



Rare Disease Endpoint Advancement Pilot Program Workshop:

Novel Endpoints for Rare Disease Drug Development

A Virtual Public Workshop

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Mark McClellan:

Hello everyone. I'd like to welcome you or welcome you back to our workshop on Rare Disease Endpoint Advancement Pilot Program: Novel Endpoints for Rare Disease Drug Development. This is being convened by Duke Margolis and our partners at the FDA. I'm Mark McClellan. I'm the director of the Duke Margolis Center for Health Policy. Also, an independent board member at Alignment Healthcare, Cigna, and Johnson & Johnson.

Yesterday, we had a robust conversation on past and current experiences with rare disease endpoint development. We heard throughout all of the day's session about the importance of focusing on areas of unmet medical needs for patients and establishing robust collaborations between different types of stakeholders to support successful endpoint development and selection. Many other points that came up, some of particular note were the importance of partnering and collaborating with patients early on in digital health technology. With regard to the development of biomarkers as surrogate endpoints, we heard that because of the distinct nature of rare disease with small populations, data is often limited. So figuring out the ways to leverage that limited data sharing it is very important.

With clinical outcome assessments, we talked about the depth of qualitative studies, how that helps even if you can't clearly quantify the impact over time through well-known natural history. And then finally, for heterogeneous diseases in that session, as is often the case with rare diseases, combining multiple primary and secondary endpoints into a single multi-component endpoint could be a useful approach. But, also, needed to have caution and thoughtfulness about making sure that distinct features weren't being missed. Several key considerations and explanatory options were provided by the presenters on that point.

So today we want to build on these and other lessons and discussions that we had yesterday with a focus on providing grounding information on the RDEA Pilot Program. Speakers today will share an overview of the RDEA Pilot Program, as well as additional information about the process and the required elements for submitting a proposal to the pilot program. We'll also hear about lessons learned from other pilot meeting programs as well.

So as a reminder, if you'd like to ask a question during the presentations and open discussion parts of the meeting, please type it into the Zoom Q&A box. Please be aware that because we are having an

active dialogue, we encourage you to submit that the questions and comments. We may not be able to get to all of them, but that does feed to the learning and enriching of the RDEA process that we're aiming for today. Also, remember that you can submit written comments regarding this event to [regulations.gov](https://www.regulations.gov) until July 23rd, 2023, and we'll put the link to that submission into the Zoom chat box. And you can also, for getting more information, visit the Duke Margolis event webpage from today's workshop.

So let's get right to it. Let me go over the agenda for today, Very quickly. Session five is going to focus on an overview of the RDEA Pilot Program. Then in session six we'll turn to an overview of the process for the RDEA Pilot Program, so first general overview then process overview. Session seven will cover elements of RDEA proposals and meetings. Then session eight will be a moderated Q&A to discuss all of these issues. Then in session nine, we'll turn to experiences and lessons learned from other previous pilot meeting programs that may be relevant here too. Session 10, we're saving for public comments, so if you have a comment you'd like to make, we'll cover it there as well.

So that's the overview for the day, and let's get started right now with session five on overview of the RDEA Pilot Program. This is intended to orient all of us to this new program and we're very pleased to be joined by Dr. Kerry Jo Lee, Associate Director for Rare Diseases in the Division of Rare Diseases and Medical Genetics in the Office of New Drugs within the Center for Drug Evaluation and Research at the FDA. And also Julie Vaillancourt, a captain in the United States Public Health Service Commission Corps and a policy advisor and rare disease liaison in the Office of the Director in the Center for Biologics Evaluation and Research at the FDA. Kerry Jo, Julie, I'll turn to you now.

Kerry Jo Lee:

Thank you so much, Mark, for your kind introduction. I am very excited to be here. And I'm here today to really talk to you about the Rare Disease Endpoint Advancement Pilot Program. Just an overview of what are the goals of the program? What are we hoping to accomplish with this? And why are we doing this in rare diseases?

Next slide. So I'm here to start off by bringing you really CDER's perspective. And this is a joint CDER and CBER program, because both of us see indications that we work together on very closely in all sorts of aspects of rare diseases.

Next slide. So from the CDER perspective, we've really seen a tremendous amount of progress in rare disease drug development. Between 2015 and 2022, we approved 180 novel drugs for rare diseases. So this is half of all the novel drugs that CDER approved during this time. Since the inception of the Orphan Drug Act, FDA has approved over 550 unique drugs and biologics for over 1100 rare disease indications. But we are very well aware that over 30 million Americans live with rare diseases, and the vast majority of them do not have approved treatments.

Next slide. Another way to look at our progress in rare disease drug development in CDER is since starting in 2010 over time on this chart, specifically, this figure shows the number of novel drug approvals from 2010 to 2022. The columns are divided into the number of orphan drug approvals in green and the number of non-orphan novel approvals in blue. And the purple line above the bars indicates the percentage of orphan drug approvals in a specific year.

So as you can see, over time the percentage of all novel drug approvals in each year that are orphan approvals has increased. And you can additionally see, that the number has been quite large of orphan drug approvals in each year. In 2022, we continued to build on previously successful years and we saw that 54% of all novel drug approvals in CDER were for orphan drug indications.

Next slide. Rare disease drug development is challenging and how CDER has decided to address this was by launching the program for Accelerating Rare disease Cures back in May of 2022. So we've just passed our one-year anniversary. And the vision of the program is speeding and increasing the development of effective and safe treatment options to address the unmet needs of patients with rare diseases. Our mission is to drive scientific and regulatory innovation and engagement to accelerate the availability of treatments for patients in rare diseases.

Now this program is governed by senior leadership from the Office of New Drugs, the Office of the Center Director, and the Office of Translational Science. These three offices are at the helm, because they are the most poised, due to their evaluation and participation in rare disease drug development on behalf of the center. Within the Office of New Drugs, that houses our clinical offices of review as well as our pharmacological toxicological offices of review.

The Office of Translational Science houses our Office of Clinical Pharmacology reviewers, as well as our Office of Biostatistics reviewers. So with senior leadership from all of these offices, they really are able to guide and address the challenges of rare disease drug development From the regulatory perspective in CDER. The program is managed by the Rare Diseases Team, which I lead. We are the program management office for CDER's ARC Program, and that is in line with our PDUFA mandates to lead policy and programming for rare diseases for the center.

As you'll see on this slide, although that is the ARC governance body and management, we work very closely with other offices across CDER as necessary. The Office of Medical Policy, when it comes to real world data, real world evidence evaluation. The Office of Surveillance and Epidemiology for post-marketing, as well as real world data evaluation. The Office of Strategic Programs, which houses some of our decision science including benefit/risk and other CDER offices and divisions as needed for their expertise.

While ARC is an umbrella program for CDER's rare disease initiatives and programming, it really works very closely with the other centers and offices across the FDA on matters that are important to rare diseases. So we work very closely under this umbrella with the Center for Biologics Evaluation and Research, with Center for Devices and Radiological Health, Oncology Center of Excellence, and many offices within the Office of Commissioner, particularly the Office of Orphan Product Development, the Office of Pediatric Therapeutics, and the Patient Affairs staff.

Now how CDER ARC, and RDEA interface, the Rare Diseases team, which is my team, is responsible for the implementation and conduct of the RDEA program, as is consistent with our mandate for the Center. And CDER ARC Program is very excited to follow the learnings and the developments from this program, and then take those learnings and developments and be able to educate and engage on them across the Center for all stakeholders involved in rare disease drug development, and that includes internal stakeholders as well as external stakeholders. Now, I'll turn it over to my colleague from Center for Biologics for her perspective.

Julienne Vaillancourt:

Next slide, please. Thank you, Kerry Jo. Hello everyone. I'm Captain Julie Vaillancourt and I serve as CBER's Rare Disease Liaison in the Office of the Director. I'm a member of CBER's policy staff. And I'm going to tell you about the RDEA Pilot Program overview from our perspective and the importance of this new exciting pilot program to our center.

Next slide, please. CBER's Rare Disease program is essentially our collective activities that support advancement of CBER-regulated biologics for rare diseases. And the mission of our rare disease program is basically to facilitate and advance the development and timely approval of safe and effective biologics

to improve the lives of children and adults with rare diseases. We engage staff across the entire center in trying to fulfill this mission and we have various objectives.

Primarily, the patient is always at the heart of what we do. Our goal is to ensure that the patient perspective is incorporated into regulatory decision making. Also, a major part of our program is policy development. Much of our rare disease-related policy development is CBER specific. However, we work collaboratively with the Center for Drug Evaluation and Research as well as other centers and parts of the agency, such as the Office of Orphan Products Development in the Office of the Commissioner.

Collaboration is also at the heart of what we do. We collaborate extensively within our center and across the agency. You heard Dr. Kerry Jo Lee mention how under the ARC program, CBER and other centers are brought in to participate and collaborate on various programs. And I just want to emphasize that we do that and we work hand in hand on many initiatives in many programs. And the RDEA program is one such initiative that we've been working jointly on to date. We're very excited about it.

Stakeholder engagement is a big part of our rare disease program. It's very important to the center to do outreach, to provide education, and to listen to our stakeholders as well. And also, training and communication, developing staff capacity, continuing to work on training. We constantly have new review staff joining our center, and we need to ensure that they are up to par on their perspectives and regulatory policy, et cetera, concerning rare disease product development. So some of this training is done internally in CBER, and much of it is also done in collaboration with other parts of the agency.

We work with CDER on an annual rare disease training that is not only a prescription drug user fee commitment, but it's very important to us, and we always focus on timely issues that affect both centers. We bring case studies to it. And I can assure you as the RDEA program progresses, we'll bring learnings to that program for our review staff. And of course, communication, both internally and with our external stakeholders is incredibly important. And this is something we focus on.

Next slide, please. So I want to share with you some data from our center. Our center is smaller than the Center for Drug Evaluation Research, roughly a quarter of the size. However, we are growing, because we've had such an influx in certain product areas and we are building our staff every day actually.

So let's look at these data a bit. I'm showing you our novel biologic approvals for use in rare diseases for the last eight years from 2015 through 2022. So the bar chart to the left shows a bar for each year, for each calendar year that is, and you can see the proportion of products in both light blue and dark blue that are for use in patients with rare diseases. The dark blue segment of each bar represents those approvals that have orphan designation. And the light blue are those approvals for use in patients with rare diseases but that do not have orphan designation. And sometimes we come across these situations.

Previous slide, please. Sometimes we'll have a product intended for use in rare disease patients. However, for a reason or another, a sponsor chooses not to request orphan designation. Or maybe it's what I refer to as an umbrella indication, where it would be used for many different rare diseases. However, it still needs to be considered because of the product development and the importance to rare disease patients. So that's why I'm showing it to you on this slide in both the bar chart and in the pie diagram.

And then of course, the white segment of each bar are the number of approvals each year for use in common or non-rare diseases. So in the last two years, more than half or half of our novel biologic approvals had orphan designation. And I would suspect that this trend is going to continue, especially, because we have so many rare disease submissions that are gene therapy submissions, and we expect in the coming years to see many more rare disease-indicated gene therapy products coming along. So stay tuned.

And on this pie diagram you can see that collectively, if you look at the dark and light blue segments, more than 60%, actually 63% or 64% of our approvals in the last eight years, excuse me, are for use in rare diseases, and 34% have orphan designation. So this is very similar to what is being seen, except on a smaller scale, in the Center for Drug Evaluation and Research.

Next slide, please. And I mentioned the influx of INDs for gene therapy development programs. And this is a really nice bar diagram that shows you that. So you can see from the year 2010 to 2022 the substantial increase in the number of INDs for gene therapy development programs. And the turquoise represents the proportion in each year that is for rare indications or uses for those gene therapy development programs. And the blue color is non-rare. So it's hovers around 60%, I believe, if I can see my own slide here clearly, it's 57% in 2022. We expect this to continue. More than half of our gene therapy submissions are intended for use in rare diseases.

So I just want to share that with you and emphasize how important the RDEA program is to CBER, because we have so many products in-house under review and gene therapy development programs present unique challenges. And one of those is just identifying and selecting an appropriate endpoint. And gene therapy products do present unique challenges that we may not see with other types of products, because oftentimes it's a single dose that has a lifetime effect. And so the risk/benefit ratio really has to be considered carefully. So this is an important aspect for endpoint development.

So thank you so much for your attention. And I'm going to turn the presentation back to my colleague, Dr. Kerry Jo Lee from CDER.

Kerry Jo Lee:

Thank you so much. And now I'm just going to take a few minutes to provide an overview on the Rare Disease Endpoint Advancement Pilot Program.

Next slide. So there's a lot of challenges in rare disease drug development. Natural history is often poorly understood, and natural history is actually critical to inform the design of a clinical trial for a therapeutic for rare disease. It determines how long your trial might be. It determines how you can look at which endpoints may be very important to select, which patient population within your disease area would be best to benefit from a therapy being proposed. And often it's poorly understood which makes these trials very challenging to design.

Diseases are also progressive, serious, life-limiting, and lack adequately approved therapies. So there's a lot of urgent need around drug development in this area. Many of these additionally have pediatric onset, which can be really an additional layer of complication when it comes to drug development.

There are small populations that often restrict study design options both in the design and the interpretation of the studies. There's phenotypic and genotypic diversity within disorders that can additionally make this hard when you're trying to select patient populations that might benefit. There's development programs that lack solid translational backgrounds. And this can be really, really important in rare diseases due to the fact that often these trials involve demonstrating substantial evidence of effectiveness through one adequate and well controlled trial plus confirmatory evidence. Well, the strength of that confirmatory evidence is quite often anchored in what is known about how strong a translational science program was for the development of the therapeutic.

Also, in the selection of surrogate biomarkers as primary endpoints that may be reasonably likely or do demonstrate or are thought to translate to the demonstration of clinically meaningful benefit. There's drug development tools that have not been developed, outcome measures and biomarkers, they're lacking often in rare diseases.

And next, if you could hit the animation, what we're really here to talk about with the RDEA program is that there's a lack of precedent including clinically meaningful endpoints for drug development in many rare diseases. And if you don't have the endpoint robustly developed and discussed in order to demonstrate that your therapeutic works, it becomes very, very challenging on the backend to interpret the meanings of your trial result.

Next slide. So the RDEA program is a pilot program that's really designed to seek to advance rare disease drug development by providing a mechanism for sponsors to collaborate with the FDA, specifically on the efficacy endpoint development process. It promotes innovation and evolving science by sharing learnings. There's a disclosure aspect to this program on novel endpoint development, and this might be through presentations, guidance documents, public workshops, and public facing, what we might present on the public facing website. And it's really, really important that we share the learnings throughout this program with the greater community. And also, the goal is to develop FDA staff capacity to enable and facilitate the development and use of novel endpoints to evaluate the efficacy of rare disease therapies.

Next slide. The scope of the program, and again it's a joint to CDER and CBER program, is that you must have a proposal that meets the criteria, and an endpoint or endpoints are considered eligible for this pilot program if the following criteria are met. It has an associated development program that is active and addresses a rare disease. So an active IND or pre-IND for the rare disease. The proposed endpoint is a novel efficacy endpoint intended to establish substantial evidence of effectiveness for a rare disease treatment.

Next slide. There are a few exceptions to this eligibility, or a few caveats. And they are that if a sponsor does not yet have an active development program but has or is initiating a natural history study where the proposed endpoint is intended to be studied, that could be considered eligible. Additionally, if a sponsor has a program for a common disease that includes an innovative or novel endpoint elements including the methodology developed for that endpoint, if there is sufficient justification, but that proposal could be applicable to a rare disease, that might be considered.

And then the second eligibility criteria definition is what do we mean by a novel endpoint? So a novel efficacy endpoint in this circumstance is if it has never been used to support drug approval or if it has been substantially modified for previous use to support drug approval.

Next slide. Just some overview in terms of numbers and transparency. So this is a pilot program. So we're starting small, and this year, in fiscal year 2023, sponsors may submit proposals beginning in Q4, which opens in under a month, and we will accept a maximum of one proposal. In fiscal years 2024 through '27, sponsors can again submit proposals, and we will accept up to one proposal per quarter with a maximum of three proposals per year.

The transparency that I talked about is really, really important to the success of this program and to all stakeholders involved in rare disease drug development. And to this end, we will conduct up to three public workshops, first of which you are attending today, thank you, by the end of fiscal year 2027 to discuss various topics related to endpoint development for rare diseases.

And to promote the innovation and evolving science, novel endpoints developed through RDEA may be presented prior to FDA's approval of a drug studied in a trial, so in guidance, on a public facing website, or at public workshops in order to share learnings from the program.

Next slide. So thank you very much for your time and attention today, and I will turn it back over to Nancy to walk us through the rest of the program.

Nancy Allen Lapointe:

Great. Thank you so much, Kerry Jo and Julie for that terrific overview of the RDEA Pilot Program. My name is Nancy Allen Lapointe, and I'm a faculty fellow at the Duke Margolis Center for Health Policy. And I have the privilege today of serving as moderator for many of the sessions. I know we're a little ahead of schedule, but we're going to go ahead and move on to session seven, or six, I'm sorry, session six, entitled RDEA Pilot Program Process Overview.

In this session, our two speakers will present the proposal process for the RDEA program. So I'd like to welcome Mary Jo Salerno, who is a science policy analyst on the CDER Office of New Drugs Rare Disease Team, and is the administrative lead for the RDEA Pilot Program. And then also welcome back Julie Vaillancourt, who was introduced in the prior session, who is a captain in the United States Public Health Service Commission Corps, and policy advisor and rare disease liaison in the Office of the Director in the Center for Biologics Evaluation and Research at the FDA. So Mary Jo and Julie, you want to come back on screen, and you can take it away from there.

Julienne Vaillancourt:

Okay, thank you so much, Nancy. Good afternoon everyone, once again, and I'm Julie Vaillancourt. I'm CBER's rare disease liaison in the Office of the Director, as Nancy said. And I'm going to start with this joint session that Mary Jo Salerno and I will present.

Next slide, please. So I'm going to provide an overview of the process for the RDEA Pilot Program with my colleague Mary Jo Salerno. And first we will provide an overview of the RDEA proposal and we will talk about the RDEA process and timelines, FDA processing of the RDEA proposal, and the meeting process for those proposals that are admitted into the program.

Next slide, please. So I'm going to start by telling you about the RDEA proposal.

Next slide, please. I'll cover due dates, the number of proposals to be admitted into the program, and I know you've heard this a bit by Dr. Kerry Jo Lee in the previous presentation, but I'll reiterate. Also, talk about who can submit an RDEA proposal, cover the eligibility criteria, discuss RDEA proposal elements... Oh, I'm sorry. The proposal elements actually will not be discussed in this session. They'll be discussed in detail in session seven by Dr. Sepideh Haghpanah in the rare diseases team in CDER. So in the next session you'll hear about the proposal elements in detail. However, I will talk about how to submit the proposal to either center, CDER or CBER.

Next slide, please. So you did hear this in Dr. Kerry Jo Lee's presentation, but let me just review it again for you. The due dates for the RDEA proposal submissions are actually the last date of every fiscal year quarter, starting with quarter four of fiscal year 2023, which begins on July 1st through quarter three of fiscal year 2027, and that ends on June 30, 2027. And we will not be accepting any proposals in quarter four of fiscal year 2027, which is the last fiscal year, quarter of the five-year PDUFA period, the PDUFA VII period that is. So again, those submission deadlines are the last day of every fiscal year quarter being March 31st, June 30th, September 30th, and December 31st, as applicable.

And as Dr. Kerry Jo mentioned previously, we will select a limited number of qualified proposals in fiscal year 2023. Sponsors may submit proposals starting again on July 1st, and we will accept a maximum of just one proposal in this fiscal year. However, for the next four fiscal years of the PDUFA VII period, that would be fiscal year 2024 through 2027. We will accept up to one proposal per quarter with a maximum of three proposals per year. So this all adds up to a maximum of 13 RDEA proposals for the overall pilot program.

Next slide, please. With regard to RDEA eligibility criteria, an RDEA proposal must meet the program eligibility criteria as stated in two resources that are publicly available. These are the RDEA program

webpage, the hyperlink is provided here, and on the Federal Register notice about the pilot program that was issued on October 27th, 2022, and the hyperlink is provided here on this slide as well for you.

Next slide please. So FDA will consider reviewing different types of RDEA proposals based on the eligibility criteria. So these are one, a proposal for a novel efficacy endpoint that would be developed under an active IND or pre-IND for a development program. Or two, a proposal for a novel efficacy endpoint that's being developed in the context of a natural history study and not associated with an active drug development program. So this case is a unique situation because there would not be an active IND or pre-IND. So in this case, a sponsor would need to request a pre-IND application number from the agency before submitting the proposal. And then the third situation is a development program where there's an active IND or pre-IND, but it's for a common disease that includes innovative or novel endpoint elements, including the specific endpoint and or methodology.

And in this case, with the proposal, we would expect there to be sufficient justification provided by the sponsor for how that proposed endpoint would be applicable to one or more rare diseases. So those are three different situations that concern eligibility criteria and for which proposals will be considered. And to clarify, a novel endpoint is an endpoint that has never been used to support drug approval or if it has been used to support drug approval, in the context of the proposals being submitted, it would be substantially modified from the previous use to support drug approval. So next slide please.

So who can submit a RDEA proposal? Well, if you were to look at the resources provided to date publicly, you'll see the term sponsor is used and for the purpose of the RDEA pilot program and is defined in the IND regulation, specifically 21 CFR 312.3, a sponsor is a person who takes responsibility for and initiates a clinical investigation. So a sponsor may be an individual or a pharmaceutical company, a governmental agency, an academic institution, a private organization, or another organization. So as you can see, a sponsor may be any one of those entities and any of those may participate in this pilot program. Next slide please.

So a question had come to our attention concerning whether a proposal under the RDEA program might affect one or multiple INDs because it seems possible that perhaps it could be applicable to multiple INDs. So the specific question is, can multiple INDs be referenced in an RDEA proposal to explicitly demonstrate and discuss the applicability of an approach across therapeutic areas? So as you've heard, there are different situations under which we'll submit or we will consider submitted RDEA proposals. And in general, RDEA proposals would need to meet the program eligibility criteria. And this in general would include an active pre-IND or IND except for the exceptions that I mentioned and that Dr. Kerry Jo mentioned.

However, I do want to say if you as a sponsor that's planning to submit a proposal, know or think that it would be applicable to multiple drug development programs under different INDs, we ask that you identify a primary IND and submit your proposal under that IND. And then cross-reference or discuss the other INDs in the context of your proposal and clearly explain how the development of the novel endpoint would be applicable to those other INDs. So again, in a nutshell, you need to submit the proposal under a single IND, but then we would like to hear how it would be applicable to those other INDs. Next slide please.

So with regard to submitting the proposal, again, I've mentioned you need to have, except for an exception, an active pre-IND or IND. So if you have an active pre-IND or IND, you would need to submit your proposal to that specific application. Now, if you don't have an active pre-IND or IND, you'll need to request a pre-assigned number for your RDEA Pilot Program proposal and then submit the proposal to that newly created pre-IND application. So this would be in the situation where you're developing your novel endpoint in the context of a natural history study. And we have instructions for electronic

submission in general, if you're not used to the process they're provided here at this hyperlink on the third bullet on this slide. And also RDEA proposals for natural history studies, they may be submitted to either center because typically if it's the other situation where you have an active IND or pre-IND, you would know to submit it to CDER or CBER depending on where that IND or pre-IND is.

However, with the natural history study, you may or we're actually advising you to, that it's your discretion where you want to submit it since you don't have an application that's active currently. Next slide please. So here's some information on this slide on how to request a pre-assigned application number. For CBER, we have an SoPP 8117 and the hyperlink is here in the first bullet. And for CDER, there's information available at the hyperlink in the second bullet for how to request a pre-assigned application number. Next slide please. And then just some important additional information. All RDEA Pilot Program submission should have this submission header, RDEA Pilot Program submission. So that should be at the top or it should be the header for your submission so that it's very clear when it's received by either center that it is specific for this pilot program so that our team will be aware of it and we'll route it to the right people and it won't get lost. We want to make sure that it's properly labeled. So that's very, very important.

The second important item is that we ask you when you submit a proposal or right after you've submitted it, please send us an email, send the RDEA team an email, and it would be to this email address, RDEA.meetings@fda.hhs.gov. And this will alert the team that you've submitted your proposal to either center and we will just be on the lookout for it. Next slide please. So now you've submitted an RDEA proposal. What happens next? At this time, I'd like to turn the presentation over to my colleague Mary Jo Salerno in CDER's rare diseases team, and she's going to walk you through this. Thanks so much. Mary Jo.

Mary Jo Salerno:

Thank you Julie, and good afternoon everybody. As previously stated, my name is Mary Jo Salerno. I am a science policy analyst in CDER, Office of New Drugs on the Rare Diseases Team. And I am the CDER administrative lead for the RDEA program. Next slide please. So we are going to go over RDEA process and timelines for the rest of this presentation. Next slide please. Here you can see a pictorial presentation of the RDEA process and timeline at a very high level, starting with when a sponsor submits an RDEA program proposal anytime during a fiscal year quarter during the PDUFA VII cycle, all the way to through FDA's evaluation of the program, choosing of a primary proposal, disclosure discussions, admission to program, and the actual holding of RDEA meetings for those sponsors whose proposals are admitted into the program. We'll be talking about each of these steps a little bit more in subsequent slides. And just of note, the timeline could possibly change at any point in time. There are some timelines that are spelled out in the PDUFA VII commitment letter and we'll mention that in subsequent slides. Next slide please.

So how does FDA process an RDEA proposal? Next slide please. So when FDA receives an RDEA proposal, they will send an acknowledgement letter within 14 days of the receipt of the RDEA proposal. This 14-day timeline is set forth within the PDUFA VII commitment letter. After that, FDA will conduct an eligibility and completeness review. The eligibility criteria have been previously stated by Dr. Kerry Jo Lee and Julie Vaillancourt, but we will take a look to ensure that all of the necessary criteria for eligibility are met and whether FDA can consider an RDEA proposal in the program.

And just as a reference, not all of the information, but much of the information regarding various criteria and elements are listed on the RDEA program webpage. And there in the resource guide for this meeting, which is on the Duke Margolis website, there are links, very helpful links which will lead you to the information. After determining that an RDEA proposal is eligible, FDA will then conduct a

completeness review to ensure that all of the required elements of the RDEA proposal, which will be discussed in the next session, are included in the RDEA proposal. And if they are not included, that rationale is provided as to why they're not included.

So if the proposal is then deemed complete, the proposal will move on to an internal FDA selection process. RDEA team members will work in collaboration with both CDER and CBER review divisions, and that's the clinical review divisions. Rare disease drug development is a multidisciplinary enterprise and endpoint development. So multidisciplinary reviewers as needed will evaluate the proposal. Clinical, statistics, and regulatory project management will be involved with all proposals. But there are additional disciplines for people who have expertise in certain areas that might also evaluate the RDEA proposal as relevant to the endpoint that was proposed. These can include psychometricians with clinical outcome assessment expertise, clinical pharmacologists, others with biomarker assessment expertise, those with digital health technology and tools expertise, real world evidence, and perhaps others.

And FDA, per the PDUFA VII commitment letter FDA will provide a 60-day notification to sponsors of the disposition of their RDEA proposal. Of note for the RDEA proposals with natural history studies studying a proposed endpoint, both CDER and CBER will be involved and consult each other as needed in the evaluation process. Next slide please. So this information about, very, very general information about RDEA proposal selection is set forth in the PDUFA VII letter, and it is also on the RDEA program webpage. FDA expects to admit a limited number of RDEA proposals into the pilot program. So FDA will give preference to certain types of proposals, those that have the potential to impact drug development more broadly, perhaps using novel approach to develop an efficacy endpoint or an endpoint that could be potentially relevant to other rare diseases. Proposals that reflect or impact a range of different types of endpoints. And for surrogate endpoints, those that use novel approaches for collecting additional clinical data in the pre-market stage to advance the validation of these endpoints.

Next slide please. So the 60-day notification to sponsor is set forth in the PDUFA VII commitment letter. And when we say 60 days, the clock begins at the end of the previous quarter. So the 60 days is after the end of the quarter in which the RDEA proposal was submitted. For instance, if a proposal is submitted in the quarter ending September 30th, 2023 60 days is November 29th, 2023. So there are various types of notifications that FDA will provide to a sponsor and this will be done in writing. FDA will choose a primary sponsor, or excuse me a primary proposal. And the sponsor of that primary RDEA proposal will receive correspondence notifying them that they will be proceeding to disclosure discussions. FDA will also choose an alternate RDEA proposal and the sponsor of the alternate RDEA proposal will receive correspondence notifying them that they are an alternate for proceeding to disclosure discussions. All other RDEA proposals will receive an RDEA proposal denied letter.

Next slide please. So we've heard a little bit about this disclosure agreement. What is this agreement? This is something that's very, very different from other types of FDA meetings. Well, this is actually another thing that is set forth in the PDUFA VII commitment letter and it's a requirement to participate and be admitted to the RDEA Pilot Program. Why do we have this disclosure agreement? Well, as of others have previously spoken to, one of the goals of the RDEA Pilot Program is to promote the evolving science and innovation in rare disease endpoint development.

The PDUFA VI and PDUFA VII have several pilot meeting programs and several of them have this disclosure agreement. And the disclosure agreement allows FDA to speak about the topic that was discussed, in this case, rare disease endpoint development within the context of the meeting program, even before FDA approves a drug. And this is something that FDA normally does not do. And FDA can share this information and these lessons learned because of the disclosure agreement at various venues and those have been discussed previously as well. So this really allows FDA to meet one of the objectives

of the program and share lessons learned even before a product is approved by FDA. So the FDA and the sponsor will discuss disclosure elements, come to an agreement.

We are not including a list of disclosure elements or listing that within the context of this meeting because there will not be that many sponsors that will go on to the, there's a finite number of those who will proceed to disclosure element discussions, but that information is available on the RDEA program website as well. So when they come to an agreement, the sponsor will then submit a signed disclosure agreement to FDA. And we're going to talk a little bit about, more about the disclosure process in session eight. Next slide please. So after the primary sponsor or sometimes perhaps the alternate sponsor have been successful in reaching a disclosure agreement, FDA will admit the sponsor of the given RDEA proposal to the RDEA Pilot Program. This will also be done in writing. So those sponsors admitted to the RDEA pilot program may participate in up to four focused meetings, endpoint development, rare disease endpoint development-focused meetings with relevant FDA staff to discuss the endpoint development.

These sponsors will have the opportunity to interact with interdisciplinary FDA experts in endpoint development as well as the associated clinical review division. And the types of interdisciplinary experts will depend on the nature of the submitted proposed novel endpoint. Next slide please. So once a sponsor has been admitted into the RDEA Pilot Program, will FDA share this information? And the answer is no. However, if the sponsor chooses to publicly disclose that has been admitted into the RDEA pilot program, perhaps through a press release, FDA can reference the sponsor as a participant in discussions about the Pilot Program. However, FDA will share aggregate data regarding the overall number of proposals the agency has received and the number that the agency has admitted into the program. Next slide.

So we will briefly discuss the RDEA meeting process and just to reiterate, RDEA meetings will be available to those sponsors whose RDEA proposals are admitted into the RDEA Pilot Program. Next slide please. So the requirements to submit a meeting request are set forth in the PDUFA VII commitment letter. Essentially, a sponsor admitted into the RDEA program should submit an RDEA meeting request to schedule an RDEA meeting. And along with the meeting request, they should include an RDEA meeting package. And these elements of the meeting package will be discussed further in the subsequent session. Next slide please.

So how does FDA process the RDEA meeting request and meeting package? Again, FDA will do a completeness review of the meeting package. If the meeting package does not have all of the required meeting package elements or annotation that a particular element does not apply to their proposed endpoint, FDA will send formal notification of an incomplete meeting package. Once FDA does, and then request resubmission in that event. Once FDA does receive a complete RDEA meeting package the RDEA meeting will be scheduled within 45 days following the receipt of this complete meeting package and request. Next slide please.

So the attendees at the RDEA meeting will include all FDA interdisciplinary experts who are appropriate for the nature of the proposed novel endpoint and FDA will send a meeting summary after the RDEA meeting. Next slide please. So completing the program. So any sponsor admitted into the program who has completed the maximum of the four RDEA meetings, or those sponsors who may have completed fewer than four RDEA meetings but don't have additional endpoint focused questions or issues can proceed with the standard regulatory and meeting process. And if they need to meet with FDA subsequently, they can request additional input through other types of FDA meetings such as those listed on the slide.

And finally, the advice that FDA provides during and as well as perhaps between the RDEA meetings is not considered binding, it's not considered a regulatory decision. So completion of the four meetings

does not guarantee approval of a regulatory submission that includes efficacy of endpoints that were discussed during the RDEA meetings. Next slide please. So enter your questions via Zoom. I see that we already do have questions. I haven't looked at them, but thank you for those who are asking questions. We'll answer as many questions as we can during session eight. Next slide. And thank you to all of you from Julie and me and I will now hand over the floor to Nancy Allen Lapointe. Thank you so much.

Nancy Allen Lapointe:

Great. Thank you Julie and Mary Jo for that wonderful presentation of the process for the RDEA Pilot Program. It was extremely beneficial and helpful and we see a lot of questions coming in, so I think we're going to have a great question and answer session in session eight. But before that, we're going to move on to session seven. This is our final FDA presentation today on Elements of RDEA Proposals and Meetings. And in this session, our speaker will discuss the elements for a complete RDEA proposal and meeting package. So I would like to introduce the presenter, Dr. Sepideh Haghpanah, who is the team lead at the rare diseases team in the Center for Drug Evaluation and Research and the clinical lead for the RDEA Pilot Program. So please take it away, Sepideh.

Sepideh Haghpanah:

Thank you, Nancy. Good afternoon everyone. As Nancy mentioned, I'm a team lead with rare disease team at Center for Drug Evaluation and Research OND, and we are going to talk about elements of RDEA proposals and meeting packages. Next slide please. The objectives of this session are to learn about the required elements for a complete RDEA proposal. Also, to learn about the required elements for a complete RDEA meeting package and to learn about available resources to assist with the development of a complete RDEA proposal and meeting package. Next slide please.

We will start with proposal elements. Next slide please. The RDEA Pilot Program proposal should include an executive summary of one to two pages. The overall proposal should be 12 pages or less. It should include all the required information listed on our website and in the following slides. If there is any part of that in the required information that you think is not pertinent to your proposal, you should clearly describe and indicate why it's not relevant and why it's not submitted. In addition to the information listed on our RDEA website, the sponsors may include additional information that is relevant to their proposal. Next slide please.

The required information include product name, IND or pre-IND number, and as it was discussed and explained, if the proposal is for a natural history study that does not have an IND number or pre-IND number, the sponsors may refer to the instructions included on RDEA website and request a pre-assigned application number. And that is mainly for our tracking purposes in the submission process. So before you start your IND, you may still apply to the program. You just need to request a pre-assigned number. The next required information is the indication, and next is if the proposal is for a natural history study, some additional information is required, including the disease being studied, prior knowledge of the disease epidemiology and natural history as described in medical literature, registries and other data sources. Additional information that the natural history study will provide should be included. It's also important to include how the design of the natural history study will support endpoint selection for future studies. Also, you need to include the projected timeline to design and conduct the natural history study if the study hasn't been started yet. Next slide please.

The next required information is when the proposal is for a common disease that includes a novel endpoint that could be used for a rare disease. There should be a clear justification to explain and support how the endpoint could apply to a rare disease. Sponsors should also include justification that the proposed endpoint is a novel efficacy endpoint to establish substantial evidence of effectiveness for

a rare disease treatment. And as it has been discussed previously, the endpoint is considered novel if it has never been used to support a drug approval in past or it has been substantially modified from its previous use for a drug development process. Next slide please. The next required information for a proposal submission is scientific justification for how the endpoint measures meaningful clinical benefit and the proposed condition and the sponsors should provide detailed description of the endpoint, including the basis of the endpoint, what type of endpoint it is, if it's a digital health technology, a surrogate biomarker clinical outcome assessment-based endpoint, or a multi-component endpoint.

And all of these were covered during the yesterday sessions in detail, and that information should be included, not the detail, but just the basis and type of the endpoint at this stage for the proposal information. Disease characteristics should be information and how the endpoint will be developed, verified, and validated. Another very important information is description of how patient and caregiver input will be considered in the proposed endpoint development program. As we heard repeatedly during previous sessions, patient's perspectives are very important and those should be considered throughout the drug development program and specifically for efficacy endpoint development, which is the focus of our program. So that should be clearly indicated and explained in your submissions. The sponsor should also provide a high-level description of how the endpoint measures a clinically meaningful change in this studied population. Next slide please.

Sepideh Haghpanah:

Another important information as part of the proposal requirement is a brief history of development program, status of product development, relevant summaries of pertinent information from prior studies. Those type of information should be included.

The sponsors should also add a brief overview of study design, study objectives, study conduct analysis methods, and if anything else related to study design.

The next important requirement is the non-disclosure elements and either related to the novel endpoint and study design, that is very important. Again, as this was discussed previously, one of the goals of the RDEA Pilot Program is to share the information and knowledge that we collect with this pilot program. So the information from the endpoint development program may be used publicly either in a guidance document or in a public facing website or at future workshops as case studies. So it is very important that the sponsors carefully review the disclosure element that is included on RDEA website and keep those in mind when they apply to the program.

The last required item is a list of questions for discussion with the agency and some information about each question. Next slide, please.

So we talked about RDEA proposals, and as we mentioned as it was discussed by Mary Jo, Julie, and Kerry Jo during previous sessions, the RDEA proposals will be received quarterly and one proposal will be admitted to the RDEA Pilot Program each quarter.

The proposals that are admitted to the RDEA Pilot Program will need to submit a meeting package for subsequent RDEA meetings with the agency. And now we are going to review the requirements for the meeting packages. Next slide, please.

The information that is needed for the meeting package are some general information about the endpoint development program and then some specific information about each type of endpoint that is being developed.

The general information include product name, IND or pre-IND application number, the proposed agenda include estimated time needed for discussion of each agenda item, list of questions for

discussion with the agency, and also if it is a follow-up meeting, the sponsors should submit a summary of new information to support continuing the discussion with the agency. Next slide, please.

Now we are going to review some of the information that are required for each endpoint. Again, with endpoints there are some information that are required for all type of endpoints and then we will go to each specific type of endpoint and we review those, the required information for those separately.

For all type of endpoints, the required information include the study population in which the endpoint is being studied. Next is description of the concept of interest and context of use. Next is description of other existing measures for that specific concept of interest or context of use.

Sponsors should also provide their rationale for the use of the novel endpoint such as natural history or pathophysiology of the disease. Also, they need to include information about the use of novel endpoint for similar conditions and other medical product development.

Another required information is the rationale for the selection of the assessment to develop the endpoint. Next slide, please.

Another important requirement for all novel endpoints includes sponsors plan to engage with patients to solicit input in developing the novel endpoint. Again, we emphasize on patients' engagement and their role in providing a unique insight and feedback for endpoint development. That information must be included in the meeting package.

Next item is if the proposal is for multiple endpoints, the sponsors should provide a detailed description of each component, how each component will assess different aspects of the disease and how the specific components will be combined to construct the novel endpoint.

The sponsors must also include their pre-specified plans to validate the novel endpoint, description of study design, study objectives, study schema, eligibility criteria, some other details such as timing and frequency of data collection and analysis methods are also important to be included.

Next item is estimates of interest and related details about that such as treatment, target study population, study selection, disease definition and diagnostic criteria, and population level summary for the variables. All of those should be included related to the estimate. Next slide, please.

The next required information for all type of endpoints are when the proposals are for real world data, use of real world data source. Additional information are required including the category of data that's being submitted, for example, if that is from electronic health records or medical claims or registries or any other source of data. Data reliability should be included. Relevance of data to the research question, timing and completeness of key data elements, validation efforts and linkage to other data sources are important to be included related to real world evidence, real world data.

The next item is description of plans and procedures to prevent and handle missing data. And the next item is the ethical and human subject protection information that should be included in the meeting package.

These that we discussed were the required information for all type of endpoints, and now we are going to discuss information that are needed for each specific type of endpoint. Next slide, please.

The next few slides include some links to helpful resources to develop each type of endpoint. And all of these links are included on RDEA website and they are also included in our resource guide related to the workshop.

For novel endpoints that include biomarkers as surrogate endpoint, the sponsors should include information for clinical or nonclinical evidence, including the clinical outcome the surrogate biomarker endpoint will predict.

The relationship of the surrogate endpoint to the causal pathway of the disease, evidence to support the relationship between the surrogate endpoint and the clinical outcome of interest.

Evidence that a change in surrogate endpoint will predict a change in the clinical outcome and analytical performance characteristics of the measurement tool must be included.

If any of the information listed above is not available, the sponsors should describe their plans, how they will generate the relevant evidence. Next slide, please.

Now we are going to talk about the clinical outcome assessment, COA-based endpoints. For these type of endpoints, the sponsors should provide evidence to support a clear rationale that a proposed COA-based endpoint is fit for purpose.

They need to provide information and evidence to support the construction and selection of COA-based endpoint, including a clear description of the endpoint, considerations taken when constructing and selecting the COA-based endpoint. For example, trial objectives or hypothesis trial duration, timing of COA assessments, strength and limitations of proposed COA-based endpoint. All of these are important to be included.

The sponsors should also include a description of pre-specified plans to evaluate the meaningfulness of COA-based endpoint in supporting the treatment benefit. Next slide, please.

For novel endpoints that involve use of digital health technology, these type of endpoints, the required information include the rationale to support that the DHT-based endpoint is fit for purpose, description that DHT captures a concept that is clinically meaningful to patients, description of how DHT endpoints relates to existing endpoints, or how the DHC based endpoint provides new means of measuring an endpoint.

Sponsors should also include description of how to create the endpoint from the data collected, and also what aspects of the data collected will be used to support the endpoint. Next slide, please.

The next item related to DHT-based endpoints include description of the design and operation of the DHT-based endpoint, rationale for use of a participant's own DHT or a general purpose computing platform, evidence that the physical parameters are measured accurately and precisely over time. Also, evidence that a clinical event is assessed properly. Usability studies are also important to be included for DHT-based endpoints, and a description of plans and procedures to mitigate potential risks related to the DHT. Next slide, please.

Next type of endpoints are multiple endpoints including composite endpoints or multi-component endpoints. Information for each individual component should be included as it was discussed in previous slides, and as we had examples yesterday for different type of endpoints.

It is important that sponsors refer to all the information including the links on this slide and also on the previous slide. For example, if their multi-component endpoint includes a surrogate endpoint, they should include that information in addition to the information related to multi-component endpoint.

Clinical importance of each component must be included, aspects of the concept of interest captured by the overall endpoint and each component should be included. Measurement strategy, instructions, training. Next slide, please.

Endpoint scoring method should be included. Endpoint sensitivity to detect change within patients over time is important to be included. It's also important to include interpretation of meaningful treatment benefit and the limitations of those interpretations by these type of endpoints.

Relevant subgroups and validation approach is also important to be included. Next slide, please.

For a natural history study, it is important to include the type of natural history study, summary of available literature for natural history data. For example, the author, the year the study was completed

or published, population size and characteristics of specific population that were studied is important to be included. Study design, if it's been a cross-sectional study, retrospective or prospective study and summary measures are also important to be included.

The sponsors should also include what additional information the proposed natural history study will provide. Also, they need to include current care options for the disease regionally and globally.

And that concludes the required information for the meeting packages. Next slide, please.

In summary, we discussed the required elements for a complete RDEA proposal and meeting package related to the proposals. There are some general information that are important, relate to all proposals, and there are some specific requirements. For example, if it's a proposal for a natural history study, that specific information should be included.

Again, as it was mentioned previously, if there is any additional information that are pertinent to the proposal and you think those will be helpful to the decision making. You may include those and if there is any required information that is requested but you're not including those, you need to clearly describe why those are not included.

Similarly, for meeting packages, there are some general information for all meeting packages and all type of endpoints, and there are some specific information for each specific type of endpoint that should be included.

We also mentioned that there are multiple guidances and resources available to help the RDEA proposals and meeting packages. All of those links that were included in the previous slides are also available in the resource guide, and those are available on RDEA webpage. We encourage the sponsors to carefully review those and depending on what type of endpoint they plan to develop, consider all of those information for a successful RDEA proposal and RDEA package submission. Next slide, please.

And I'd like to thank you, all of the colleagues who have been working on this program. Many of those participated in different sessions past few days. It's been a teamwork between CDER, CBER and multiple disciplines within the agency. And I also like to thank our team, specifically Mary Jo, Julie, and Kerry Jo during this program. And most importantly, thank you to all of you, all the participants in this program. And also thanks to Duke-Margolis.

Team, if you have any questions, all the participants, please let us know and we will try to cover as many questions as we can. I turned the podium back to our moderator, Nancy, thank you.

Nancy Allen Lapointe:

Great, thank you so much. That was really helpful walking us through the details of the program. I think, really a lot of great information there. We are running a little ahead of schedule, but we are going to go ahead and move into Session 8, which is our question and answer session. So I think we will have a little bit more time to answer folks' questions.

While registering for the workshop, I know many of our audience had an opportunity to submit questions about the RDEA program, and we're going to use this session to address many of those questions as they relate to the presentations today from our FDA speakers.

In addition, we are going to try to address as many of the questions that you submitted in the Zoom Q&A feature as well. I know some of them have already been addressed live online through Zoom, but we will try to get to as many of those as we can.

So what I'd like to do is invite all of our speakers from today's sessions to come back on screen. So Sepideh, Kerry Jo, Mary Jo, Julie, and in addition, we're going to have a new member join us. So I would

like to introduce Stefanie Kraus, who is the Senior Regulatory Council in the Office of Regulatory Policy within CDER, who's going to be joining us for this question and answer session.

So thanks everybody for jumping on the screen and joining us for this session. For the first few questions, these are going to be the ones that came from the pre-submitted questions from our audience members, and I will direct them to an individual, but please, if others have information they'd like to share or expand upon, please feel free to do so.

The first question we had is, looks like it's going to be for Julie, and the question is, "Will a sponsor seeking accelerated approval with a surrogate endpoint be eligible for the RDEA Pilot Program?"

Julienne Vaillancourt:

Okay, thank you, Nancy. Actually, the RDEA Pilot Program does not distinguish between different approval pathways, so as long as a proposal meets the eligibility criteria, it will be considered for the pilot program.

Nancy Allen Lapointe:

Okay, great. Thank you.

Julienne Vaillancourt:

You're welcome.

Nancy Allen Lapointe:

Julie, I think this one's going to be for you as well. "Will a proposal for an efficacy endpoint for evaluating a new indication for an already approved product be eligible for the pilot program?"

Julienne Vaillancourt:

Okay, that's a good question. And similar to my previous answer in this regard, the RDEA program doesn't distinguish between proposals for novel endpoints being developed in the context of a novel product or an innovative product, versus an already on the market product for which a sponsor is developing a new indication under an IND or pre-IND. So again, as long as the eligibility criteria are met, the proposal would be considered.

Nancy Allen Lapointe:

Okay, great. Thank you. I think this next one is probably going to go to Sepideh. This one, it is a little long, so just bear with me for a moment here. "Recognizing this program is intended for those developing an endpoint relevant to a specific rare condition, but will prioritize applications with broader implications. It would be good to know what portion of a submission should highlight impact for the specific disease of interest versus other rare diseases."

Sepideh Haghpanah:

Thank you, Nancy. That's a very good question. As mentioned for submissions to RDEA Pilot Program, the preference will be given to the proposals that have the potential to impact the drug development more broadly, and potentially be relevant to other diseases or proposals that reflect a range of different types of endpoints.

It is up to the sponsors to determine where they need to include their justification for such proposals. For example, they may submit that relevant information under the rationale for the endpoint or any other part of the application. It may be related to indication, or if they think it could be explained better under the study population or any other part of the proposal, they may include it in the relevant part.

And alternatively, the sponsors may provide that information under a separate section. In addition to those that are already listed in the proposal as requirements, they may add a new section and describe their justification for their proposal.

Nancy Allen Lapointe:

Okay, great. Thank you. So I think this is a question for Stefanie and I think this disclosure agreement, I know there was some good information presented about that, but I was wondering that one of the questions came up. "Can you walk us through how the disclosure agreement process works?"

Stefanie Kraus:

Sure. Just to briefly introduce myself, as Nancy said, I am Stefanie Kraus. I'm a Senior Regulatory Council in the Office of Regulatory Policy in CDER, and I'll be leading the disclosure aspects of this program.

As Kerry Jo and Mary Jo mentioned, a critical part of this program is sharing our learnings, but we can't learn as a community from what we can't talk about. So disclosure will permit FDA to discuss important learnings from the pilot program regardless of the status of approval.

So in terms of the disclosure process, we've made this very easy for all potential applicants by posting on the RDEA webpage, the categories of information we expect to disclose as part of the learning process. So before applying to the program, please go to the RDEA webpage and review the disclosure categories.

These are the disclosure categories that will be in the disclosure agreement that we will send to you after you're selected to proceed to disclosure discussions. Some categories won't be relevant for every development program depending on the type of endpoint proposed or the study design.

So when we talk about disclosure discussions with the agency, this is not about eliminating any categories of information from the agreement. It's about whether there's something specific to the development program that may need to be described in a certain way. For example, saying around a certain number of days as opposed to actual days if there is concern for the integrity of the trial.

So in the application for the program sponsors should not identify an entire category of information as non-disclosable because it contains confidential commercial information.

What we already know, that the information may be considered confidential commercial information at this time, and that's the point of the disclosure agreement. So we can talk early about information that can otherwise not be disclosed now and we can all learn.

So you will get your disclosure agreement, presumably you'll have reviewed the categories and will be smooth sailing from there.

And as a note, the agency has had really good success in other programs that require disclosure and we've actually found sponsors eager to participate and co-present with FDA at public fora. So in some the disclosure process is fairly smooth and we look forward to your submission and those discussions.

Nancy Allen Lapointe:

Great. Julie, did you have something to add? I saw you came off mute there.

Julienne Vaillancourt:

Oh no, thank you.

Nancy Allen Lapointe:

Okay. All right, great. So next question. I think this is going to be another question for Sepideh. "How do you see the timing of an RDEA meeting at the pre-IND stage versus the pre-IND meeting? What phases of drug development is this pilot best suited for?"

Sepideh Haghpanah:

It is important to note that the RDEA Pilot Program is in addition to other interactions with the FDA, including the pre-IND or other interactions with the review division through the IND submission process. These two are separate.

RDEA meetings are a series of focused meetings to discuss novel efficacy endpoint development versus other type of meetings, such as pre-IND meetings or other type of IND-stage meetings that could be related to a wide variety of questions related to nonclinical, clin pharm questions or dose finding trial design, statistical considerations, et cetera. So those are separate RDEA meetings are in addition to other meetings that could be done.

And as far as the timing, it is again, up to the sponsors where they think they need to get feedback and they need to start their interactions with the FDA. And in general, with RDEA proposals and with any other type of interactions with the FDA, we encourage the sponsors to come early and come often and continue those interactions.

And again, even at the time of the endpoint development specific to RDEA program, they may start that communication at the time of the designing non-clinical studies if they think that they have enough information about novel efficacy endpoint development to be considered at that stage. They don't need to wait until they start their clinical trials or later phases of drug development.

Nancy Allen Lapointe:

Great. Thank you so much. So I think this next question will go to Mary Jo. "Is there a type of question/feedback that you can expect that goes beyond what you might receive from FDA review division formal IND meeting, in which endpoints are discussed?"

Mary Jo Salerno:

Yes, thank you, Nancy. So my answer will compliment what Sepideh just said. The RDEA meetings are intended to provide the sponsor an opportunity for enhanced engagement with FDA experts, specifically regarding the development of their endpoint for a rare disease therapy.

So it's specific to rare disease endpoint development. And so during the meetings, other types of drug development aspects will not be discussed, and the sponsor will have the opportunity for up to four RDEA meetings with FDA if they're accepted into the program. So they'll have additional opportunities over what they would normally have during another type of formal IND meeting to interact with FDA, and most specifically, with the interdisciplinary experts who could speak to their proposed novel endpoint. Thank you.

Nancy Allen Lapointe:

Thanks, Mary Jo. So next question we have, and I think I probably heard this in the presentation, but we'll go ahead and clarify this anyway for folks. So this I think is going to go to Julie. Can an RDEA proposal be resubmitted if it is initially denied?"

Julienne Vaillancourt:

Thank you, Nancy, for that question. The answer is yes, and as you've heard, we will be accepting a limited number of proposals starting with the fourth quarter of fiscal year 2023. So starting on July 1st, where we will be accepting into the program or admitting into the pilot program, one RDEA proposal among all those that we receive.

So, obviously, there will be some denied and those that are denied certainly may resubmit in the following quarter.

And I also want to emphasize this is a pilot program, and as you've heard, one of the objectives is to learn from it, to have lots of learnings that we can share as a whole community with all our stakeholders so that we can progress and development of products for rare diseases. So there are other mechanisms for discussing endpoint development if a proposal is not admitted into the pilot.

So I want to mention that as well, because it doesn't mean that your plans to develop a novel endpoint for a product that's intended for a rare disease would stop if you are not admitted into the pilot. It just means you're not admitted into this special pilot, which has the benefit of sharing learnings.

But again, to answer the question directly, yes, a proposal that's denied may be resubmitted.

And then one final reminder that very last quarter of fiscal year 2027, we will not be accepting proposals. That's the very end of the PDUFA five year period, and that last quarter we're not accepting proposals.

Nancy Allen Lapointe:

Okay, great. Thanks Julie. And before I get back to, I think we had one more pre-submitted question, but this question there was a lot of related questions, Julie, to this in the chat, about if a proposal's not accepted into the pilot program. Certainly as you just said, it is possible to revise a proposal and re-apply, but one of the questions came up, "If it's not selected in the first cycle, will there be any priority or advantage to a resubmission and next cycle?"

Julienne Vaillancourt:

In terms of priority? There are no plans for prioritizing. I think what we're going to do is look at all the proposals that we have that have been submitted for a given quarter and be assessing them and evaluating them and identifying, selecting one. So there are no plans for prioritizing based on what has come in previously. Each set that we have received for each quarter will be looked at and assessed. And I would defer to my colleagues if they want to add anything. Dr. Kerry, Julie, do you want to say anything in this regard or Dr. Haghpanah?

Kerry Jo Lee:

I'm happy to hop in. Each quarter is a new quarter. I think when it comes to prioritization, we've been under the scope of the commitment fairly clear, but the priorities are really going to be given to those that have the ability to impact on a broader scale through an innovative methodology or a novel approach. And those are sort of the areas for priority. And then as the program progresses, ensuring

that if there is diversity in terms of the types of endpoints selected, but that is considered as part of the evaluation.

Nancy Allen Lapointe:

Great, thank you so much. And Kerry Jo, I think this last one is for you, although I think you did a good job of covering this in your presentation, but because it came in as a question, I figure it's worth giving some extra time to, and it was, is the RDEA program mutually exclusive of the ARC program?

Kerry Jo Lee:

Yeah, no, and this is a good question. It's part of why I tried to address it in my presentation because it's not an uncommon question. So CDER ARC is really an umbrella program that takes a 360 degree view of all the rare disease initiatives and programming going on across the center in terms of how to best position those so that we can advance drug development. So as part of the umbrella, RDEA is specifically a PDUFA VII commitment. So it's a separate commitment under PDUFA VII. However, CDER ARC is certainly excited to look for the learnings that are coming out of that and determine as part of our engagement strategy, what guidances or materials do we have available that we may enhance with learnings coming out of RDEA similar to any of the other initiatives in rare disease that CDER participates in.

Nancy Allen Lapointe:

Great, thanks Kerry Jo. And now I'm going to turn to some more questions that we had through the Zoom Q and A. So I'm going to just throw these out. Some of these I think we've touched on a little bit, but I think maybe because they came in as questions, we might be able to dive a little bit more into them. So the first one here is, would it not be possible to get FDA input before submitting an IND? FDA input in the endpoint is likely... and I'm going to paraphrase, to be critical in designing the protocol used for opening the IND. So I'm not sure who wants to try to take that and give us some thoughts on that.

Kerry Jo Lee:

I can just start off, but I certainly would invite any of my colleagues to add something and CBER. Julie, if CBER has something different to add. So the FDA does have mechanisms to engage prior to an IND, right? So we have pre IND meetings and there's actually a guidance that I would invite people to look at entitled Early Drug Development and the Role of pre-IND Meetings. It's part of the Rare Diseases guidance series. It's an important one to look at. We additionally have Interact meetings and those are also intended to fill a role if you have questions about a novel approach or methodology that might be incorporated into your drug development program. So there are ways to engage to get feedback prior to the submission of an IND. I don't know if anyone has anything to add.

Julienne Vaillancourt:

I think you answered that question well and I would agree with everything you say Kerry Jo, and I just want to go back to the conditions of the program as well because if a sponsor doesn't have an existing program, that is why we have the option for a pre-IND as well as part of the program. So you could be submitting your proposal as a pre IND-submission rather than as an IND submission. If you don't yet have one that's active in either center. And again, everything that Kerry Jo said would apply to CBER as well as to CDER. Thank you.

Sepideh Haghpanah:

Thank you both. And just adding that as Kerry Jo and Julie mentioned and as it was mentioned in previous sessions, there is information on the website how to request a pre-assigned number and that is when they don't have an IND and they don't have a pre-IND, but they have questions and they may request a pre-assigned number and they may submit their proposal.

Nancy Allen Lapointe:

Okay, great. Thank you. And this one, I'm not sure exactly what they're looking for you to answer, but I'm going to throw it out there because I think it is related to this, to your comment about come to the FDA frequently and et cetera. So it says, we are advised to come to discuss with FDA early, but the requirements of data to be submitted seems quite extensive. Can FDA comment on this? So I don't think you want to comment more broadly, but maybe within the context of rare disease endpoints or the RDEA program, how that might sort of fit together with some of the other things that are there.

Kerry Jo Lee:

Yeah, I think from the Rare Disease Endpoint Advancement for the purposes of this pilot program, this is really to help people... The number one requirements, unless you're submitting a natural history study, are you have an active pre IND or IND, right? So this program should be somewhat in development by a sponsor. Therefore the types of information that we would need to consider a proposal and in order to give you productive feedback during the meeting packages is why we have outlaid the elements that we have. I mean, the end goal is really to further this along for a program that may result in a therapy that is beneficial to patients.

Nancy Allen Lapointe:

Great, did anyone else want to comment on that? No? Okay, all right. And another question from our zoom link is, does the FDA intend to issue guidance following the RDEA pilot regarding specific criteria FDA will consider and data that FDA will require to provide sponsors with a more clear understanding of how to get biomarkers qualified, especially in the case of rare diseases with very small patient populations. And I'm not sure if they're referring to true guidances or just sort of guidelines or suggestions, recommendations, those sorts of things. So I'll let you sort of tackle that.

Kerry Jo Lee:

Yeah, I can start off then if anyone else has additional things. So as part of FDORA, we are actually required to issue a guidance in association with the RDEA pilot program. So we will be issuing a guidance that we will hopefully translate the learnings that we have gained from the program. In terms of qualifications specifically of a surrogate biomarker, so qualification is something that's a little bit different. There is a drug development qualification program, which I would encourage people to read about that. That is different. If you're talking about the utilization of a surrogate within a specific therapeutic context. That's something that's always ongoing discussion as part of a drug development program.

Nancy Allen Lapointe:

Great, anybody else want to comment on that?

Mary Jo Salerno:

Yes, I would like to comment and as well, thank you. There are links to helpful resources for drug development tool qualification programs in the resource guide that's available on the Duke Margolis

website. So I would refer attendees to that resource guide for links to some resources they might find helpful. And we also have a frequently asked question which touches at a very, very high level on the difference between the RDEA program and qualification programs. And so I would recommend that if you have that question, take a look at the RDEA frequently asked question webpage, which is accessible via a link from the RDEA program main webpage. Thanks so much.

Nancy Allen Lapointe:

Great, thanks Mary Jo for reminding us of that. And that plug for that document I think is a tremendous resource that is on the Duke Margolis event that's on the event website. We can try to post that link again for anyone who doesn't have it handy. But yeah, that is a tremendous resource I think of links and information for folks to take a look at. Okay, another question from our audience is, for a natural history study application studying a proposed endpoint, must the proposed endpoint already be included in the study protocol at the time of our RDEA proposal application? Or is an intention to include acceptable? I'm not sure that seems like that's going to Kerry Jo, but I let you guys decide.

Kerry Jo Lee:

Yeah, I can start. I think it's interesting. I'm not sure I've ever quite heard it put as... So this is a little bit challenging, right? Because we do have the ability to work with people who are initiating a natural history study. You should be fairly solid that this is the proposed endpoint that you intend to study. Otherwise it could be a lot of time and effort spent on an endpoint that you do not intend to utilize as your proposed endpoint in a current or future trial. It would certainly be eligible to be proposed with all of that information available. And am I missing any other part of the question?

Nancy Allen Lapointe:

No, I think that's it. That was kind of the way I interpreted that as well.

Kerry Jo Lee:

Yeah.

Nancy Allen Lapointe:

Anyone else have anything else or hear anything different there? Okay, great. So this one, I'm going to send to Julie because Julie, I think you did answer this one for someone online, but I think it is probably worth bringing up here as well. And it was a question on which eCTD section would be most appropriate for submission of RDEA proposal?

Julienne Vaillancourt:

Oh, thank you Nancy. Yes, I did answer that and I think it's a really good question because the whole eCTD backbone and all the different sections, the modules and the subheadings and all are really intended to be helpful and will say we don't have, or we're not requiring that proposals be submitted to a specific location in the eCTD structure as of yet. But this is a pilot and we're learning as we go along. So if we update and want to put it, we may end up putting some advice in the future on the website, but right now this is something that we would be leaving up to the sponsor unless we update our website anytime soon. I mean, there are certain modules that might seem more appropriate, such as I would say module one from my personal perspective. But again, we haven't identified a specific location to date and I would also defer to any of my colleagues who are here if they want to add to that response.

Sepideh Haghpanah:

I agree with what Julie said, nicely and thoroughly. It's up to the sponsors to decide where in the submission they need to include the information. And then again, that is a pilot program and as we move forward, we collect more information, we will be able to provide more granular information in the future.

Nancy Allen Lapointe:

Great, thank you. And I think this is going to be our last question and I think it's really a good one to end our Q and A session on, but then after this I will ask for any final remarks from anyone as well so you can start thinking about those as well. But given that there are so many actively engaged patient advocacy organizations and patients with rare diseases, the question came, what role do you see patient organizations in this pilot? How can we partner on this great idea? And I think several of you can probably give us some insights into thoughts there.

Kerry Jo Lee:

Yeah, I'll just point out that any time you are considering an endpoint, and you'll see it in multiple documents that we have for proposal and the meeting package, what is the clinically meaningful benefit to patients and how have they been engaged in defining that and determining that because that is absolutely critical because at the end of the day, you're trying to create a therapy that's going to help patients and their day-to-day life. And so I think patient input early and that's why we ask people to demonstrate how they've reached out and incorporated that input into their endpoint selection is a really important way that patients can play a role in endpoint determination and validation.

Nancy Allen Lapointe:

Great, thank you. Anyone else want to comment on that? No? Okay. Oh, go ahead Sepideh.

Sepideh Haghpanah:

Just adding to what Kerry Jo mentioned that patients and their perspective and feedback are very important to us, and the information that they can provide are really unique to the development of efficacy endpoints. As far as how the patient organizations would be able to interact through this program, one of the requirements for this program is having an IND or pre-IND, and if the patient organization has an IND or pre-IND, we would gladly start to consider them for the proposal. But a lot of the feedback that we receive from patients are coming to us from the sponsors. The sponsors will initiate that process and they will include patient's perspective in their INDs or pre-INDs or different requests that they submit to the agency. And we will welcome that and we will definitely consider those.

Nancy Allen Lapointe:

Great, thank you. Very important point there. All right, to I think wrap up this session, I want to give each person just a moment if there's anything we missed, anything more you'd like to share for final remarks, I won't call on folks, but I'll let you go ahead and step up and speak if you'd like.

Kerry Jo Lee:

I can start really quickly and I just want to amplify something that has already been said by at least Mary Jo on this panel and others. This is not easy novel endpoint construction and particularly not easy in the rare disease setting. There has been a tremendous amount of thought and effort gone in. I think part of

the problem sometimes is people don't even know the resources that are available to them that the FDA has that can assist them with this. And so there's been a really big effort to pull together these resources and many of them are on the Duke Margolis website page right now. They are or will be soon on the RDEA webpage. And so please refer to the materials that we have when you're thinking about constructing your endpoints and in the submissions because we've tried to provide as much guidance as possible.

Nancy Allen Lapointe:

Thank Kerry Jo. Go ahead Mary Jo.

Mary Jo Salerno:

Yeah, if I could just complement what Kerry Jo said. FDA recently had a very large update to the RDEA program website. We have four additional webpages that were added to the website, one on process, one on the content format of the proposal, one on disclosure, and one on the content format of the meeting request and the meeting package. The meeting package page specifically has hyperlinks to many of the resources that are also included in the resource guide that Duke Margolis has on the conference website, the workshop website. So the meeting package in particular has lots and lots of links to other resources within FDA. So thank you.

Nancy Allen Lapointe:

Thank you, and Go ahead Julie.

Julienne Vaillancourt:

Thank you so much, Nancy. Yeah, there I did want to make a comment, and this is something I meant to say in my talk and it's not a slide, but we had had a little discussion internally at FDA and it's a detail with regard to submission of proposals and when proposal is submitted under an existing IND and we require that the form FDA 1571 is included in any submission. And I just want to advise potential sponsors who would be submitting a RDEA proposal to an existing IND that it would be helpful to us if you check off box 11 other and just write in RDEA proposal or RDEA proposal submission. So that's just a little detail I want to add and I don't have any other comments just to emphasize that this is again, a joint CBER and CDER program and we have been working hand in hand and it's very exciting for CBER as I alluded to in my opening slides with Kerry Jo.

So I just want to emphasize that again, it's a joint program and I did see a question in the chat asking, will the three proposals that are submitted in each of the subsequent fiscal years following fiscal year 2023, will it be three for CBER and three for CDER? And the answer is no. It will be three proposals accepted into the program across both centers. So it's a limited number for the whole agency, 13 across the whole PDUFA VII period. So I hope that clarifies that as well. Thank you so much.

Nancy Allen Lapointe:

Yeah, I did see that one in there that you had answered. So thank you, Julie. Any other comments to close out?

Mary Jo Salerno:

I just wanted to compliment Julie's mention of CBER-CDER working together. I believe there were some questions about, will, CBER and CDER both participate in the meetings, et cetera, et cetera. So this is a

joint program. We will consult each other as we deem appropriate to consult each other. The centers are organized a little bit differently. There might be slightly different expertise in the different centers. And so we will consult each other as we need to in both assessment of the proposals and then our meetings for those who are admitted into the program. Anything to add to that, Julie?

Julienne Vaillancourt:

No, I'm glad you brought it up. Thanks so much Mary Jo.

Nancy Allen Lapointe:

Yeah, great. And for those of you on Zoom, the Duke Margolis folks have posted again the link to the website there that you can go to that we've talked about here that has the wonderful reference materials that Mary Jo and others have talked about. Sepideh, did you have another comment?

Sepideh Haghpanah:

I'm just echoing what everyone said. It's a joint program. We are working together, multiple internal and external subject matter experts participate in this program. We really thank you all for your time, for your efforts. Thank you to Duke Margolis. And also we are very excited about this program and I thank you all the participants who attended this workshop and will be reviewing and will be submitting their applications. We really look forward to collaborating with all of you applicants, sponsors, patients, organizations, all the stakeholders in area of rare diseases. And we hope that the meeting will be productive and the end result with the program will be helpful for everyone and for the patient community, the most important.

Nancy Allen Lapointe:

Yes, great. That's a perfect way to end this I think. So again, thank you all so much for taking the time to answer questions today. We are going to go to break. We are going into break a little bit early, but we're not going to start any earlier. So we will be back here at 3:20 for session nine. So 3:20, we will resume for session nine. Thanks everyone.

Mark McClellan:

All right, thanks everyone for those great discussions so far today and welcome back. We're now going to start session nine on experiences and lessons learned from other meeting pilot programs. In this session, we're going to include some presentations and panel discussions about what we have learned from other PDUFA pilot meeting programs with features broadly similar to those in the newly established RDEA pilot program.

The presentations will include an overview of the complex innovative trial design or CID and also the model informed drug development programs and experience to date. And that'll include a discussion of the disclosure agreement aspects of the CID meeting program. A sponsor participant in the CID meeting program is also going to discuss the sponsor experience with the CID program. And we're going to start with two presentations followed by additional remarks and moderated discussions. So I keep up those questions and comments in the Q and A as well and we'll try to work those in too. I'd like to introduce our first presenter, Dr. Rajanikanth Madabushi, who is the Associate Director for Guidance and Scientific Policy in the immediate office of the OCP. Rajanikanth?

Rajanikanth Madabushi:

Thank you, Dr. McClellan. Am I coming through clearly?

Mark McClellan:

Yes.

Rajanikanth Madabushi:

Awesome, thank you very much. And you can call me Raj. Yeah, like Dr. McClellan said, I'm Raj Madabushi, Associate Director for Guidance and Scientific Policy. I'm also the CDER lead for the Model Informed Drug Development paired meeting pilot program. And I will share some of our experiences and probably in this session some of the lessons learned during this pilot program, which was launched as part of PDUFA VI. Next slide please. Before we go ahead real quickly, some level setting what is Model Informed Drug Development? It's essentially development and application of exposure-based biological and statistical models derived from preclinical and clinical data sources to address drug development and regulatory issues. And on the right, in this cartoon are the various approaches which are most commonly invoked under this broad umbrella term Model Informed Drug Development. Of note, the model informed drug development MIDD excludes concepts around statistical designs involving complex adaptations, Bayesian methods, and other features which you are going to hear, which are part of the CID program from Dr. Price.

So very quickly we'll pivot to the Paired Meeting Pilot Program. Next slide please, next slide. So under PDUFA VI, one of the goals that was stipulated was to conduct a Paired Meeting Program and like RDEA, MIDD Paired Meeting Pilot Program is jointly administered by both CDER and CBER. The Office of Clinical Pharmacology leads this program on the side of CDER, whereas the Office of Biostatistics and Epidemiology is the lead office on the CBER side. Next slide please. Essentially, this particular pilot program provides a unique and a dedicated forum for facilitating regulatory interactions on the application of various modeling and simulation approaches to inform specific drug development programs and these applications... next slide, please... were primarily initially focused on dose selection and optimization, clinical trial simulation and mechanistic safety evaluation. Though these were the initial focus areas, we eventually opened it up to all avenues in drug development where model informed drug development approaches could be applied.

Next slide please. So under the PDUFA VI goals, it was stipulated for us to conduct at least, or to grant at least two to four proposals per quarter. And those that were granted next would get at least a pair of meetings over a period of 120 days. And those that would not be granted, they would be provided an opportunity to look back into the conventional regulatory interaction paradigm. So with that as the high level overview of what this Paired Meeting Pilot Program is, what the focus is and what in general are the stipulations around this program, I will, over the next couple of slides, focus on our experiences before summarizing some of the lessons learned. So next slide please. Under the Paired Meeting Pilot program, as I said, this was both jointly administered by CDER and CBER.

What I'll be presenting are the experiences from CDER Office of Clinical Pharmacology and over the PDUFA VI duration, we received around actually 66 meeting requests. And if we were to take a closer look at this. Next slide. We will find that there was an increasing demand over the duration of the time. You will remember that we were stipulated to grant two to four proposals per quarter, which would equate to one to two proposals per center. And you can very clearly see that with each and every year, we have either met or exceeded. Though 2018 was a partial year to be noted. What I'm also showing here are the number of programs that were accepted into the program that were granted, which are the green bars here, and those which we granted into the program through a written response only paradigm, those which are the orange ones, and those which were denied, and the blue ones. Clearly

there was an appetite for this program right from the beginning and it kept on increasing throughout the duration of the pilot program.

Next slide, please. So let's pivot to the actual program experience except fairly busy slide or figure that you're seeing here. I'll try to break it down. Next, you can see over the PDUFA duration, the experience that we gained was applicable across a wide spectrum of therapeutic areas, close to around 15 different therapeutic areas had meeting requests or meetings conducted during the PDUFA period. Next, the second aspect I want to bring to your attention is these numbers under the total, which the first one are the number of sponsor meeting conducted. Those were around 60, but most importantly, the amount of preparation that it took to bring all the stakeholders onto the same page like RDEA. This is a multidisciplinary engagement and it takes a lot of effort to bring everyone to have their shared understanding of the problem at hand and the methods that are being applied and the residual uncertainties that may exist.

So these are resource intensive, multidisciplinary engagement with stakeholders. Next. Lastly, given the demand that we had, we were flexible enough to explore alternatives such as written responses only as a way of gaining more experience as part of this program that highlights our flexibility. And we were also, in some instances, able to provide the preliminary responses, which were transparent and clear to such an extent that in some instances, the sponsors thought that they got the response that they were looking for. So this in a nutshell, is the program experience by the numbers and also by various areas where the applications were. Next slide, please.

If we were to look at the impact of this pilot program, next, we can summarize the impact. At least from our perspective, we were able to summarize the value that this program brought under these four broad buckets. The first one is primarily technical in nature, where we were able to provide lots of insights on development of these models and their applications. The next three are the impacts that were on the strategic front, either with strategies for dose selection, optimization, and risk mitigation, or finding alternative approaches for therapeutic individualization. And most importantly, gaining alignments on regulatory pathways for approval of either a new dose, dose enrichment, formulation, et cetera. Next slide please. And through this program, to date, there have been four regulatory approvals that came through this program and resulted in a positive action. Here are some of the examples that I'm presenting. We will not go through the details, but all of these, you'll notice, highlight the uniqueness of the MIDD paired meeting program such that we were able to obtain patient-friendly updates to the dosing information through the use of modeling and simulation approaches. So this is a perspective from our end.

Next slide please. I will provide a brief perspective from how the industry stakeholders are looking at it. There was a publication in the Journal of Clinical Pharmacology and Therapeutics where member companies of international consortium for innovation and quality in pharmaceutical development conducted a survey, and they shared their findings, their perspectives of the paired meeting pilot program. So at a high level, if one were to summarize, next. This paper concluded the impact in terms of the time, savings that were there, resulting in accelerated timelines, reduced sample sizes, and getting to the right dose faster.

Next was the impacts that were seen on cost savings, in some cases up to a dollar amount of 70 million. In some instances, modeling and simulations replaced the need for standalone clinical trials and also the path to potential new indications for obtaining. The next benefits that were articulated were the ability to obtain key alignments and understandings on the modeling approaches, whether there was a technical feasibility or not. And more importantly, traction was gained by the technical experts on both sides of the table as to whether certain approaches were applicable or not. And lastly, one of the key feedback that we got both verbally and also as part of this particular manuscript was, the clarity in the

feedback that was obtained, even in instances where the decision did not go in favor of the sponsors, which allowed them to appropriately tailor their programs to figure out how to progress to the next step in their drug development program.

So this is a nutshell of a perspective of what is out there from the industry side about this program. So in summary, next slide. The MIDD paired meeting program not only met but exceeded the goals that were stipulated under PDUFA VI. Clearly demonstrated tangible benefits to direct development and regulatory decision making for approvals coming through the program as part of the pilot. And most importantly, the pilot provided this kind of a forum to stand up and operationalize a regulatory interaction avenue, which was not there previously, provided as valuable experience across, not only the spectrum of drug development, but also therapeutic landscape, and allowed us to explore some pragmatic solutions to meet the demands. With that, I conclude the presentation. I look forward to the panel discussion to clarify any questions.

Mark McClellan:

Raj, thanks very much for that great overview of the MIDD program. Next I'd like to turn to our second presenter, Dr. Dionne Price, who's deputy director of the Office of Biostatistics in the Office of Translational Sciences within CDER at FDA. Dionne.

Dionne Price:

Thank you Dr. McClellan. In addition to being the deputy director of the Office of Biostatistics, I also served as the CDER lead for the CID pilot meeting program. Today I will briefly share our experiences with the program. Next slide, please. Complex innovative trial design or CID is a rather broad term that may encompass a variety of trial design. In the PDUFA VI commitment letter, CIDs were referred to as complex adaptive, Bayesian, and other novel clinical trial designs. However, we clarified in our guidance document on Interacting with the FDA on CIDs, that there is no fixed definition of CID because what is considered innovative or novel can change over time. For the purpose of the CID pilot meeting program, our guidances and other related efforts, CID includes trial designs that have rarely or never been used to date to provide substantial evidence of effectiveness. Next slide please. Examples of designs or features that may fall under the heading of CID include complex adaptive designs, formal incorporation of prior information. For example, one might augment the placebo arm with external controls or other data sources.

Use of a posterior probability to determine trial success criteria in a Bayesian paradigm, use of master protocols, and sequentially multiple assignment randomized trial design. Next slide, please. Prior to PDUFA VI, there was an acknowledgement that CIDs had the potential to increase trial efficiencies, such as reduce the sample size, accelerate drug development, and optimize drug development, meaning getting the maximum information from the research effort. Although CIDs held promise, especially in areas of unmet medical need and rare diseases, there was limited use of CIDs to provide substantial evidence of effectiveness outside of oncology. Next slide, please. To advance the use of CIDs, FDA committed to developing the CID pilot meeting program.

The program was a joint effort between CDER and CBER. Sponsors submitted designs and those selected had the opportunity to have two meetings approximately 120 days apart with a multidisciplinary regulatory team. The FDA selected up to two submissions per quarter and could use the designs as case studies for continuing education and information sharing. This disclosure aspect was a unique aspect of the pilot program that had not been done in the past. It allowed FDA to present investigational new drugs or IND examples publicly before the drug had been approved. The meetings were led by

statisticians with participation from all relevant disciplines and the pilot had a five-year duration. Next slide, please.

Our eligibility criteria were designed to ensure the focus was not on hypothetical or research proposals, but focused on trials intended to provide substantial evidence of effectiveness to support regulatory approval. Of note, a criterion was that the sponsor and FDA could reach agreement on the trial design information to be publicly disclosed. Next slide, please. Over the course of the pilot program, we accepted six submissions which spans several therapeutic areas including neurology, analgesia, rheumatology, and oncology. Some of the features of the designs included Bayesian modeling, use of formal priors in a Bayesian setting and formulation of a master protocol. Next slide, please.

A success of the CID pilot meeting program was the disclosure aspect. Because of disclosure, I can share information about the submissions that FDA would not normally be permitted to discuss. Due to time constraints today, I will not go into great detail, but you can see from the case examples, the population study included Duchenne muscular dystrophy, pediatric multiple sclerosis, pain, next slide please. Lupus, diffused large B-cell lymphoma, and pediatric patients with epilepsy with myoclonic atonic seizures. In addition, the selected submissions all utilized Bayesian framework. Next slide. In addition to being able to discuss the case examples at various forums such as the RDEA workshop, we've also provided summaries of case examples in a 2021 publication and on our website. Next slide.

There were several lessons learned during the CID pilot program. Resource requirements. CIDs often require increased planning time, staff, and computing resources. Timing. CIDs are iterative. The initial design may change based on discussions between the FDA and the sponsor. The iterative nature made the time between meetings challenging due to the sponsor's need for time to iterate, and FDA's need for ample review time. Also, the time in which challenging within the context of a sponsor's development program and the FDA's quarterly acceptance. The content of submissions. For meaningful discussions to occur, substantial information was necessary in the meeting packages. Consistency. Stakeholders desire consistency and advice across therapeutic areas where appropriate, as well as alignment among global regulators. And education and shared learning are instrumental in realizing the promise that value added CIDs hold. Next slide.

A few additional observations are, each proposal was unique and raised novel questions. There was a desire for clarification on the term CID. As a result, we provided clarification in the guidance for industry Interacting with FDA on CIDs. Since initiating the CID pilot meeting program, we have seen an increase in CIDs in late phase development in CBER, and in exploratory and early phase trials in CDER. We also saw an increase in master protocols during the pandemic. Innovative designs are iterative. The initial proposed design may change based on discussions. For the success of a CID, multidisciplinary dialogue and collaboration is key. And there's considerable interest in the use of Bayesian design. This is not surprising, as Bayesian approaches may well be suited for some CIDs because they provide flexibility in the design and analysis of a trial.

In addition, Bayesian inference may be appropriate in settings where multiple sources of evidence are considered. Next slide, please. There's still much to be learned regarding innovative designs. So the pilot program will continue under PDUFA VII, as the CID paired meeting program. Hallmarks of the program will continue to be science, education, and communication with the shared goal of bringing effective treatments to patients. Thank you for your attention.

Mark McClellan:

Great. Thanks very much for that presentation, Dionne, and looking forward to further discussion of that experience and also Raj's experience with MIDD. So this is going to be the discussion part of this session, I'd like to kick off this part of the discussion by welcoming in Susan Warner, who's global regulatory

affairs executive director for North America at Eli Lilly, who's also going to be participating in the discussion. But Susan, if you don't mind, would like to kick off with some initial experiences that you can tell us about from your organization's participation in CID.

Susan Warner:

Sure. Thank you. So thanks for inviting me to participate in today's workshop. It says my video's not coming through. Sorry. I'm here to represent Lilly's participation in the complex innovative design CID pilot program. We participated in 2019 and 2020, and when I think about both the CID pilot program and the RDEA pilot program, really finding alternative ways to design clinical trials in both these cases and have a collaborative approach with FDA can benefit all parties involved, including sponsors, FDA, and ultimately, the patients that we're both here to serve. So Lilly did submit a chronic pain master protocol, which is now an ongoing phase two study that evaluates multiple investigational agents and multiple pain types simultaneously with the flexibility to allow new investigational agents to come through into the master protocol over time.

Ideally, this master protocol will speed up the evaluation of potential new treatments for patients suffering from chronic pain, which is a really huge unmet medical need, especially in the United States. The study design was very innovative from both a statistical and a medical perspective. So Lilly completed both meetings as part of the CID pilot program, and key aspects of the design were improved because of those interactions. We did actually have protocol changes after the first meeting and then again after the second meeting. There were several important statistical and medical discussions and changes that we made as part of those meetings. So that's basically the intro that I have. Is my video not coming through still?

Mark McClellan:

It is not, but I appreciate the comments. Your comments came through loud and clear, so thank you for that.

Susan Warner:

All right.

Mark McClellan:

And it's quite all right, and let's keep building on those comments with the rest of our discussion, time together.

Susan Warner:

Sure.

Mark McClellan:

We have a set of questions that I think we're going to put up on the slide for the moment and then we'll share in the chat as well. Related to some of these, the participants have already talked about some of the key lessons learned. I've already touched on some of those. We'll go into those a little bit deeper. And one of those lessons, question three relates to best ways to work together, especially when you have to bring a number of different perspectives together. And for new programs, there's always a learning process for how to execute effectively. So we'll try to get to that and questions related to, how do we know as this program is moving forward, if it's really working or not?

So we put those questions in the chat as well. I think we can take them down now. And maybe if you don't mind, let's do a little bit of follow up to start with on the lessons learned from CID where Sue and Dionne, I think you can help. You both highlighted several themes that seem like are going to be relevant here as well around the iterative nature of the process, around building and public disclosure of the results. Something that sometimes companies might be nervous about, but really important since the goal of this program, like CID, was to provide precedents and examples that go beyond guidance for how these approaches could improve drug development. I think, Dionne, you said at the end of your comments, the goal of getting better evidence on safety and effectiveness of treatments for patients' needs faster. Anything that you'd like to add, particularly on those points? Dionne, maybe we could start with you.

Dionne Price:

Sure. And I'll touch on the disclosure aspect. So at the time when the CID pilot meeting program started, we were in uncharted territory with the disclosure aspect. However, feedback was positive, and development really benefited from sharing of those case examples in various forums. Similar to RDEA program, in addition to disclosure, multidisciplinary participation will be instrumental. The CID pilot meeting program was led by statisticians because of some of the nature of the analysis type discussions. But the program would not have been successful without participation from all of the disciplines that were needed for the different submissions. And I think I'll stop there, but I will say, I think with the disclosure piece, initially, it was uncharted territory, but we found that it actually was a successful venture and I'm really happy to see that RDEA has added that piece as well.

Mark McClellan:

Great. Thanks. Sue, anything you'd like to add?

Susan Warner:

Sure. I think overall, Lilly thought having the joint discussions with the statistical experts through the CID program and Dionne's group. And then also, the division was there and contributed heavily. So that was very beneficial to us, to have those discussions before our protocol was finalized. I can't underscore that enough. But also, I think, and this probably really also applies to the RDEA program. We were doing something very novel, that Lilly hadn't really implemented a master protocol, especially in pain with different investigational agents being run through at the same time, there's added operational complexity when you do something new, often. And so, going through the pilot program and having FDA come along the ride and endorsing the design, I think went a long way for the internal and external acceptance of a novel study design. And I can see a similar type of result with the RDEA pilot program.

Additionally, I think, because this was statistical heavy, we learned a lot about how to communicate statistical simulation plans to the FDA, which we don't always have to do that for our different studies. And we also had a novel simulation technology that we were trying to pilot and we were able to share that with FDA through the program. There were a couple things that, I think as we're sharing, and Dionne actually touched on the timeline with the CID that may be different than the RDEA. But I do think the CID pilot program and even the ongoing program, our timeline from start to finish was 10 months, and that that's a good amount of time for a sponsor to carve out, to go through the development of a protocol. Certain things, I think in that timeline, in the process, could be shortened. For example, the timeframe between the briefing documents submitted and then the actual meeting for the second CID meeting is 90 days. That's longer than a type C meeting, for example.

So I encourage, I think, try to stick to more formal guidance meeting durations if possible. I know the content is super complicated with some of these meetings, but we would hate for timelines to be a reason that a sponsor doesn't want to participate in a pilot program. And then lastly, I think... And I think we talked about this at the second CID meeting. When the pilot program is over and you, you've really focused on how to design your studies upfront, put a lot of effort into that around the pilot program and during the meetings, then we don't really have another touch base after the results are generated and the study's over. So it's almost a missed opportunity not to reconvene or at least have another touchpoint with the FDA and the sponsor to say, "Were our assumptions correct, did this work after the pilot program is over?" And you can resume a formal meeting or you can approach it that way, but that is something that I think I would like to see done a little bit differently, I think, through the pilot programs moving forward.

So those were some key learnings that Lilly had going through the process. But overall, again, very beneficial to do this. And I agree with Dionne. The disclosure process was new to Lilly. It was discussed as part of the PDUFA negotiations, but there were some Lilly team members that were surprised by the disclosure terms. They weren't necessarily [inaudible 02:27:40] but they are on there now, and they're on there with the RDEA pilot. So I think they're reasonable, and we haven't had any issues with inadvertent things being disclosed. So it's been very acceptable and we've had joint presentations with FDA. So I think all that's been a very good thing.

Mark McClellan:

Great. Sue, thanks for all those comments and certainly some lessons that seem applicable here around timing and other issues. Let me turn, Raj, to you and similar question for MIDD, you already talked about some of the lessons. I was particularly struck by what you described in terms of getting effective multidisciplinary engagement and how you all consciously work towards transparency and clarity and the guidance that was coming out. But other points that you'd like to emphasize in terms of lessons learned that could be relevant here?

Rajanikanth Madabushi:

Yeah, thank you, Mark. While the MIDD program doesn't have the disclosure element, there are several aspects which would be very much applicable, is what I would think. First is, you cannot underestimate the amount of time and resources that would be required, especially with these novel programs where there is not much of a precedence. Maybe one can say RDEA has a little bit of precedence with the two pilot programs, but there will be some unique aspects there, and it requires bringing a lot of multidisciplinary stakeholders to have the shared understanding. And that's not going to happen immediately, it takes time. It takes different avenues of engagement. Engagement during the program is very much restricted by the timelines, right? Susan was pointing out, there is so much of time that is left. So as to ensure that we can maximize our interactions during the clock, we'll have to put a lot of stakeholder engagement in the background.

In fact, Dionne can also attest, we internally had to engage our counterpart disciplines by having all hands presentations and things like that, which they just don't get added to this particular program's efforts, but they're all important to raise awareness because these are using novel, cutting edge quantitative approaches to bring to bear. And sometimes these are precedent setting. And there will be a lot of anxiety and nervousness, and it requires to bring people along for this ride. So you cannot underestimate the amount of work that goes in, not only on the clock, but also off the clock here. So that's something that's very important. The other aspect I would want to touch is, there is going to be a lot of apprehension and uncertainty on sponsors' part to get into a new program.

They're getting into this, we do not know the rules of this game, would it end up hurting us or something like that? And I would think, in our experience, people who reached out to us to ask questions, clarifications and things like that probably would have benefited the most because they got responses. We did put up on our website a list of FAQs based on those interactions, to be able to spread that word out there. But it would be very important on the sponsors or the stakeholders outside of the FDA to actually facilitate, reach out and ask for clarifications. So those are the two things which we thought were very important and probably would be applicable for any new pilot programs.

Mark McClellan:

Thanks for those comments. You all, in the course of these lessons, have already touched on some of the issues around experience with sponsor disclosure and some aspects of sponsor engagement. We've just got a few minutes left. In that time, I'd like to ask maybe all of you for any comments on lessons learned for effective collaboration between stakeholders and regulators in a program like RDEA based on the experience of these pilot meeting programs. Anyone who wants to start?

Dionne Price:

I can try and take an initial stab and then turn it over to Susan and Raj. So one thing that we learned was very helpful in the discussions was to have as much information as possible in the meeting packages, and that would allow for a very meaningful and informed discussion. So that was one thing that helped with those discussions. Another thing I would say is communication. As Susan mentioned, timing has been discussed. We did try and add some flexibility to that, but I think just enhance and increase communication between FDA and the sponsors is important. As we said, these are multidisciplinary efforts, so ensuring that all the needed parties are at the table for the meetings and when you're developing the meeting package, and of course, keep the end goal in mind. We're doing this to provide effective treatments to patients in an efficient manner.

Mark McClellan:

Thanks.

Susan Warner:

Did my video turn on?

Mark McClellan:

Your video is on, Sue.

Susan Warner:

[inaudible 02:33:31] I switched.

Mark McClellan:

If you have a comment to add.

Susan Warner:

I've been on the call all day and then of course, my computer just said, I have to switch. So anyway, I agree with that, Dionne. And I know as a sponsor, I always try to put myself in FDA's shoes when I'm working on a briefing document. So ask clear questions, what kind of information do we need to put in

the background of the briefing document to make sure that they have enough information they can actually answer our questions, and also work closely with your RPM? I've worked with Mary Jo Salerno during our CID program, so I'm glad to see they've moved her over to this new pilot program. She was a very good communicator, and that certainly helps. Other things too, I think when FDA provides the preliminary comments, receiving those a few days before the actual meeting is always helpful for sponsors so that we can read those thoroughly and then help prioritize what we need to actually discuss at the meeting.

So if you get them the night before the meeting, and I'm not saying that happened, it didn't. But it makes it more challenging to really prioritize what we need to discuss together. Oh, and one more thing. I think having consistent attendees, if you have more than one meeting from both the sponsor and the FDA's side, certainly helps move the project forward. If you bring in new people to subsequent meetings, we tend to rehash things that we've already discussed so I would also encourage both sponsors and FDA to try to keep a project team together through these pilot programs.

Mark McClellan:

And clear supporting records too, it sounds like.

Susan Warner:

Yeah.

Mark McClellan:

So this is a great comment.

Raj, we're about out of time.

I think you all did a nice job of covering our last topic on recommendations for sponsors, but Raj, any final recommendations that you'd like to highlight for either sponsors or sponsors and FDA working well together?

Rajanikanth Madabushi:

Susan and Dionne did a very good job.

If I can add one thing, I think the meeting requests when they're put in, it would be very important to clearly articulate what is being achieved, how that is being proposed for.

That actually helps because that's where most of the selection happens, so that's a critical element.

Mark McClellan:

Yeah.

Susan Warner:

Yeah.

Mark McClellan:

Great.

Well, I want to thank you all, Sue, Dionne, Raj, very much for a great discussion of...

Both sounds like some really interesting and valuable outputs from these other pilot programs, but a lot of relevant lessons to RDEA becoming a success as well. Thank you very much for joining us-

Susan Warner:

Okay.

Mark McClellan:

... and we're now up to our last but also a critically important session for today.

I'm going to turn this over to my colleague, Nancy Allen Lapointe, to help introduce this public comment session.

Nancy Allen Lapointe:

Great. Thank you so much, Mark.

Before we turn to that final session of the workshop, I just wanted to give one final reminder to all attendees that stakeholders may submit public comments to the docket until July 23rd.

All right, now let's move to our final session today, our public comment. I'd like to welcome the speakers for this public comment session who each submitted a request for a speaking slot in advance of today's workshop.

What I'm going to do is call on each speaker by name and affiliation, and once you begin speaking, you will have three minutes for your remarks.

Timing reminders are going to be sent to you via the Zoom chat so please keep an eye on the Zoom chat box so we can ensure everyone gets their allotted time.

We're going to start off with our first speaker, Karin Hoelzer from NORD.

Karin... There we are.

Go ahead. You may begin speaking now.

Karin Hoelzer:

Thank you very much, Nancy. I'm very excited to be here. It's been a fantastic two days.

I'm here representing NORD, the National Organization for Rare Disorders.

NORD is an umbrella organization for about 330 rare disease specific rare disease organizations. We were founded by patients for patients 40 years ago as a result of passing the Orphan Drug Act, and we've been huge components of the RDEA pilot.

Developing efficacy standpoints for rare diseases is challenging. Developing efficacy endpoints that appropriately capture what means most to patients and what matters most to patients is even more important.

We very much appreciate the comments and the discussions during this workshop. We also very much appreciate the emphasis on the patient perspective and patient focused drug development throughout the last two days.

What we would like to ask FDA to emphasize further is the importance of engaging patients early and often, ideally before the application process, bringing patients to sponsor meetings with FDA and really capturing endpoints that are really meaningful to patients front and center in the pilot.

We know that oftentimes the concepts of use that matter most to patients are not necessarily the easiest to study and we know that there's a tremendous opportunity, as we heard yesterday, for instance, on multi-component endpoints, et cetera, to really think critically about how to use novel endpoints that really drive home what patients... or, what matters most to patients, so we have big proponents of the idea pilot.

We're looking forward to the next workshops and we very much appreciate the opportunity to provide comments today.

Nancy Allen Lapointe:

Great. Thank you so much, Karin.

Our next speaker is Amy Brin from the Child Neurology Foundation.

Amy, I think we've got your audio there. Do you want to go ahead and begin your comments now?

Oh, there we go. We got your-

Amy Brin:

Yeah.

Nancy Allen Lapointe:

... video too.

Great. Thank you.

Amy Brin:

Good afternoon. I'm Amy Brin. I'm the CEO of the Child Neurology Foundation.

My comments here today are done so in collaboration with the St. Jude Children's Research Hospital's Pediatric Translational Neuroscience Initiative. The mission in our two organizations overlap and so we are pleased to join together in today's comment.

In the United States, one in five children live with a neurologic condition. These conditions can be a primary diagnosis like epilepsy or autism, but they can also be comorbidities of an existing rare diagnosis like seizures or behavioral issues that are the leading symptoms affecting quality of life, as in Rett or Angelman syndromes.

There are several challenges that impede the development of treatments for this population.

First, conversations regarding endpoints, like the ones happening yesterday and today, often really focus on a single disease in isolation versus looking at a larger community of patients with different diseases that share the same primary impairments. This is a very narrow view.

We know that 90% of rare neurologic disorders originate in childhood and share common symptoms such as seizures, ataxia, dystonia, and so on. These are the phenotypes that drive researchers to utilize the existing endpoints and potentially developing new therapies. However, endpoints developed for adults with a given symptom do not necessarily capture how the symptom is expressed in a child. For example, counting daily seizures for a child who's experiencing hundreds of daily seizures is not meaningful; same as the six minute walk test to measure neuromuscular symptomatology when a large percentage of these children are not even ambulant. This is why CNF and St. Jude were so very excited to see today's notice, and I'm here to ask that you consider prioritizing the rare child neurology community in your work.

Rather than focusing on a single disease state, please prioritize the development of an innovative approach for evaluating these children where common symptoms can be captured. An umbrella type design would facilitate development of drugs for a variety of rare diseases having shared common symptoms and which utilize the same chemical category of drug. For example, an ASO.

Please also partner with patient advocacy organizations, researchers and clinicians who are intimately involved in the lives of these patients to ensure there is congruency between scientific rigor, patient centricity, and no natural history of disease.

By shifting your perspective from a single disease state to a larger patient population of several diseases under one umbrella, we believe a greater impact can be gained, so let me close by emphasizing that we will never be able to efficiently bring forth safe and effective therapies to children living with rare disease if we continue to only see them as a single disease being.

This is not how they live, this is not how they clinically present, this is not how they are cared for or how they are loved, but to do so we must act as a rising tide that lifts all boats, for a win in one of these phenotype endpoints would mean a win for all the children whose quality of life is affected by that symptom.

Thank you so much for your time and your reflection today.

Nancy Allen Lapointe:

Great. Thank you so much, Amy, for those remarks.

Our third speaker is Leslie Harden from Biotechnology Innovation Organization, and we've got your video. Go ahead and proceed. Thank you.

Leslie Harden:

Thank you.

Good afternoon. I'm a director on the science and regulatory policy team at Biotechnology Innovation Organization, which is the world's largest trade association representing biotechnology companies, academic institutions, and more.

It is a tremendous pleasure to be able to provide comments on behalf of our membership today.

BIO appreciates FDA's initiation of this pilot program via PDUFA VII and are hopeful that the pilot will provide greater clarity for sponsors on how to develop novel endpoints, identify current limitations to regulatory flexibility regarding acceptance of novel endpoints for rare disease drug approval, and improve or establish more effective, efficient, and sustainable regulatory pathways for endpoint development beyond this pilot.

To ensure that participants in the pilot can contribute to gleaning early successes and therefore timely insights, we ask that the agency be forthcoming and publicly iterative where possible so that operational hurdles can be mitigated in the beginning cycles and not only in the post pilot analysis.

Earlier insights into any issues that have occurred would be extremely helpful for mitigating them in the future for applicants.

BIO further recommends that FDA considers selecting applications for the pilot, which features the following characteristics: programs addressing areas of high unmet need, rare diseases with some notable failures due to endpoint issues in the past, situations where the ability to employ regulatory flexibility is high and where biomarker data may be supportive of clinical outcomes trending in the right direction, programs which offer equal opportunities to advance both CDER and CBER regulated product

development, and we agree on the preference for pilot applications that have detailed plans for patient engagement and commitment to pre-competitive collaborations on endpoint development.

Given that the timeline currently suggests that the disclosure agreements could be discussed any time between day 60 and 90 and we understand that there might be some flexibility or changes made there and that this would occur after application acceptance, we implore the agency to consider providing as much of the general disclosure agreement stipulations as possible prior to the review process so that applicants can self-determine their ability to participate, thus ensuring that each cycle is able to be useful to the overall pilot.

In reference today, one of this great workshop, BIO strongly supports the collective emphasis on making tangible progress sooner rather than later in the regulatory acceptance of patient experience data via clinical outcomes assessments and other tools like digital health technology tools and decentralized clinical trials.

We further encourage FDA, as well as applicants, to consider the diverse patient populations within rare diseases, who are often disenfranchised or underrepresented, who would stand to substantially benefit from the use of DCTs, DHTs, patient experience data, and other tools to capture their needs in rare diseases.

BIO's task forces have been responsive and will continue to be proactive in these discussions going forward, and we have some tools available on our website to address some of these concerns regarding of DHTs, DCTs, and PFDDs, and then could be leveraged within rare diseases.

Bio thanks FDA and Duke-Margolis for the opportunity to publicly comment on the RDEA pilot program and in today's workshop, and we look forward to continuing to engage with all stakeholders involved, especially patients, FDA and other relevant stakeholders, to drive rare disease endpoint advancement and regulatory acceptance, and we plan on submitting comments to the docket later this month as well, so thank you so much for the opportunity to comment.

Nancy Allen Lapointe:

Great. Thank you so much, Leslie.

Our next speaker is Brian Kaufman from the CLL Society.

Brian, if you have video or you can proceed with just audio, want to go ahead and begin?

There, we've got your video.

Dr. Brian Koffman:

First, thank you for this opportunity to speak on novel agents for rare disease drug development. It's been a great workshop and I've learned a lot.

My name is Dr. Brian Koffman.

As a physician turned patient and as the CMO and executive vice president of the nonprofit CLL Society dedicated to the unmet needs of those with chronic lymphocytic leukemia, small lymphocytic lymphoma, CLL or SLL, I would like to address the important issues raised by this topic as they pertain specifically to CLL and other rare indolent lymphomas, from a patient's perspective.

For context, there is approximately 18,000 diagnosed with CLL every year. Some will never need treatment and some, like myself, will usually find out sooner or later that they exhausted all treatment options.

Since CLL is neither an acute cancer nor a solid tumor, some commonly used endpoints of objective response in cancer trials are not applicable to our patients. CLL is most often indolent and incurable. There is usually an excellent choice for frontline and even second-line therapy.

Therefore, for all these reasons, namely its heterogeneity, its indolence, its response to early therapies, overall survival, especially early in treatment, is not the best measure for trial results.

The situation is radically different for the few but growing number of patients with double-refractory disease who have failed the only two approved classes of small molecules. Their prognosis is dismal and survival is measured in months. However, trials in earlier lines of therapy can take years to show changes in overall survival. Instead, progression-free survival, time to next treatment, duration of response, and the novel biomarker on minimal or measurable residual disease or MRD may be a more meaningful and practical endpoint.

Increasingly data suggests that MRD in several therapeutic settings can predict overall survival.

MRD measurement has other potential benefits. It can guide decisions on whether to continue treatment, change therapies, and most importantly, from a patient's point of view, stop therapies.

Patients with a CLL diagnosis know they will likely live the rest of their lives with cancer, but endpoints that cannot only show increased survival but allow us to be treatment free and therefore side effect and cost free are particularly meaningful.

With respect to the RDEA program, we welcome this opportunity to work with the sponsor and the FDA to use novel and emerging endpoints like MRD and to assess the role of PFS, MRD and other markers as stand-ins for overall survival and in an indolent cancer like CLL.

For patients with chronic diseases, developing new treatments is our lifeline. We ask that appropriately validated endpoints be considered in expediting the drug approval process and look forward to participating as patient advocates.

Nancy Allen Lapointe:

Great. Thank you so much, Dr. Koffman.

Our next speaker is Adora Ndu from BridgeBio Pharma and EveryLife Foundation.

Adora, yes, we've got your video. Please proceed.

Adora Ndu:

Thank you.

Good afternoon. My name is Adora Ndu and I serve as the Chief Regulatory Affairs Officer for BridgeBio Pharma, a biotech company focused on developing medicines to treat patients with rare genetic diseases and cancers with clear genetic drivers.

I'm here as a member of the EveryLife Foundation Community Congress and co-chair for the EveryLife Foundation for Rare Diseases Regulatory Working Group.

The EveryLife Foundation is a nonprofit, nonpartisan organization dedicated to empowering the rare disease patient community to advocate for impactful science-driven legislation and policy that advances the equitable development of and access to life-saving diagnosis, treatments, and cures.

The EveryLife Community Congress includes many diverse stakeholders including patient organizations, rare disease therapy developers such as BridgeBio and other rare disease stakeholders.

I offer these comments on behalf of the foundation's regulatory working group.

Firstly, we appreciate the agency's approach to engaging with interested stakeholders to ensure its successful implementation of the pilot. Innovation in endpoint development is a longstanding priority for the rare disease community and drug developers for many reasons.

The small size of these patient populations, disease heterogeneity and limited understanding of natural history are just some of the characteristics that make clinical trials for such conditions challenging, lengthy, costly, and often leading to delays in access for patients who need treatments the most.

The goals of the pilot, as stated, are important and provide an opportunity to make a significant impact on drug development for rare diseases.

The pilot aims to advance drug development for rare diseases by improving collaboration with sponsors, share learnings from novel endpoint development, and develop FDA capacity for supporting novel endpoint development, and we are pleased to see this pilot moving forward and provide the following recommendations.

First, we recommend that the agency expand the implementation and reach of the pilot. Given the over 8,000 rare diseases and the numerous developers of drugs for rare diseases, we have concerns that three pilot proposals per year over a three year span will not sufficiently address endpoint development challenges.

Secondly, we recommend clarifying the scientific framework to enable a clear and streamlined approach for use of primary disease activity biomarkers as a surrogate endpoint for accelerated approval.

When the pathophysiology of a disease is well understood and the mechanism of action of the drug is well characterized, primary disease activity biomarkers can support accelerated approval of treatments directed towards the underlying disease biology due to the direct plausible link to the root cause of disease.

A scientific framework for characterizing such biomarkers to enable its use to support accelerated approval would be beneficial.

Third, we recommend ensuring appropriate application of regulatory flexibility even for products under development for rare diseases that aren't enrolled in the pilot program, especially given the limited number of proposals possible through the pilot.

In line with the goal of improving collaboration, we recommend that the program seek to expand the improvement of collaboration with sponsors developing drugs for rare diseases, especially given that it's one of its goals.

For example, earlier this year, the Center for Biologics announced an Operation Warp Speed initiative to accelerate the pace of development of cell and gene therapies for very small populations with high medical need.

We encourage the agency to expand the modalities that would benefit from this program to also include small molecules and biologics.

Incorporating the patient voice in pilot and non-pilot programs continues to remain important. The patient perspective is critical in drug development and rare diseases and understanding the outcomes that are meaningful to patients, and also incorporating the patient voice in the regulatory process is important.

We hope that the pilot will include a robust patient engagement strategy across the program selected.

Clarity on intermediate clinical endpoints and its use would also be valuable, as well as internal education efforts.

In line with the goal of the pilot we encourage FDA to share its internal education efforts related to the rare disease endpoints, particularly efforts to better familiarize review staff with novel surrogates, and we encourage the agency to lay out how it would enhance review or understanding of novel surrogates, with a focus on resolving concerns about surrogate endpoints as early in development as possible, well ahead of late stage regulatory actions.

This concludes our commentary and we thank you for the opportunity.

Nancy Allen Lapointe:

Great. Thank you so much, Adora. And our final speaker for this session is Jessica Tyson from PhRMA. Jessica, please proceed.

Jessica Tyson:

Thank you and good afternoon everyone. My name is Jessica Tyson and I am a senior director of science and regulatory advocacy at the Pharmaceutical Research and Manufacturers of America, or PhRMA.

PhRMA is a trade association that represents America's leading innovative biopharmaceutical research companies, which are devoted to discovering and developing medicines that enable patients to live longer, healthier, and more productive lives.

PhRMA and its member companies are dedicated to advancing drug development for rare diseases. We appreciate the opportunity to participate in today's public meeting and the discussion related to scientific and technical issues associated with developing study endpoints for rare diseases.

PhRMA appreciates FDA convening this workshop consistent with PDUFA and FDORA.

As recognized by industry and FDA under PDUFA VII, there are unique challenges when determining the appropriate efficacy endpoints for clinical trials for rare disease therapies.

By offering additional engagement opportunities with FDA during product development, the Rare Disease Endpoint Advancement pilot program will help support novel efficacy endpoint development and help expedite the approval of new, innovative therapeutics.

As clearly communicated requirements for a pilot application will be key to ensuring that this program is effectively utilized by sponsors, PhRMA appreciates the recently posted submission information on the FDA, RDEA's website.

We look forward to seeing the application of lessons learned from previous PDUFA pilot programs during the workshop, such as CID and MIDD, to this pilot program.

Under PDUFA VII, FDA will also develop staff capacity to enable and facilitate development and use of novel endpoints. This staff will support the review work necessary to evaluate novel endpoint development with a focus on the challenges of trial designs utilizing small populations.

Industry looks forward to knowledge sharing from the pilot as outlined in PDUFA VII and FDORA, including through FDA presentations, workshops, guidance and reports.

Our learnings from the development of efficacy endpoints, especially those that could be relevant to other diseases or those that utilize a novel approach to endpoint development, can help advance the broader development of rare disease treatments.

We also appreciate the other rare disease initiatives FDA's undertaking, including CDER's ARC program, and look forward to seeing how these programs can collectively help support rare disease drug development.

PhRMA shares the FDA's goals of utilizing the pilot to facilitate more dedicated attention and resources to endpoint development that can result in greater availability of treatments for patients, especially those with rare diseases.

We'd like to thank FDA for bringing together stakeholders today to provide their perspectives.

Thank you for your time.

Nancy Allen Lapointe:

Great. Thank you so much, Jessica.

Thanks to all of our participants in this public comment session. This marks the conclusion of our event.

As we end, I can't help but reflect back upon one of the first things that Dr. Lee mentioned this afternoon, and that was that 30 million Americans live with a rare disease and the vast majority do not have appropriate treatments, so thank you to our panelists, presenters and attendees for the stimulating and productive conversation today on this extremely important topic.

As a reminder, additional meeting materials will be posted to the Duke-Margolis website in the coming days, including a recording of this two-day workshop.

I would also like to thank the FDA staff that played an instrumental role in planning this meeting. This meeting was truly a joint CBER, CDER effort.

Many thanks especially to Mary Jo Salerno, Kerry Jo Lee, Sepideh Haghpanah, and Julienne Vaillancourt for working to make this meeting possible.

Lastly, I would like to thank the Duke-Margolis team. Thanks Tori Gemme, Dure Kim, Gerrit Hamre, Caleigh Propes, Luke Durocher, and Hannah Vitiello for all of their efforts to put this event together.

With that, we adjourn this event and wish you a great afternoon.