the delivery of care. While I'm the first to say clinical outcomes are important, it's only one of multiple aspects that are important to people with chronic disease and disabilities.

I'll ask the audience how many people play the horses? Anyone willing to admit they play the horses? In horse racing there's something called the trifecta and it means you pick the top three winning horses and if you do you win more money. For a patient perspective there's a trifecta. Clinical outcome is absolutely important but as we all recognize in the room if you have chronic disease you're likely not having a clinical outcome that means you're cured. You're probably going to have that condition, it's probably going to worsen, and you're probably going to die. That is the fate of 133 million people with chronic disease and disabilities in this country. Most of them have multiple chronic conditions not just one. That is what they're living with. Now, the clinical outcomes to the extent that they can manage their disease is critically important but at the end of the day, it's the journey they take towards those clinical outcomes, and the social indicators that make that journey possible. Both geographical but also financially, education, health literacy, culture, religion. Am I taking care of two children as a single mom with a chronic disease while I'm caring for my mom with Alzheimer living in a rural setting? All those issues have impacts on your ability to manage your disease and they have impacts on whether or not the treatments are viable for you. In addition, everybody lives for a reason; nobody lives to go get their blood work done. You all live because you want to meet some milestone, you have some aspiration. You're looking to achieve something. It may be that you're living to make sure your two daughters don't become a single mom without an education like you. It may be you want to see you daughter walk down the aisle, you may want to play golf in retirement, and you may be living because you've got 10 good years left of work in you. Everybody has a milestone. It may be just taking care of a pet.

If you can get a treatment that allows you to take five steps and stay in your home, that's huge. Those motivations, those aspirations that drive you on the journey to the clinical outcomes, it's that trifecta that drug companies need to understand when they're shooting for targets. It's not just the clinical outcomes, they're important, but that's only one aspect. Right now, not only do we not incentivize companies to go out and get that information, but we put up a lot of barriers. Not intentional but we need to take those down. We need to clearly articulate that it's appropriate to do this and that these things matter when you're developing a treatments. We also have to be careful it's not used inappropriately. You do not want companies coming in with preference patient data that is rigged to get an outcome, and that's been alluded to already. Critically important but we need to make sure this is a viable option and we should begin to incentivize it in appropriate ways.

Theresa Mullin: Thanks Marc. Jennie do you have any further reservations or questions for the panel?

Jennie Spotila: I have two quick observations. The first is I really understand the appeal, from multiple perspectives, of an item bank type approach or a measure that's been validated well enough under enough conditions that we think it measures fatigue well, or pain well and it can translate to another context and generate the issue that we're grappling with in our working group – the difference between

fatigue and something like [inaudible] which has a number of different symptoms, not just fatigue, that worsens after all kinds of different sorts of activity.

The other issue we haven't talked about is the ceiling effect or even the floor effect. So with a condition like to CFSME, the definition already requires substantial reduction in your function. Sometimes even a 50% or more reduction in your ability to work, to go to school, etc. So we are always skewed to one end of a measurement tool and so something like computer adaptive learning that is going to test people based on earlier answers that they gave, the feedback questions that capture that extremity or developing additional questions to measure the range at one end of that spectrum is an additional challenge.

The other point I wanted to make on the issue of diversity, obviously it is an issue in terms of race or education level or access to health care. And since it's experienced in something like breast cancer, whether you're estrogen positive or not, stage one or stage four, I think we all recognize there's diversity there. But there's also diversity in a community and we have to make sure we don't look at the patient community as a monolith. How do you know which organization you need to go to in order to get the best access to the most patients? Is there an organization that's ready to take it on? What are the resources of that organization, like Kim mentioned. So you have to look at any community as a multifaceted entity. And you have to understand that group in order to begin to understand that group.

Theresa Mullin: Thank you Jennie. Roz, do you have observations or questions?

Roslyn Schneider: It's been a great day so thank you for inviting me and I think we heard some of the same themes repetitively that I hope we'll all take back to each of our organizations so that separately and together we can work on some of these things. I also want to go back to some of the things that Marc brought up about legal limiting us and regulation limiting us. We also limit ourselves, because I think before I said, real or imagined, that we sometimes have a kneejerk reaction to say we can't because it's something that will take some figuring it out. And I think we're at the point where it is not acceptable for us to say that, and we in the industry have to be willing to reflect on where we can do better in actually picking up that ball and not assuming that our lawyers would say "no you can't" but actually having a conversation with our lawyers and throw out a lot of our assumptions. I think that's what I heard as a theme today as well, that we're starting to throw away the assumptions of what we can't do, of what we shouldn't do and where have to sit at the table but we're actually coming to the table together and exchanging really important thoughts about how we can move forward.

Theresa Mullin: Thank you; Daniel do you have observations or questions?

Daniel Mullins: I look at the fact that patients and their healthcare providers have questions that they want answered, and that's a very valid request, "I have a question, I want an answer to that question." And then there are product

manufactures who want to be able to make statements like, “my drug improves the quality of life” along some dimension or “my drug is safer than the competitor”. I think in the context of it being research and have a research question. And so if we think about the statement that ultimately we want to make, it seems to me that we should be able to frame the question and then ask the question, “When you decided you wanted to make that statement, if we knew what the question was in advance, is what you did the right way to answer that question?” So if we bring together this request for answering questions, with statements that manufacturers want to make; if we really think about bringing those two things together, the way we would do in the context of research. The way my graduate student defended his PhD this morning. He had a question and he answered the question and so to really marry those two together, and I think the FDA is ideally suited to help us with it. The FDA doesn’t really appear to have a question per se. They are kind of weighing in on whether somebody can make a statement. And so if this was the forum by which we could get a statement and the question that preceded that statement more aligned, I think we’d be further along on this journey.

Theresa Mullin: Thank you Daniel.

So we have those two cards, so before I go to the microphone and I know we’re running short on time. We may even have another public comment person, but here’s a question this panel can try and take on. We may have addressed it to some extent or to the best extent we can:

Question One: When COA’s are not primary endpoints could a LEGO approach to COAs be used based on symptoms or drug – I can’t make it out (speaker couldn’t make out remainder of question). What the drug addresses maybe?

Question Two: Think of when focus groups are asked what drives their car purchase decisions. They speak of size, safety, image, and price and comfort. However, for some the number of cup holders is a major determinant. If the number of cup holders doesn’t matter in general, does it mean the number is not important?

I guess it’s philosophical...I don’t know. Let’s just go back and ask this question. I wrote a note that although I haven’t had small children for a long time, LEGO does make a lot of special parts as I recall, and special scenes, but with that aside, let’s ask our panel and I’d like to ask the sealed team as well at this point. Electra and some others may join us because we’re going to go into the public comment.

The thoughts about this LEGO approach or piecing together to address diversity?

Paul Kluetz: I’m so glad you linked that LEGO to piecing together thing. I was still grappling with what LEGO meant. I think it fits right into my paradigm which is just because a patient reported outcome that was measured was not statistically in the hierarchy in the primary or secondary endpoint hierarchy, and believe me Electra and Ashley, and Marie and all of us have seen this multiple times. We look at it at

great lengths and we stress that result, let's say it's pain, this happens in prostate cancer trials, not infrequently, they test pain in time to pain progression. I'll get that result and I'll test it. I'll beat that result up from all sorts of different angles and see if it holds up to scrutiny. Different definitions of how time to pain progression, how much missing data was there and despite the fact that it was an exploratory endpoint, in one instance, it was integrated into the label as supportive data to another endpoint timed to opiate progression which was in the statistical hierarchy. Now this did not have P values or hazard ratios or it was not a superiority claim, it was a supportive note. So do we take exploratory patient reported outcome data seriously? The answer is yes. We look at it very carefully. We look at it very carefully if it goes the right way and we look at it very carefully if it goes the wrong way. It still goes back to standardization and great trial design and collection of the data in a very rigorous fashion. The more rigorous it is, the more we will integrate into the overall picture.

Elektra Papadopoulos: I hope I understood the question. I think as I mentioned before that when we're looking for a tool for a specific purpose, the first thing we do is look at what is existing. Then we look to see does the existing tool fit the purpose that we want to use it for? So I think that's what the question was referring to with the LEGO approach. Because we know that it is extremely time consuming and expensive to develop something from scratch. I think there is quite a bit of flexibility on the part of the agency and looking at existing instruments and trying to use those instruments as they can be applied.

Theresa Mullin: Thank you Elektra. We have a question from our webcast. Why don't you all proceed?

Question from Webcast: This question is from Stacey. As a means of obtaining patient input, do you think the agency will be open to using patient reported diagnoses, via patient panels and advocacy groups in the near future and provisional trials, or will clinician confirmation always be the standard?

Elektra Papadopoulos: Patient reported diagnoses, I think that's a term I haven't heard before. Actually, this isn't so much my area but that is a tough one and something that we struggle with because we want to make sure that we're getting the input from the population that we think we're getting that input from. And so there is a tension there. You know we want to facilitate getting this input and having broad representation but at the same time we want to be focused and knowing exactly who is providing the input and how they're reflective of our clinical trial population. So there is an inherent tension and challenge in the process. But I think we always have to remain open.

Theresa Mullin: Thank you. Are there any other... I have a question on this card and while I'm reading this question, which I think is really for the audience, but if you have any questions you'd like to ask maybe you could work your way up to a microphone so we can wrap up this portion and move to the public comment or the open comments section?

Here's the question: When those who think the PRO guidance standards are too rigorous, suggest that the standard should be lowered what exact portions of the guidance should be changed?

So I guess that's really to any of you who have felt that the standard was imperfect? Any thoughts on that? Anyone want to comment on this question? The person who wrote it also could comment or elaborate.

Marc Boutin: One comment to that question is that if you are ultimately doing patient preference data mining to have it ultimately to be used as a Patient Reported Outcome and make it onto a label, there has to be some pretty rigorous standards with that. I don't think we in the patient community argue against that. However, if you as a company want to say we've got these 20 assets we'd like to develop, we think the mechanism of action is "x", if it's successful this is how we think it will impact your life. Is that important? You could answer that with a focus group or a series of in depth interviews. That is very different than doing patient preference data mining for a patient reported outcome. So then you have to look at what the purpose is and where we are on the continuum. But I would suggest that if we could get standards around this, which has been pointed out multiple times. And if we can give a clear indication to companies that you should be doing this along the continuum, it doesn't necessarily need to be at the level of patient reported outcomes. But if you are doing this at other steps along the way, you're going to get greater experience with this and it's only going to elevate the quality of work you do for patient reported outcomes and make that easier to actually get that into the review process and then into the label.

Debra Silberg: I've had experience in two patient recorded outcomes that were not considered to be up to snuff...let's put it that way. And sometimes it was subjective issues, like should you really be asking frequency? Is it more important to ask for severity, and things like that? I don't think it's not so much the rigor, it's the subjective issues that maybe it's okay that you asked that, that you don't need to change it. Because every time you change an instrument, you have to go through another round of cognitive debriefing, I mean if you change things. So I think it's more that than we would like everything to be up here and for everything to be perfect? Of course, we always strive for that, but there were probably, even with the two instruments I worked on, were probably usable, maybe they weren't perfect. And I think that's what we're getting at is that let's make sure that drug development can move forward maybe without perfection but with the best that we can do right now. Keep working at it but we need to move forward. There are certainly patients that are waiting for a lot of drugs that we are stalled because we're waiting for the perfect instrument or we're getting mired in trying to make these things work. I'm really happy in terms of the PROMIS because you do look at things as ok we have these symptoms, they're similar in multiple diseases. I'd like to bring a lot of that into the FDA. I'm glad you're here because I have seen two pathways and not really converging.

Marc Boutin: I think that point is critically important. What I hear from people is just that. It's not a question of rigor, it's a question of do we accept this as being appropriate and valid. And I think that's where there is real opportunity. When you look at these issues that are clearly important to patients and are very subjective, and yet it is very difficult to move that along. I think there's a lot of opportunity to shift the paradigm. I completely agree with that.

And that gets to the cultural issue that needs to happen within all of our organizations. I think that's a cultural shift within FDA, I think it's a cultural shift within the bio-pharmaceutical sector. I also think it's also a cultural shift within our patient organizations. We've historically thought we owned the patient's voice. When realistically we clearly have a role to play in this, but it's only a role. It's not the entire role.

Theresa Mullin: Thank you Marc and Deborah. One thing I would actually like to come back to something that Jim said earlier. And maybe to me the underlying question is how do we maybe make more explicit the path if we are planning the path forward? Where do you look at PROMIS and see what's available there? I think what I'm understanding about the compendium of the measures that are it's defined a little bit differently it's...and I'm not going to get this exactly right so you may have to correct me, but these are measures that have been used in previous applications that have been approved. So they've gone through the regulatory review process at FDA. I don't know if that's true of everything in PROMIS, but it's clearly another very important resource to go and look at. I mean if you have a disease, or you're developing something in a particular disease area maybe you're finding out what the patient cares about and start there collecting that input but where do you look next? Maybe you do sort of a gap analysis. You're looking at what's available. I think Ashley's slides alluded to this, patient focus may produce a set of things to look at. What can you find in the compendium? Is it a material there you can work with? Maybe the next question is or at the same time you're asking what does PROMIS offer? How do we work with PROMIS? So to me it's built into a next steps process but I can envision that we might want to work on.

Jim Witter: Just in that regard when you look at one way you could conceptualize it is that since PROMIS contains all the best of the legacy instruments, what you put on a list, you already sort of have it. And as an example, when you look at the physical function bank that we had, the adult bank, it was developed by Jim Freeze, who as you know was the originator of HACK, right? The HACK is in the label for the HR205070. Jim Freeze himself, and I confirmed this recently, is pushing now that wherever HACK is we should insert PROMIS. Because it hits that floor and ceiling issues which we've been paying attention to since day one. It's a better measure so, in a way PROMIS is already going to be in whatever you put, even if you don't use the word.

Elektra Papadopoulos: I just want to speak to that. I think PROMIS does hold great promise and we actually would encourage getting more experience with the

PROMIS measures in their appropriate settings in clinical trials. And I think it's been said before having the PROMIS measures used as maybe first as exploratory endpoints to get more experience with them. I just wanted to put in a plug for that.

Paul Kluetz: I also just want to make a statement about what I said earlier, to speak to what Jeff was talking about early drug development and how fast things are going in oncology. I do not want to dissuade the single arm trial as completely useless for PRO. Actually, in the case of looking in an exploratory way at things like PROMIS and how they respond in your specific disease setting using your individual patient as its own control so to speak and see how it moves along throughout the drug development or throughout the patient receiving their therapy that would be very valuable similarly PROCTCAE would be very valuable to inform dosing. If you're looking at what the right tolerable dose is we are horrible in oncology with dosing right now. A lot of dose reductions occur again because we're using an old paradigm.

Theresa Mullin: Thank you. Yes, go ahead

Comment from Audience: Earlier today we were having a conversation with some of the speakers about the walk down memory lane from 2006, and I'm going to date myself and a few other people in the room that recall there is an original draft of a draft guidance, that came out from DDMAC in 1995 and we were all in a room like this 20 years ago talking about the draft-draft guidance back then, so I wanted to comment number one, that we've come a long way in 20 years. This is a very different conversation than it was 20 years ago, but we have a lot of people in this room to thank for what we've accomplished and I think they deserve a lot of credit. Laurie was here and Bob Temple was here earlier. Pat on all the backs to those in this room that got us along this road in 20 years.

The other thing I wanted to say is one of the things I think we need to keep in mind as we're talking about the compendium and measures, is that people use these measures for things other than clinical trials and drug labeling. So one of the examples I can think of most recently, in the last couple of years is the conversation about trying to get to quality measures and measuring healthcare quality, and how we need to get to measures of quality that get at outcomes and more recently measures of quality that get at patient reporting outcomes. So there's a big discussion on the translation of taking patient reporting outcome measures and translating them into quality measures. There's a lesson there in that there have been some people who, and I've been in many situations, where there have been some people who say, "Well, this PROs validated. Therefore, we can just take it and put it in a quality measurement environment." I feel like the TV commercial where you see the old woman smashing candy on the table and she says she's playing candy crush and people look at her and say no that's not how it works because it just doesn't work that way. I'm always having that conversation. No, that's not how this works. Just somebody somewhere, in some population said it was validated, you just can't take it and plunk it into any situation. My fear is that with the compendium, we

are going to possibly be running into the same situations. Even though a few people said it today, I think we can't stress enough that people should look at the compendium as examples and as stepping off points for something else that might be the next step, but I fear that if people just say "Of course I can just take this and put it in the quality healthcare environment and determine whether or not I'm going to pay physicians more or take a cut in their payment because it's been validated." Now it's in the compendium and that's just one thing I think we need to be really aware of.

Theresa Mullin: Thank you. I think it's time to turn to the public comment period. We have at least one public commenter.

Pujita Vaidya: Hello everyone, I'd like to thank you all for coming today. We are now moving into the public comment session. Please keep in mind that we will not be responding to your comments but they will be transcribed and be a part of the public record. Since we would like this to be a transparent process, we encourage you to note any financial interest that you may have that are related to your comment. If you do not have any such interests, you may state that for your record. If you prefer not to provide this information, you may still move ahead and still provide your comments.

So we collected a sign up before the meeting and we have one person. You'll get two to three minutes to present your comment. May I please have Sally Yoakin to the microphone? Is Sally here? Maybe she left? One last call, Sally? No, I guess not. With that, I'd like to call Elektra to the podium for the closing.

Elektra Papadopolous: I just wanted to thank everyone for coming, for staying until the end. It's been a long day. And for your very valuable input. I'd like to thank my co-chair Lisa Mullen, and all the speakers, panelists and participants today.

I'm just going to make a few very brief comments, and I know that we all have travel plans but one of the recurring themes that I think has been stated is the importance of clear and open communication among all stakeholders and it's our hope that the efforts that we undertake under the clinical outcomes initiative, really represents a multi-faceted approach to coordinate the many moving parts needed for efficient instrument development for regulatory use.

I think we've heard generally, positive feedback regarding the value of this compendium of COAs, COA tools, methods of communication tool, and also to address some of the regulatory uncertainty that sponsors are thinking about when starting drug development in a particular therapeutic area.

And we've had really valuable feedback with, I think, on where we can go next with this scope of this compendium and how we can measure its success going forward. We've also heard a lot about the value of continued collaboration among multiple stakeholders, subject matter experts and clinical trial design and analysis, clinical

outcome assessment development, clinicians, regulatory scientists and importantly, the patients themselves; and early and transparent communication with all the stakeholders can better enable us to do a better job of measuring the things that matter most to patients in their daily lives.

I think we've also had a lot of input for next steps. We heard that there's a need for communication of review standards, applicable to other clinical outcome assessments in addition to PROs. And we need processes in place for gathering input on proposed COAs for the continuum going forward. We also need to articulate our standards for the compendium. Where do they fall? What's in that continuum of evidence that we just discussed? And also how do we identify, utilize and articulate methods for sound patient engagement?

So with that I'd like to thank everyone and we will adjourn.