FDA-University of Maryland CERSI Public Workshop:

ADEPT 10: Addressing Challenges in Neonatal Product Development - Leveraging Rare Disease Frameworks

Moderated by An Massaro, MD

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A P P E A R A N C E S

List of Attendees:

An Massaro, MD; OPT/OCMO/OC, FDA

Rebecca Chiu, PhD; OB/CDER, FDA

Ryan Michael McAdams, MD; University of Wisconsin School of Medicine and Public Health

Hussein Ezzeldin, PhD; Office of Medical Policy, CDER, FDA

Kanwaljit Singh, MD, MPH, MBA; INC, C-Path

Danny Benjamin, MD, PhD, MPH; PTN, DCRI (by videoconference)

Michelle Campbell, PhD; Office of Neuroscience, CDER, FDA

Shannon Hamrick, MD; OPT/OCMO/OC, FDA

Rachel G. Greenberg, MD, MB, MHS; PTN, DCRI (by videoconference)

Augusto Santos Schmidt, MD, PhD; NRN, NICHD, NIH

Klaus Romero, MD, MS, FCP; C-Path

Debra Regier, MD, PhD; RareCap, Levine Children's Hospital, Advocate Health

A P P E A R A N C E S (Cont'd)

List of Attendees:

Ralph Bax, MD, MA; Paediatric Medicines Office, Scientific Evidence Generation Department, Human Division, EMA (by videoconference)

Sarah Zaidi, MD; OPT/OCMO/OC, FDA

Cynthia Rothblum-Oviatt, PhD; RDT/DRDMG/CDER, FDA

Amy C. Rick, JD; Rare Disease Innovation Hub, FDA

Erika N. Torjusen, MD, MHS; OOPD/OCMO/OC, FDA

Janet Maynard, MD, MHS; ORPURM/CDER, FDA

Najat Bouchkouj, MD; OTP/CBER, FDA

Gerri Baer, MD; DHN/CDER, FDA

Yuliya Yasinskaya, MD; DRDMG/CDER, FDA

Annapurna Poduri, MD, MPH; Harvard Medical School

Susan McCune, MD; Scendea

Antonello Pileggi, MD, PhD; MSCTI, NICHD, NIH

Ronald J. Bartek, Friedreich's Ataxia Research Alliance (FARA)

Betsy Pilon, Hope for HIE

Lynne Yao, MD; DPMH, CDER, FDA

P R O C E E D I N G S

DR. MASSARO: Okay. Good morning, everyone. Thank you for joining us again for our ADEPT 10 meeting.

We had a wonderful discussion yesterday, a great intro to our meeting, talking about these two important and challenging areas of medical product development in neonates and in rare diseases. And then a wonderful discussion about some of the ethical considerations and challenges we have in both of these spaces.

So we're going to continue on today with our meeting and just a brief reminder of what we hope to cover today.

We're going to start with a session with a series of brief talks. And you'll, hopefully, have some time for some questions for our speakers, but going through various topics from study design and statistical considerations, artificial intelligence, and digital health technologies, using real-world data, and then platform trials and master protocols.

And then end up with a discussion about outcomes, which we heard some of -- some discussion about yesterday as a topic of interest.

And then we'll have a panel discussion with various stakeholders and talking about leveraging different networks, consortia, public-private partnerships, and global harmonization across these trials.

Then we'll have a short break for lunch and then come back with our regulatory panelists from FDA; and Ralph Bax from EMA will join us to talk about some of the available, currently available, expedited programs/pathways and how these can be leveraged both for neonatal conditions as well as rare diseases.

And then we'll end with a multi-stakeholder panel to kind of reflect on what we've heard over the last day and a half and think about priorities, gaps, and, you know, our priorities for future directions. And we'll have some closing remarks.

So, with that, I would like to jump

right in and get started with and introduce Rebecca Chiu, who is our -- with the Office of Biostatistics here at FDA and CDER. And she's going to talk to us about innovative trial designs to address small populations.

DR. CHIU: All right. Good morning, everyone. Thank you to the organizers for inviting me to speak today. I'm really excited to get this session going and kick off the morning.

So my talk today is going to introduce how innovative clinical trial designs can address some of the challenges that we face in rare disease drug development, with the hope that some of these will be leveraged also for the neonatal population as well.

And as was just gone over, my goal is to provide a bit of framing and context that you'll hear to kind of set the stage for the subsequent case studies that are going to be provided in this session. And as was mentioned, I'll be speaking today from my perspective as a statistician in CDER.

And I'll also note, throughout the talk

I'm hoping to point you all towards relevant FDA guidance documents and programs. So hopefully those conversations can continue.

So as a standard disclaimer, this presentation reflects my views and should not be interpreted as official FDA policy. And the examples I'm going to share today are meant to be illustrative and not prescriptive.

So I'm going to start by just briefly going over what we mean by an innovative trial design. And since that term can mean very different things to different audiences, we'll go into detail of a few specific types.

I'll focus on some common challenges we see in the rare disease space and how those innovative approaches might help with those challenges. And I'm going to end with a few examples from the rare disease space, as well as some practical considerations you may consider when you're going through these innovative approaches.

So, the term "innovative trial design"

can be challenging. There's actually no fixed definition or universally agreed upon definition of what makes a trial design innovative.

Typically, what we consider as innovative tends to change over time as our methods become more familiar or more widely used. But in general, we do use this term to refer to designs that have been rarely or never used to establish substantial evidence of effectiveness or designs that apply some kind of complex features in some new ways to a particular given indication.

And, importantly, innovation is very context dependent. So, what might be considered innovative in a rare disease space may look different from what is innovative in other therapeutic areas.

So innovative designs can really span a wide range of approaches. I just have a few examples here. So, these can include Bayesian methods, adaptive designs, externally controlled trials, master protocols, among some others. And many of these approaches are particularly relevant when traditional

trial designs are difficult or impossible, which is often the case in the rare disease setting.

And I think a lot of speakers so far have gone over these common challenges that we're all very familiar with. But rare diseases, and also applicable to neonatal conditions, face a number of recurring issues.

First, the hallmark is that we have a very limited number of patients available for our clinical trials. Second, the natural history of the disease may be poorly understood, which makes it difficult to select endpoints or even estimate expected treatment effects.

Many of these conditions are very serious and life-threatening with few or no approved therapies available, leading to a very high unmet need. And there's often a limited consensus or experience around appropriate endpoints or timing of those endpoints, and as I alluded to, expected effect sizes.

And, finally, we frequently see in the

rare disease space, substantial genotypic and phenotypic heterogeneity even within a single disorder.

So together those challenges make it very difficult to conduct more conventional trials, even when there's a strong motivation to do so.

So innovative designs may be able to help in that they can aim to maximize the efficiency and improve our decision-making in the face of these constraints.

This can be done in a few ways. So, for example, we may aim to reduce the number of patients needed or somehow increase the power or precision for a given sample size. And these approaches can also help accelerate developmental timelines and optimize how evidence is generated across the development program.

At the same time, you know, innovation does come with important trade-offs. These designs often require careful planning, often require extensive simulations and prespecification to avoid

increasing the chance of erroneous conclusions and introducing bias into the estimates.

They can also introduce some logistical complexity, particularly, for adaptive designs and master protocols. And in some cases, our gains in efficiency can be offset by losses elsewhere, such as increased lead time due to planning or need for those simulations.

In other cases, there can also be some scientific constraints. For example, if we have a minimum sample size that's really needed for safety, that may limit how low we can actually go in enrollment.

For Bayesian approaches, specifically, we may depend on some -- or we do depend heavily on the availability and the relevance of prior information, which may not always be the case.

And, importantly, when we're looking at adaptive changes, even when they are statistically valid, they can result in some interpretation difficulties.

Let's see. There we go. So let's dig into a few of these approaches in a bit more detail, starting with Bayesian methods.

So, Bayesian approaches work by formally combining prior information with new trial data to obtain an updated understanding of the treatment effects. In drug developments, this often means borrowing or leveraging information from earlier trials or related populations. And when it's appropriate, the potential payoff is greater efficiency, which can be particularly valuable in our small populations.

So, I do want to highlight, we just issued a draft guidance on Bayesian approaches, which I know a lot of people have been looking forward to. And so this guidance really reflects and builds on some of our growing experience with Bayesian methods, and I hope it's helpful for everyone moving forward.

Let's see. So, one example where a Bayesian approach was used in a rare disease setting is in childhood-onset systemic lupus erythematosus.

So, childhood-onset SLE is rare, and it's pretty difficult to study. In this particular program, we did observe that the pediatric and adult patients showed similar disease characteristics, similar responses to treatment, and similar safety profiles.

So, in this case, the review team conducted a post hoc analysis with a Bayesian approach that combined the pediatric trial data with prior adult belimumab study results. Just to get a little bit technical, what was actually done was using a robust mixture prior, which combined a skeptical prior assuming no treatment effect with a meta-analysis of the treatment effects observed in the adult studies.

And what we found was when the adult studies contributed a sufficient weight to the analysis, the posterior credible interval could exclude the no treatment effect. So it provided support of efficacy.

And while this analysis was done post hoc, it did play an important role alongside the PK

safety secondary endpoints and, of course, the adult data in supporting this approval in the rare disease setting.

So, if you're interested in learning more, we do have a publication describing this Bayesian approach. So that's linked in this slide as well.

Another major category of innovative designs is adaptive design. So adaptive designs allow us to prospectively plan modifications based on accumulating data. And some types of adaptive designs are relatively common and well understood, such as group sequential designs and sample size re-estimations. But even these are not that frequently used in the rare disease space in my experience.

There are also more novel adaptive approaches including adaptations to the population, allocation changes, endpoint changes, and all of those are discussed in a couple of our guidances. We now have two.

One is the FDA draft guidance on -- I'm sorry -- the FDA final guidance on adaptive designs published in 2019. And then we also have E20, which came out just this past year, in which FDA statisticians have contributed significantly. So I think both of those resources are very helpful.

I did want to share one novel adaptive design example. It actually came through our Complex Innovative Design program, our CID program, which involves both adaptive and Bayesian elements.

So, this example focuses on epilepsy with myoclonic-atonic seizures or EMAtS, which is a rare pediatric epilepsy syndrome.

And the proposed design combined Bayesian borrowing from historical studies in related indications with an interim analysis that used a novel approach to adapt the sample size using predictive probabilities.

The potential benefits of this design included needing fewer patients, which improves the feasibility in this rare population. And the sponsor

also proposed a dynamic borrowing approach, which to get a little bit technical, helps mitigate some of the concerns of borrowing from potentially non-compatible patient populations.

Of course, there are challenges with trying something new. So, some of the items that came up during our discussions in the CID meeting were that this approach requires extensive simulations to understand the operating characteristics. And there was a strong emphasis on the sensitivity analyses that would be needed to assess the robustness to the assumptions.

Another innovative approach we are seeing more frequently in the rare disease space is the use of externally controlled trials. So those trials compare outcomes in treated patients to outcomes from external data sources such as historical or real-world data.

They're most appropriate when the disease course is well understood, spontaneous improvement is unlikely, and the treatment effect is

expected to be quite large. We do have a guidance on this as well that discusses the externally controlled trials. It's not specific to rare disease, but I think a lot of those considerations are helpful throughout the guidance.

So, one very recent example of this approach is copper histidinate in Menkes disease. So Menkes disease is an extremely rare and largely fatal condition without any treatment.

In this case, we had two single-arm trials that compared treated patients to a contemporaneous external control. And what was found was that the early treatment really led to a large survival benefit. In comparison, there were no untreated patients that survived past six years in that external control group.

So, this evidence ultimately supported our approval, the first treatment for Menkes disease, and it highlights when I think external controls can really be persuasive in a rare disease setting.

The last design approach I'm going to

touch on in more detail is a master protocol approach. Master protocols use a single overarching structure with multiple sub studies.

So, these can include basket trials, which evaluate a single therapy across multiple diseases or subtypes; and umbrella trials, which evaluate multiple therapies within a single disease; and platform trials, which are similar to umbrella trials, but they allow multiple therapies to come in and out of the trial in a perpetual manner.

So these designs can be particularly powerful in rare diseases because they can allow for sharing of infrastructure and in some cases allow for sharing of controls.

And, again, we have a guidance, a draft guidance, on this topic if you're interested in learning more.

So just one example where basket trials, in particular, have been successful is in the tissue-agnostic drug development space. So basket trials here have enabled development based on

molecular alterations rather than a particular tumor site.

So, just one example is selpercatinib, which was approved based on a non-randomized basket trial that pooled across 14 different rare tumor types in the primary analysis. So, despite small numbers within those individual subtypes, the overall response was quite compelling, in addition to looking at those individual subtypes as well.

So, approval was ultimately supported by a strong biological mechanism, previous evidence from related cancers. But this enabled access to rare genetically defined patient subgroups.

So, innovation is not limited to trial design alone; it can also involve the choice of analysis. So, a few examples include the use of global tests, novel approaches to incorporating longitudinal data, some alternative approaches to non-inferiority margin derivation. Those are just a few examples.

Innovation can also involve endpoint selection and development, and I think we'll hear a

little bit more about that in some of the sessions today. But this can include novel clinical outcome assessments, composite endpoints, surrogate endpoints, incorporating digital health technology.

And, of course, I've made it to this point in my talk without mentioning AI, but certainly use of AI to advance development would be considered an innovative approach.

If you are considering an innovative approach, I do want to just leave with a few broader considerations. Even when we are innovating, I think it's important to remember the fundamentals of trial design such as randomization and blinding and why those are important and emphasized in the first place.

At the same time, in the rare disease setting, thoughtful departures from those may be reasonable, particularly when feasibility is a major constraint.

But these decisions often involve some kind of a bias-variance tradeoff. So potentially improving our statistical efficiency, but at the cost

of an increased bias. So, an example of this might be the use of a non-concurrent control arm in a platform trial.

So, determining whether that tradeoff is acceptable usually requires some careful consideration and discussion of the feasibility constraints, the unmet need, the potential sources of bias, such as temporal changes in a control arm, and the methods that may be available to address those biases.

So, from our perspective, this is exactly the kinds of discussions we encourage sponsors to have with FDA early and collaboratively, rather than kind of viewing innovation as something that's fixed or predetermined.

So, FDA does continue to encourage innovative approaches. We have a few programs that I wanted to highlight before I close.

The CID Paired Meeting Program, which I alluded to with one example earlier, continues through 2027. The CID Paired Meeting Program, it's designed to support early and in-depth discussion of a complex

innovative design, particularly when the simulation or modeling play a central role.

We also have CDER Center for Clinical Trial Innovation or C3TI, and it serves as a hub to improve the efficiency of drug development through innovative trial designs.

And then specific to the rare disease space, the LEADER 3D initiative and the RDEA Pilot program aim to really better understand and address the challenges related to end-of-point development and other innovative approaches.

So, again, all of these programs are intended to really support that early, thoughtful engagement, and we strongly encourage you all to participate.

And last but not least, I just want to acknowledge my colleagues and collaborators across CDER and the Office of Biostatistics who contributed to this work. It really reflects a broad collaboration across multiple groups. So, thank you.

DR. MASSARO: I think we have a few

minutes for questions in case anybody has questions, feel free to come up to the microphone, or if there are questions online, we'll monitor that as well.

I guess while folks are thinking, I guess one question is we hear a lot about external controls, and then we heard a lot yesterday about the variability in the NICU environment, in particular with standard of care and some of those difficulties with kind of establishing an external control group.

Can you provide a little bit more on, you know, approaches to that or how you handle that statistically, or recommendations there?

DR. CHIU: Yeah. Sure. Yeah. External control trials, I think they do hold a lot of promise, but kind of as I alluded to, there are certain circumstances where they will work well and other circumstances where they won't work as well.

We do, generally, need to have a strong understanding of the natural history, which I -- unfortunately can be challenging in the rare disease space. We also need to have an understanding that

there won't be spontaneous improvement in the outcomes. And, again, that can be challenging when we don't have a strong natural history.

And I will say external controlled trials are most convincing when we do see a large effect on -- usually on an objective endpoint. So, I am -- we are definitely open to the idea of externally controlled trials, but I would say that there are challenging settings. Yeah. Lynne's going to add.

DR. YAO: Yeah. Hey, Becky. No, no. I actually have another question that's follow on. So, you know, we've heard about externally controlled, and that's where you have essentially no randomization. You just, you know, and you have a control group that you've created.

But we heard yesterday about something that's, I think, even a step beyond that, which is the baseline control or patient control trials. I was wondering if you could comment on that.

DR. CHIU: Yeah. Thanks, Lynne. So the considerations are actually similar in my opinion,

for a baseline control to an external control. The external control, we do have the additional variable of it being compared to an outside source, as opposed to the baseline control where it's so -- within patient comparison.

But, similarly, in that setting, we really need to understand the natural course of the disease to ensure that whatever effect we are seeing can actually be attributed to the treatment itself. So certainly there again are circumstances where it can work, but it is -- requires some careful discussion.

DR. PODURI: Ann Poduri from Boston Children's. Thank you so much. I think your breakdown of the basket versus the umbrella versus the platform trial should be something that every physician hears about.

In med school and in training, we hear those terms used sometimes interchangeably and they're obviously not, but I -- I'm thinking about this in the context of multiple rare conditions. You've mentioned

a rare epilepsy, but rare genetic conditions where the core features really can be sort of summarized as: there's a developmental outcome; there might be a behavioral outcome; there might be an epilepsy outcome and so on.

And so I wondered in the context of the umbrella trials, for example, where there's multiple diseases, generally, are you talking about trials where you have to have the same scales and outcomes applied to all of them? And if not, how do you take what's already known out there in terms of the measures and allow multiple diseases to benefit from a therapy?

DR. CHIU: Yeah. That's a good question. So, I think there's a lot of promise in the master protocol space, and it actually -- not at all the rare setting, but I think where it got a lot of attention most recently was the COVID space.

But, again, that's a little different from the setting you're describing.

So, I think there's some variability.

Some master protocols will only share their infrastructure, meaning their sites, their training of their investigators, their protocols, but won't be doing any kind of sharing of control arms or data or endpoints, which I think was the case you were alluding to.

So, I think there can be advantages to that. It won't be on the statistical side, but it would certainly be on the logistical side. So that's definitely a consideration.

If there is a plan for more sharing of, for example, the control arm or the treatment effects, there would be -- need to be more, I think, consistency across the endpoints and probably a good understanding of the relationship between the different disease types. Yeah.

DR. ROMERO: Yeah. Klaus Romero with the C-Path. One of the key things that I don't think we should forget -- and I loved your take on this -- is that the fact that the ethical consideration should never trump the epistemic needs when you're designing

these trials to generate actionable evidence.

So, one of the key things is understanding where you're starting from, right? Because sometimes it will be ethically unfeasible to do a full variability shrunken traditional trial.

And I think that's one of the key pieces that is captured across all the guidance documents from FDA. So I -- I'd like your take on that emphasis in how the different guidance documents connect.

DR. CHIU: Yeah. So just to clarify, you just wanted to emphasize that ethics plays an important role in both our feasibility and how we approach different clinical trials?

DR. ROMERO: Right. Because sometimes if you -- it's always important we -- and we get into these conversations about the variability and the bias with external controls and baseline controls and all that, but sometimes it would be ethically unfeasible to do it any other way.

And so when you're facing that, you

have the guidance documents and they emphasize those pieces, and that's how the guidance in my mind connect; and I think that's an important point of leading up to a point where you say, "Yeah. That's all great, but we need to live with the variability and the potential bias and all those epistemic questions, but ethically, there's no other way to do it."

And I think that's an important point that we should not forget.

DR. CHIU: Yeah. Yeah. Absolutely. Yeah. Thank you for bringing that up. And the good thing is these are always multidisciplinary discussions, so I come in it with a statistical perspective and my colleagues will bring me back and point out what is practical and ethical. So important, important point. Thank you.

DR. MASSARO: Yeah. One more.

DR. BERENT: A great talk and I think that question actually leads into a really important question from a logistical and ethical side as well as

just a logical side in which, if you have rare -- in rare disease, there's not a lot of competition, but some diseases -- in my world it's Angelman syndrome -- there are plenty of competitive programs out there both on the CBER and the CDER side.

And we as a foundation create relatively master protocols in which we're ensuring all endpoints are being used in the same way at the same frequency in similar populations.

The problem is, you know, when you really think about placebo or sham control, that's much harder to do from a gene therapy, cell therapy side, of course. And ethically, how do you really do that in order to be able to be in a master protocol in which you can't?

And so therefore you're really trying to borrow from those that are doing those types of controlled studies, but there's no motivation for them to share that data. And encouraging industry to share data in a way in which it can leverage -- be leveraged by the field is really important.

And I believe the only way to do that is that it has to be implemented through the Agency; that there's a requirement and a request, that there's some incentive for them to share that placebo control and sham control data because we, at the advocacy level, we can't force them to do it.

And, therefore, you're left with natural history as your comparator in which there's all the biases as we're talking about here.

So, I believe there has to be a new infrastructure to be able to do that. And that's incentive in rare disease because industry works toward incentives.

DR. CHIU: Right.

DR. BERENT: So, I think that's a new framework we need to think about as an entire field in order to be able to get that data and have the best statistics possible to truly show evidence.

DR. CHIU: Yeah. Yes. Thank you. That's all great points. I do want to highlight, so I think Amy is in the room. Good.

We do have a RISE workshop that's coming up at the end of March that's going to particularly focus on data sharing in the rare disease space. So I hope that will be helpful, but I very much empathize with this challenge.

DR. MASSARO: Thank you so much.

DR. CHIU: Yeah.

DR. MASSARO: We are going to move on. I know there are a few questions in the Q and A, so we'll pass those on and see if we can get responses back to folks.

So next, it's my pleasure -- we're going to do a series of brief talks and case examples in some of these tools that are innovations that we've -- that have been mentioned and nicely overviewed.

So first I'm going to introduce Ryan McAdams, who is a Professor of Pediatrics and a neonatologist at University of Wisconsin, and he's going to talk to us about AI and digital health technology in the NICU.

DR. MCADAMS: Thanks, An. Good morning, everybody. So, I'm really grateful to be here and thankful that we're focusing on neonatology. So I appreciate the FDA doing that.

And I just want to recognize the voices of the parents that we heard yesterday. So,, I think it's wonderful to hear their insightful, lived experiences and the powerful advocacy. So I think that really adds to this. So I'm very grateful for -- that they're at the table because that's how we're really going to learn and move forward.

And so when we think of neonatal care, this is really a team, ultimate team sport, when we're trying to take care of these babies. A lot of effort goes into this, and we need a lot of people to get this right.

And need for timely diagnosis and speed in the NICU is not a new concept. And so the challenge now is, like, can our learning keep up with our need to kind of have, like, the care that we need to deliver? Can we sync those up?

And I think with AI, one of the exciting things about it is that it may help us do that, bridge that gap. So, the goal is we can detect signals, a signal or signals, better early and then have action faster. So that signal to action gap, can we narrow that? And I think that's the hope with some of these AI technologies.

This is my disclosure.

So, we take care of really tiny babies. So, if you look at your tables, some of your water bottles, we take care of babies that weigh a lot less than that or their coffee cups. So, down to 21 weeks at some centers now.

And so to keep these babies alive, we have to have technology. Without it, these babies don't survive. And so that's not necessarily a new concept, but bringing AI into the NICU environment is a newer concept. And I think that might help us do even better with helping these babies thrive and survive.

And so if we think of our goals is to

have a baby, get them healthy, and get them safely home, have good information along the way, and be on the same page. And so to do that, we need to understand these babies better. I'd say right now, there's still a lot of stuff we just don't understand.

Well, why is AI potentially important? Because it can decipher complex non-linear data, which is what we produce as humans. And so in this, using an AI platform, it may allow -- what would seem like rare diseases but actually make up a high fraction of the cases we take care of in the NICU -- it allows us to kind of understand these babies, and hopefully be the bridge to provide better care and safer care.

And so, since in November 2022, not that long ago, that's when ChatGPT first came out. We're now at version 5.2. There's a lot of other foundational models. So, we've got Claude and Gemini and Grok, these very powerful tools that can provide us a lot of -- right? -- just with our phone is in our pocket, give us a lot of information and capabilities, whether that's making a song, making a video,

modifying a picture. So that's generative AI.

We've had things like Google's AlphaFold, which won the Nobel Prize in 2024. It was able to take decades worth of ability to look at proteins and narrow that down into, like, months.

We have things like DeepMinds, graphing for material exploration, which has discovered 2.2 million crystals as well as 380,000 new materials that might be used for future technology. That's 800 years' worth of time condensed into, like, a year.

So that's the compressive scale that AI can offer, where it can now function out almost as like a team of scientists and help us out. And so I think the challenge is AI, it's all over. It's in the news; it feels like it's everywhere. It's kind of overwhelming the pace of things with really new stuff coming out weekly.

And so, you know, we used to forecast, oh, this will happen in the next decade. It's hard to predict even a year out. Even if you think back about a year ago, we wouldn't have predicted what we

have today.

And so why are we talking about this right now? AI obviously is a hot topic, but I think when we think of, like, the NICUs, we're overwhelmed with data. So we have, per patient, gigabytes of data. If you think of what's capable with, like, if you had video. We don't even capture audio. There's a lot of signals we're not even really looking at.

But just -- they have some, you know, they come in with some fixed data. But then we have intermittent measurements and we have continuous data. We get lots of labs, lots of imaging. These are very data dense areas.

And then when you combine that all, it produces this massive amount of data that we need a better way of understanding it. And I think because of the power of AI and its capabilities right now, it gives us this potential to potentially do that.

But I think the one important thing is most of the studies right now are preclinical. So there's a lot of promise, but these things aren't

being used all the time in the NICU. So, if you look at a lot of studies, they're done at single centers, it's a smaller cohort, but they haven't been generalized across hospitals, devices, and populations.

And so that's a real shortcoming with a lot of this, and a lot of these models where they go to die is when you generalize them. And so I think from maybe a public perception, there may be this, like, we're using this all the time. In most NICUs we're not because we haven't validated these models.

And so it's one thing that a model may work in a center, but you have to generalize and say, is it going to work in a system and how do you implement it?

The other big piece of this is with a lot of these things, who's paying for it? So, until we figure out reimbursement for some of these models, hospitals aren't going to adopt them because they have to figure out a way to pay for this as well.

So what do we have right now in the

NICU? Well, we have HeRO Monitoring. So this looks at heart rate variability. So this got clearance by the FDA in 2003, really just to look at heart rate variability.

But then Karen Fairchild did a study in 2013, where they tied this to sepsis, so early sepsis detection to reduce mortality.

And this is a device that, you know, people can have in their ICUs. I had it in one of our ICUs, but it hasn't been a -- despite some of the promising literature on how it might allow you to detect sepsis and prevent mortality, it hasn't been widely adopted. Whether that's due to cost or for what reasons is not clear.

But that's an example of something we have right now and we all worry about sepsis. It kills babies. So, this is a potential device that could help, at least, with heart rate monitoring detection to clue you in on sepsis.

With ROP, which is a leading cause of blindness globally, and a lot of our preterm babies

are at risk for this. We screen for it, but retinal specialists are hard to come by and they're busy.

And so we have cameras that we can use to screen babies that then can have -- you can have an algorithm. So, there's this i-ROP Deep Learning model that was -- has been cleared. It was actually introduced as a breakthrough device in 2020, January of 2020. So not totally cleared, but it performs well and it's performed well using U.S. data and large data sets in India.

So, this is very promising where it's done a great job screening babies with a device that someone can be trained to use. And then if it detects advancement of the disease, then the retinal specialist can be notified and then do the proper care for that baby.

So, I think these types of devices where you take an image -- and AI is great at reading that image because there's a lot of pixels in a high-density image; there may be 10 million pixels that it can look at.

And that's why we have fields like oculomics now and other areas where you can look at the eye and determine whether someone had a heart attack or if they're at risk for Alzheimer's or what their sex is.

And so there's -- these are powerful emerging tools that will continue to kind of be developed. If you've been to the NICU and you're a parent in the NICU, one thing you're really familiar with is, we have a lot of wires. Babies are covered in wires. They're covered in tape and tubes.

These are really constricting. So there's been a lot of, like, what's the future going to look like with Next Generation? Well, it's other modalities that may be able to monitor the baby. So it's using cameras or infrared or radar to look at a vital sign like respiratory rate.

Now, that type of non-contact technology, most of these have just been looked at for accuracy, and haven't really been implemented for safety or utility. And a lot of those have been,

like, offline where they -- it's not giving you real-time information. They've looked at it later on, and it's a pretty narrow use case.

As far as wearables, where it can detect, let's say, heart rate or your saturations, those are more real-time informative and they may be helpful as well. So I think once again, it's a cost issue.

So, we'd love to get rid of the wires and all the -- all that to allow better freedom for the baby, hold them better, you know, to hold them and also not affect their skin as much.

But the challenge is a lot of the studies haven't been scaled to other centers, and so they -- they're -- they may be accurate, but they haven't really been shown how to implement them. But I think this is also where we'll be moving forward in the future. A lot more wireless, Next Generation Technology.

So in a Level 4 NICU, it's not unusual, I think, if you ultimately get genetic testing on a

baby, like a whole genome, where you might have a hit rate of like 30 percent in your NICU of some -- that explains maybe something that's going on with the baby that took weeks to months to find out due to like insurance approvals and things like that.

So, what currently happens while you're waiting? Well, we do a lot of tests. We order a lot. We spend a lot of money. We poke the babies. We cause pain. We prolong that uncertainty, and it causes a lot of frustration. That's current state.

So, I think the hope is, like, can we understand some of this earlier and allow us to act on it, which I think would be better care. And I think that's also the opportunity in front of us.

So, an interesting study came out of Seattle. They did this -- instead of, like, the current process where you have to exclude all these things and go through this, like, laborious, kind of, like, you finally get the approval to do this genetic test weeks later and wait for the results.

They had a much more inclusive

approach, where they kind of opened the front door more to say, like, you know, unless there's things that are clearly, like, limited exclusion criteria but a much more open inclusion criteria.

And what they showed is by doing it this way, they diagnosed considerably better and had a -- and earlier. And so -- and this also, especially babies who were non-white and black, the diagnostic rates were much higher.

So I think this is an interesting approach that will become probably more commonplace, where you change that workflow for how we're looking at who might be included in a study because your hit rate's going to be pretty high, and then it's going to change -- it's going to be actionable as well.

And so this was -- you could automate this, and so this is a -- this study where what they did is they essentially used a way to screen electronic health records. So you can do a clinical natural language processing to look for certain Human Phenotype Ontology terms.

So, they had this Mendelian phenotype search engine, which used machine learning to screen the chart and flag kids who might qualify. And this was a very effective way to prioritize whole genome sequencing on kids and get an accurate diagnosis for those who had it.

And so I think this took that kind of Seattle workflow and you can automate that; and I think that also might be a great way to kind of detect these children earlier and figure out what they have.

What's really exciting moving forward is this paper just came out. So, historically, with a lot of the genetic tools, there's been some limitations for, like, you get these unknown variants or you -- you're not sure, like, will they have this -- we're able to read the sequence, but we don't really know how this is going to play out. How is this going to affect gene splicing? How this is going to affect different chromatin regulation.

And so what this tool does -- this was the AlphaGenome, so this is the Google group again.

This kind of overcomes the problem where some of these tools were more nearsighted. So, they could -- you could see, like, good resolution but you couldn't see long DNA sequences.

Others were more farsighted. They could see long sequences, but they didn't have good resolution.

This kind of does both; it can see a million base pairs down, but it has single base pair resolution. So, what this allows essentially is they can determine based on the non-coding region. So, 98 percent of our genome is non-coding. So, it's not what codes for proteins but it's regulatory.

So, by kind of looking at all this, they're able to determine, like, actually how the genetic code is actually going to play out, what this is actually going to look like.

And so this is able to take this in silico and kind of predict what's going to happen. And so this is a kind of very exciting technology that I think will continue to revolutionize our ability to

understand when you have this issue, what does this actually mean for the patient, which can inform the family.

So, I think there's this -- and this is you know, perfect for machine learning, deep learning, things like that because of the powerful, like, a transformer tool which, like, powers our large language models can be used in medicine to understand this really complex data and makes sense of it for us so we can use this at the bedside.

And so I think, you know, what is the NICU of tomorrow going to look like? Well, physically I'm not sure how that's going to look. It will certainly look different, but, like, we're not going to rebuild every NICU.

There will -- we'll start to introduce some of these algorithms and some of these tools that will allow us, I think, for rare diseases to like look at data, all the omic data that we gather.

Hopefully, data starting with mom early on, fetal imaging data. And then this will continue

to kind of inform us with our care so we can really do more precision medicine tailored to that patient.

And I think the ability to take the multimodal data altogether, which we gather a ton of, and understand that, is something that we have a hard time doing as humans. But with the aid of these machines we can partner with some of these tools to enhance care.

So this, you know, there's people working on digital twins. So, this is a concept where you literally have kind of an in silico you have a model that represents either an organ system or a full body system.

And then you could under -- this is an evolving twin. As you gather more data, the twin continues to get enhanced. But you could use this and do, like, literally, like, millions, if not billions, of in silico scenarios to predict what would be the optimal treatment, predict outcomes, and things like this. So, I think this is a area that will continue to evolve as well.

There's a lot of issues ethically around this, like who owns the data? I mean that -- all these things need to be deciphered, but I think the capability to have something like this might scare people, but it also might be exciting where you could understand something in an in-silico model that would inform your care and could be dynamic. So, as you're going along, it would inform good care decisions and also hopefully predictability for down the road.

So, the future will also have the machines at the bedside, will be this concept of Internet of Things. The machines will have machine learning in them. They'll talk to each other. They'll be coordinated so they could adjust things.

If you think through the NICU environment, it would be great to tailor to that baby to adjust lighting and sounds and temperature based on their physiologic state. We can do a much better job with parents, where we have less jargon and more clarity with our reports.

We can also do better with data driven

prognostics. We can't even tell them when they're going to go home based on their feedings. We can't even predict kind of a lot of stuff that would seem very simple.

And I think in the future we'll look back and say, gosh, you couldn't tell them this; and we just haven't had the ability to do that. I think AI's going to help us do a better job of that and counsel better.

The other concept is, you know, when you're in the NICU, alarms are going off all the time; and if no one's in the room and the alarm's going off, what's the point of that alarm? It's -- all it's doing is stressing the baby out and disrupting them.

So, we need to do a better job with, like, who should hear that alarm and where is that nurse or that provider, that clinician. And AI can help with that to kind of tailor these alarms to get to the right people at the right time and not disrupt the baby otherwise or other providers. And so I think this will -- there's a lot of potential there.

We certainly have lots of different biases. So think of all the different biases that we have. We need to consider the data that we have and how that might have an embedded bias and how we don't want to perpetuate that.

We also need some reasonable level of explainability. I don't need full transparency with how these models work. We don't totally understand them, but I need to know somewhat how they work. Just like a ventilator. I don't need to know how to build the ventilator, but I need to know enough about it so I can use it safely.

So, I think the same thing with these tools. We need some level of accountability. You know, if everybody's responsible then no one's accountable. So who's responsible for these models? Who's going to govern these things?

And also who's going to pay for it? Because you could have something that's a safe and effective tool, but if there's no reimbursement pathway, it's going to stall the use of that tool.

We also have to make sure the data doesn't go somewhere where we don't want it to go. So safety is really important. Who owns the data? There's a lot of ethical questions I think that sometimes are not being really -- they're an afterthought instead of a forethought.

So, I think the NICU is an environment that is very ready for AI. It's very data rich, you know, so I'm hoping we'll have these models that are preclinical. We'll find ways to generalize them and understand them better. I think there's ways to use some of the current tools we have better. They're underutilized.

And the pipeline for a lot of these things that are really complicated diseases like chronic lung disease and necrotizing enterocolitis, I think we can better understand them and the different maybe subphenotypes so we can improve our care by using AI tools.

I do think we need to figure out how to do this better, like, so we can generalize

multicenter, whether that's federated learning or different approaches to try real-world trials.

And then I think we also need to figure out, like, these models, what level of transparency do we need? How are they promoting fairness? How are we able to interpret them and use them? And also some clarity with governance as well.

So, I think there's a lot of promise with this technology and excitement. And I think, you know, meetings like this, it's the right people together. I think it's just moving forward. How do we do this in a way that kind of doesn't delay things so we can use a powerful tool that could help someone in a timely way.

Because it's, like -- it's this balance of if you had something that could help and you're not using it, why aren't you using it? But you also don't want to use it too early if it's going to cause harm. We also have to be honest. What's our current level of ability to, like, what's our benchmark?

And I think we don't even have

benchmarks for, like, a clinician myself. Like, how often am I right? What's my performance card look like? You know, so we just assume, like, we'll know if we say it, it's probably right. And so we don't even know that benchmark.

So, if the AI, what mark does it have to hit before we adopt it? We need to know its limitations. But if it's --let's say it's, oh, it's performing at a 92 percent level, but we want at a hundred. But what if we knew the clinicians are at 60 percent or 70 percent?

So, when do you adopt these tools? How do you figure out that performance metric? So there's still a lot of information we need in current state to better understand these new tools. But I do think we have this opportunity right in front of us, and I'm hoping, collectively, we can do this in the right way so that we enhance care.

So, in the next three to five years, these tools are being used safely at the bedside and we're improving the care for these babies, especially

babies with rare diseases, which is not uncommon in the NICU.

So, I'm going to stop there and thanks for your attention.

Do we have time for questions or should I sit down?

DR. MASSARO: Thank you. I think what we'll do is move on to our next talk, and hopefully we'll be able to group some questions at the end of the session.

So it's my pleasure to introduce our next speaker, Hussein Ezzeldin, who is with the Office of Medical Policy in CDER and works closely with our Digital Health Center of Excellence in CDRH and will give regulatory perspective on some of these issues.

DR. EZZELDIN: Good morning, everyone. Thank you so much for having me today. I'm very honored and excited and grateful to share with you some of the work that we've been doing here at the FDA.

And I cannot thank Ryan enough for

setting me up. I hope this was done on purpose, but I was worried, I -- how can I convince you that AI and digital technology have a great opportunity in NICU and neonatal care, but Ryan did all this work for me, so thank you so much.

So, let's start by looking at what FDA can bring here to this field. If you are also only thinking about artificial intelligence and digital health technology and how it can fit into medicine, you're really missing a huge component, which is the regulatory science part of this.

And FDA brings this regulatory science component to lay the foundation so you are able to leverage these evolving technologies to benefit neonatal care and further the field of medicine. And this is what I'm going to be speaking about.

And to think about this -- this is going to be a very busy slide, but one thing I wanted to bring to you, is this did not happen overnight. So if you look here all the way to the far left, before even 2019, before AI and machine learning was a buzz,

FDA has been investing a lot of effort into artificial intelligence and machine learning.

We had a community of practices. We had trainings. We were able to bring our community together to disseminate the knowledge, bring the nerds that are coding and doing modeling on their computers to everyone else and they can think together.

And then moving forward, we didn't only do this within FDA, but we also worked across international regulators as well. So from 2021 when the Center for Devices worked with Health Canada and MHRA in the U.K. on putting together some good machine learning guiding principles, this was work that highlighted how we are really interested in developing this field forward.

Maybe I move a little bit further and give you this slide together so we don't spend a lot of time on this.

These are very select efforts and workshops, discussion papers, guidances, that the Agency put out. And you can see here, this is not

recent. These are years of investment into artificial intelligence and digital technology. And we have been building on this for years.

And the hope to show you this is that when Ryan mentioned that the opportunities now, my message is that the FDA is ready for this. We have been investing in this for years, and we are willing to engage and further this field forward.

So -- let's see. Okay. Ryan alluded to this, but we all know that AI has applications in different fields, especially when you are looking at the drug development cycle itself. So, there are uses of artificial intelligence in drug discovery, nonclinical research, clinical research, as well as manufacturing and post-market surveillance and monitoring.

We, FDA, as a regulator, our purview starts from the nonclinical research phase. So, we typically, don't look at what's happening in the discovery phase, but there are a lot of areas where artificial intelligence can provide a lot of insight

and accelerate these phases of clinical development and bring cures faster to patients.

So how does this look from the inside? The Center for Drugs, as well, the Center for Biologics had this question on mind. It's, like, how much AI are getting into our submissions?

So, Center for Drugs, CDER, and the Center for Biologics, CBER, conducted two landscape studies to understand at the high level how the ecosystem looks like from regulatory perspective.

And you can see here that across these two tables, CDER at the top and CBER at the bottom is that there has been an increase in the number of AI-related submissions that are coming indoors.

And on your right, you will see the different therapeutic areas that these AI uses have been involved in. So, in both Centers, we've seen the most use has been in the oncology space, gastroenterology, infectious disease in CDER, four, by neurology and hematology in CBER and CDER as well.

So, there is a substantial use of

artificial intelligence in regulatory submissions. And this is something that we have been looking at since 2016 and engaging with.

Another thing that I also wanted to show you is that when we looked at how these submissions were distributed across the different phases of drug development, we've seen the majority of these uses of AI, artificial intelligence and machine learning, was in the clinical development phase followed by preclinical. And then the third is pre/post-market.

We found very few cases in drug discovery, but this is not really surprising since this is something that we don't really engage in and regulate or comment on when we are looking at submissions.

So, one of the very important things that happened in this very busy slide that I showed you about the efforts the Agency put out, was the landmark guidance that came out January 2025 about the considerations for the use of AI in drug development.

And one of the things that we put in this guidance was this risk-based approach. And the reason for this is that as you've seen, you can use AI in many ways, in different areas of the drug development cycle. This doesn't mean that every single use case has the same risk when you are looking at it from a regulatory perspective.

And the way we were trying to communicate our thinking to the Agency as well as to our staff when they are looking at these submissions is that you need to look at these submissions across two dimensions.

The one on the bottom is the model influence, which looks at how much of your information is coming relying on this model that you are reviewing or considering to be deployed in this clinical development program.

The other factor that you are going to be looking at is the decision consequence. Meaning that if this technology or model gets it wrong, what would be the consequences of this?

And these are the two things that we look at and we try to find where your use of this technology is going to land on this landscape or surface, if you will.

And based on this -- this doesn't mean that you are going to be turned away or maybe asked not to use this technology. This absolutely is not the case. This only is going to impact how much information the Agency is going to be interested to review.

So if you have a high-risk case, the Agency is going to be interested to learn more about what you did to develop this tool or model or technology.

If you have a lower use case, then maybe it's going to be -- have less requirements for documentations and proving its risk -- its efficacy and safety.

Now, moving to digital health technologies. We know that aside from neonates, which is a very vulnerable population, we always have a

challenge on how can we ensure that these digital technologies are used properly; how we can ensure that the data collected is accurate. We also have a lot of variability, the quality of this collected data.

I think neonates and neonatal care brings a lot of opportunity here, but also a lot of challenge because the population is very vulnerable. It tends to be a low -- a high-risk population when you're looking at, but at the same time, unfortunately, your patients are captive in your NICU, and you are able to collect a lot of information when they are in this unit.

And Ryan did a great job looking at how artificial intelligence and digital health technologies can benefit you in the NICU.

I will also add that one of the great things that can happen is that once they transition out of the NICU, these technologies, specifically digital health technology, would be an amazing opportunity to continue monitoring these patients, but most importantly, lower the burden on the parents who

are really not at a point where they can document a lot of things, engage with the clinicians, provide a lot of feedback.

You can leverage these technologies to collect this data that you're interested in, see what treatments or products that you used during this period when they were vulnerable within your unit, how this is going to impact when they are transitioning into life and start moving.

Oops. Okay.

This slide, just to highlight that over the life cycle of the product, digital health technology exactly have the same presence, and it can help in different stages during prototyping and nonclinical and clinical as well as post-market monitoring as well.

So, one of the very exciting things about these digital health technologies is that they can help us start focusing on these digitally-derived endpoints. And today, Dr. Campbell is going to speak about clinical -- electronic clinical outcome

assessments.

And I listed here a few of the things that digital health technologies can help with from clinical outcome assessments, remote monitoring, as I mentioned, digital biomarkers.

There are a lot of things that these technologies can help, and they are very promising in allowing clinicians and physicians to monitor their patients inside the NICU and even when they transition into home care, but also reduce the burden on the parents and the caregivers, which is very, very important.

I mentioned that we're ready, so I wanted to share with you some of the opportunities that you can leverage and pursue if you are interested to engage with the Agency.

There are a lot of opportunities here and a lot of programs that would allow anyone interested to come and speak early with the Agency about what they are thinking, how they can leverage these artificial intelligence or digital health

technologies in the drug development and the care of this very vulnerable population.

And I'll just conclude by reiterating what I mentioned is that the use of AI machine learning has been increasing in multiple folds over the years. As you saw, it's been primarily used in clinical development phases of the drug development cycle.

We are trying to leverage this risk-based regulatory approach to balance between allowing innovation and use of these emergent technologies and at the same time ensure that any use of this technology is safe when it's put into these programs.

And then, of course, based on these, the risk classification of these technologies, verification validation of these technologies is going to be very important.

And as we always would like to close, is that we always encourage people to come speak with us as early as possible so we can think together on

how you can leverage these technologies to further the care of our patients.

And with that, I can't really claim that any of this was possible without the enormous contribution from all our colleagues across the Agency. And thank you so much.

DR. MASSARO: Thank you so much. Those were a wonderful pair of talks. I don't see any questions in the Q and A. Just a lot of gratitude and thanks. So I think we will move on.

And it's my pleasure to introduce Kanwaljit Singh from the International Neonatal Consortium and C-Path to talk to us about real-world data use in the neonatal drug development.

DR. SINGH: Thank you so much, An. Such a pleasure to be here, an honor, really.

As an introduction, I'm Kanwaljit Singh, Executive Director of Critical Path Institute, International Neonatal Consortium, which is a public-private partnership of stakeholders from industry, academia, regulators, including FDA and

others, and patient groups, where we are basically working on common, you know, pre-competitive public health tools that actually help with expediting drug development for a bunch of different areas in neonatal drug development.

One of the things that I wanted to really highlight by -- before starting is, you know, we really do consider neonates as therapeutic orphans. This has been a term that has been used widely and for quite a long period of time.

Somebody mentioned yesterday that, you know, up to 90, or more than 90, percent, of drugs used in the neonatal space, NICU space, are actually used off-label. And there have not been any new drugs approved for major neonatal diseases for over 30-plus years.

It's a real big challenge. I know that it's a challenge because I work with industry stakeholders who have been slowly and slowly disengaging from neonatal drug development space.

So, you know, our effort is basically

just a small effort to change that trajectory from industry disengaging to actually, you know, make it easier for everybody to get engaged in the neonatal drug development ecosystem.

So why exactly do we call neonates as therapeutic orphans? Simply because as I told you -- right? -- very few drugs are developed or labeled specifically for neonates. There's a lot of off-label use. More than 90 percent of drugs in this space in the NICU are used off-label. No new therapies in close to 30 years.

Many diseases like BPD, NEC, so on and so forth, have not seen any new approved therapies. It's a kind of a multifactorial issue why this happens, rapidly evolving physiology, week-to-week changes in PKPD, organ system maturity, injury happening and injury healing at the same time as the body's -- baby's developing.

You know, and the biology making extrapolation from adults to children or older children to neonates is, you know, very unreliable.

And also because, you know, these diseases are very specific to the premature age, which adult -- lack adult analogs. And as I said before, it limits applicability of adult-anchored development pathways to neonatal drug development.

Plus, in addition to just physiology, there are other really important issues and important challenges. I think Marshall Summar alluded to, at least in summary yesterday, there are few validated endpoints, surrogate endpoints, or validated biomarkers that can be used in a surrogate manner.

And because they do not exist, most of those clinical trials have to rely on functional endpoints like Bayleys at two years and even further, which entail very long-term follow-up for the babies.

And then, you know, it really does increase the burden on a small pharmaceutical company that might be thinking of engaging in neonatal drug development space to whether or not they would, like, rather invest their dollars in neonatal drug development program or some other development program,

which probably would have a higher probability of technical and regulatory success. This is reality.

And, again, you know, because of that reality, the perception of risk/reward kind of shifts towards high risk and low reward because of fragile patients, ethical constraints, small populations, perceived liability. It basically kind of skews the risk-benefit calculus, reducing industry willingness to invest into neonatal space.

And I know it's the truth. It has been happening for way too long, and this off-label cycle actually exacerbates it because, you know, if somebody is saying, oh, yeah, you know, 90 percent of the drugs are being used off-label, it is just fine. Why do we, you know, need to do something that's already working?

And that, basically, perception that existing practice is good enough, it further disincentivizes dedicated neonatal drug development. It basically keeps a -- creates a cycle that keeps on going on and on.

So, it's not only due to lack of intent,

but multifactorial causes that keeps perpetuating on itself. And breaking this cycle really does require, in my opinion, at least in part, quantitative data solutions, data-driven solutions that can de-risk the conduct of neonatal drug development and neonatal clinical trials.

This is where, you know, I believe and also use the term "it takes a village." It really does take a village. I don't think there's -- we -- I'm not planning to say that INC is the only organization that's capable of doing it, but it is one of the organizations that can claim itself to be the village; that hosts multiple stakeholders from industry, academia, regulators, where people are collaborating with each other, rather than competing with each other in their day-to-day jobs.

And, you know, we exist simply because, you know, there was -- there -- I do not think that, you know, any single entity, any single investigator, any single university, any single pharmaceutical company working together can actually solve those

enormous, enormous challenges.

So, INC is a part of Critical Path Institute established in 2015 as a result of persistent lack of drug -- neonatal drug development. And we have this interest in multiple different neonatal stake -- drug development areas, like, you know, ROP, GI, brain injury, and so on and so forth.

As I told you before, you know, at the -- at least in part, quantitative drug development tools and solutions are required to de-risk neonatal drug development simply because, you know, as it was discussed yesterday, most of those clinical trials are way too long, way too uncertain. And the tools that actually de-risk the conduct of those clinical trials, at least as of now, do not exist for vast majority of neonatal drug development.

Neonatal diseases, like innovative trial design methods, that was already discussed today, earlier before, validated biomarkers and surrogate endpoints. They simply do not exist for any of the neonatal diseases that I know of.

Regulatory data-grade platforms that are actually required to create those solutions, you know, they have started to come on board, but, you know, they can potentially be made more useful.

So these tools, they depend upon availability of data, as I told you, right? It needs scale. It needs longitudinality, and it needs heterogeneity to understand real-world clinical trajectories. Given the fact that, as I told you, neonatal drug develop clinical trials are few and far between, you know, they themselves cannot generate this evidence.

On the other hand, the data that is very abundantly available, every single baby always admitted in the NICU setting, always, always admitted in the NICU setting with high resolution EHR data, is available if somebody can only, you know, leverage that data and use that data to create that real-world data into real-world evidence, so to speak.

So, if only that data can be curated, harmonized, and made analyzable. So real-world data

is not just a convenience. It really is of all the disease areas I would believe that it's in the NICU setting, it's probably, you know, the most, one of the most useful type of data to de-risk neonatal drug development.

And that's exactly what we have been doing within INC over the past five years as a result of a really ambitious collaborative program with industry academia, with generous collaboration from with FDA.

We created this real-world data analytics platform which, to my understanding, is probably one of the high, you know, largest, freely available EHR resources comprising more than 350,000 NICU patients across three hospitals.

It's hosted and curated by C-Path and we are -- we have been using this for a whole lot of context of uses and simply because as I told, you know, neonatal clinical trials are simply by themselves incapable of providing that scale and depth necessary.

We have been using it to create disease trajectories, outcome variabilities, and we have been using it for very specific level, reference ranges tool that I'm going to show in the next slide.

There are a bunch of other use cases like using that data to create granular external control arms, predictive models, trial simulation tools. There, I think, the use cases are pretty much endless insofar as the use of EHR data and real-world data in the NICU is concerned.

So, this is one example that I wanted to highlight and show to you because this is, you know, one of the most, I would say, mature and demonstrable tools that is easily available and accessible for anybody to use.

The problem in this specific instance was in the NICU setting, probably, you know, somebody who works in NICU clinic and conducts neonatal clinical trial will know that there are no standardized neonatal reference ranges for most commonly used labs in the NICU setting.

So, it leads to inconsistent safety assessment and inability to use those lab values in trial design. And there's a high inter-site variability.

People just basically kind of make up their minds in terms of, yeah, this is -- this range level for this lab value is kind of okay in my experience. Sometimes they're basically extrapolated or from older children. It just is not standardized.

So, we created this app that -- in which we integrated, you know, several thousand patients from the data that we already have in our real-world data platform. And we basically created reference curves that show for a given specific gestational age for a given specific postnatal age, what would be expected, you know, lab value.

In this specific instance, I've just shown platelets. You know, this graph will basically pretty much show you what is the 50th percentile for a given gestational and postnatal age, going as down from 2.5th to 10th percentile to 25th to 50th to

97.5th percentile.

Obviously, you know, there is no normal-normal when it comes to a premature baby because you know, otherwise they will not be in the NICU. So we do not call them as normative ranges, but as reference ranges.

Again, as I said, you know, this tool harmonizes potentially, like, something, like, 15 most commonly used lab values. This is going to be a work in progress, but even now this tool is freely available to use. Whoever wants to use and access it, they should be able to use and access.

There are other examples that I briefly refer to in addition to what I -- what we showed you, the lab values tool. These are some of our upcoming projects within INC because the reason is simply because neonatal trials are underpower delayed, ethically constrained, small populations.

This electronic health record data, if it is granular enough and if it has depth enough, can actually be used to create really high-quality

comparator data in cases when randomization is infeasible.

It can also be used to create digital twins. I think somebody also before this, my talk, talked about predictor models that can reflect individual neonatal trajectories using large longitudinal clinical data. You need, like, really granular, high quality, complete dataset to actually do that.

It can be used to create trial simulation tools, disease simulation models to test feasibility endpoints and enrichment strategies before a clinical trial has even started.

You know, these approaches are adjunct to randomized control trials. They're definitely not replacements, but it -- they do provide huge amount of context and interpretability for these neonatal trials that are very difficult to conduct anyways. And a huge effort to de-risk conduct of drug development in this very fragile population.

Again, you know, circling back,

neonates still remain therapeutic orphans. I'm going to keep using this definition until this is no longer the case.

This gap it exists not only just from the lack of intent, it's definitely not that. But, you know, lack of other issues, like fit-for-purpose tools and whole bunch of other things and which stem from unique physiology and trial feasibility constraints, and the unique populations.

Addressing these barriers demand new quantitative tools that have never been made available for a neonatal population and no single organization can do this alone.

And that's exactly the purpose of INC. We would love to collaborate with you, work with you and, you know, solve these really complicated challenges together. So please feel free to contact us if you have any questions or if you would like to collaborate. Thank you.

DR. MASSARO: Kanwaljit, I just have one question for you.

DR. SINGH: Yes.

DR. MASSARO: I know that C-Path, obviously, also has a lot, a big real-world data effort in rare diseases.

DR. SINGH: Yes.

DR. MASSARO: So, can you talk a little bit about how those efforts have cross talked between what you're doing in neonatology and in rare diseases?

DR. SINGH: So, we have actually learned quite a bit from what other disease areas in rare disease space have actually done.

For example, our efforts in -- to create external controls, you know, something that we are actually very actively interested in, have been directly inspired by some of the work that has been done in Friedreich's ataxia, in which this program took registry data from Friedreich's ataxia and then, you know, used it to create regulatory grade external control arms that were actually pivotal in getting the first Friedreich's ataxia drug developed.

Again, you know, there are other things

that we have also learned from. For example, Duchenne muscular dystrophy program has a very mature sort of a clinical trial simulation program tool that we are actually, for our HIE program within INC, we're actually using what they had learned, how they created their clinical trial simulation tool, to create a similar type of a clinical trial simulation tool for HIE also.

There are a bunch of examples too, you know, like your -- our lab values initiative was actually, you know, to a great extent, inspired by the trial, the design, that was used in our Type 1 diabetes program.

So, you know, everything that we do is basically cross talks; it's kind of one C-Path approach that we use. Somebody has already made a bunch of mistakes in doing something. We actually learn from that, and that makes our own work a little bit more easier and faster and more efficient.

DR. MASSARO: Thank you so much. Thank you. I think what C-Path is doing also kind of really

is -- resonates with what we're trying to do at this meeting and learning from these two spaces where there's a lot of overlap.

So next I'm going to introduce Danny Benjamin, who is a distinguished professor at Duke and part of the pediatric trials -- chair of the Pediatric Trials Network of NICHD. He's joining us remotely and going to talk to us about platform trials and lessons learned.

DR. BENJAMIN: Hey, great. Thanks, Marianne. Can you either give me a thumbs up or put into the webinar chat that you can hear me; and I'll just keep rolling and hope that that's the case.

I'm sorry I could not be in person. I'm on the inpatient service this week and was able to break away for this discussion. I happen to be the chair of the Pediatric Trials Network.

Next slide please, Marianne, if you would.

And Pediatric Trials Network is a part of the Best Pharmaceuticals for Children Act. It's

the off-patent arm of the BPCA. It's sponsored by the NICHD, and the task is to improve dosing, safety, labeling, and, of course, ultimately child health.

Ninety-some percent of the work under the -- this part of the legislation, really is a focus on off-patent therapeutics. We've done a few device trials, and we occasionally will have a on-patent therapeutic as a comparator to an off-patent therapeutic in a trial.

Go ahead. Next slide, please.

Folks have already talked about basket trials and umbrella trials. I'm going to use a platform trial very similarly to before, but I'm going to extend it a bit; and it's going to include multiple treatments or diseases that have -- are evaluated in the same protocol. And it applies not only to therapeutics or devices or to standards of care.

For today, I'm going to give you three slides on experience that we've had. I'm going to do that because most people who talk about platform trials come along to you with a slide deck and they

have done either one platform trial, or they're doing a platform trial, or most likely, they've never done a platform trial, but they've got some slides for you.

I'm going to convince you that we do have some experience here. And then I'm going to, based on that experience, I'm going to pass on three or four lessons learned.

Can you hit the next slide, Marianne?

And I -- there's really three stages of research. I've now been through all three stages. No one can do this. In 2006 when I first proposed platform trial for off-patent PK studies to then network that was funded to do this was told that this was a horrible idea. It's impossible to do. It got voted down like three times, and we finally were allowed to do it.

Go ahead. Next slide, please.

You know, "Hey, you can do this for your disease state, but we cannot do this in our disease state." I hear this -- I've heard this at least once a year for the last 20 years.

And then "We've always done this," and this was a real joy for me when I was at FDA as an invited speaker and was informed that doing PK studies in babies by an FDA employee, I was informed that "They're easy to do."

This was about 2015, and I thought, "Wow, that's awesome." That meant you guys were doing it all throughout the 20th century. No. Actually, we weren't.

So I hope you can achieve all three stages of research. "No one can do this. We cannot do this. We've always done this."

And I'm here to tell you that if someone who is as mediocre a researcher as I am can do it, it's my firm belief that anyone can do it.

Go ahead. Next slide, please.

All right, so here's a summary of some platform trials that we've designed, and I am simply one of a number of investigators that have really led these. In fact the invest -- my role as the chair is broad oversight, the invest, with the exception of

POPs and CUDDLE. Most of the rest of these trials were designed by others.

So, this first one, pediatric off-patent PK study, or opportunistic PK study, is a modest amount of safety and some PK.

And so for most drugs in children, we actually don't even know the proper dosing in neonates or even have a good idea of exposure when we started the POPs platform 20 years ago.

And the consent form here is, "please give us one or two drops of blood. Your physician has prescribed this to you per standard of care. We want to bank samples and find out what's the right dose for the -- for babies in the future."

And we will have this protocol up and running at 30 to 60 sites, and we'll combine data every couple of years to at least describe exposures.

And the number of -- the amount of time that we need to do enrollment has varied from about a year, is very fast, to about five years, to even just get 12 or 14 babies to provide samples. We've used

this as a funnel. We really use it to understand what's needed in the pediatric domain.

We now had over 30,000 biologic samples. It's been on -- it's been continuously and extramurally funded for, in one form or fashion, for 20 years now. We have over -- and the Peds Trials Network has been going strong with this.

We have done over a hundred validated assays. We've done over 50 assays completed and submitted those data to FDA. We've done everything from 300 different sites, 145 different molecules.

We've looked at not only neonates but also children on extra corporeal membrane oxygenation. If you take all the blood out of a human being, spin it round and round the machine, oxygenate it, and cram it back into a human being sometimes dosing is different. Obesity and breastfeeding and SARS-CoV-2.

Once we realized we could do breastfeeding in the POPs model, we actually spun off a study called CUDDLE, which looks at the PK in a modest amount of safety in a dedicated study for

mothers receiving medicine per standard of care.

So, a timed sample from the mother's blood linked to a timed breast milk sample linked to a timed infant sample, that has now about 30 drugs in the pipeline either completed, submitted data to FDA, or enrollment ongoing, or entering that particular platform.

These next three studies are much more around safety and efficacy. So, this is around antibiotics used in premature infants. You can do considerable amount of extrapolation with anti-infectives, and so the sample size here is considerably less than doing 1,000 or 1500 patient neonatal trial that the neonatologists are sometimes able to achieve.

This is a different kind of effort, where we were randomizing for five different molecules at dosing stratified by postmenstrual age and looking at stricture and resistance.

The long-term safety of anti-psychotic medicines. This is -- I bring this up because this --

in this we looked at safety for five and ten years rather than just what's 48 weeks in the label.

It's not to tell you that neonates are going to be receiving antipsychotic medicines, but rather when we think about a bunch of the therapeutics for parents, what they care about, parents care about, is not the what's going to happen to my child in the next 12 weeks on this therapeutic, but necessarily what happens to my child in the long term.

ACTIV-1, obviously, this was in adults, and we were asked to do this platform study and it's -- we led that and held -- I held the IND through those molecules and that was an international pivotal randomized trial that enrolled a little over 1900 human beings.

Go ahead. Next slide, please.

These are the platform trials for the Pediatrics Trials Network, and I only provide you these, not to describe these in any painful detail, but rather to just let you know we've done a bunch of this work and we just wanted to pass on a little bit

of lessons learned.

Go ahead. Next slide, please.

These are the molecules that we've studied. You can see these molecules are not necessarily for folks to read or to memorize, but we've touched most therapeutic areas. We've touched several dozen of these, more specifically in neonates as the patient population.

A couple dozen of these were also in other rare diseases. So everything from sickle -- children with sickle to -- sickle cell disease to children with other life-threatening rare diseases.

Go ahead. Next slide, please.

So really, what are some lessons learned? One of the strengths of the platform trial model, especially in a place where there's not a lot of patients to be enrolled, is that it's very difficult for investigators to keep a reliable study coordinator employed and to keep a clinical trials as a site shop open.

It's almost -- I mean it's incredibly

difficult in today's environment for these investigators at a site. And although we have provided limited compensation for POPs, because 20 or 30 or 40 therapeutics are in the trial at the same time, this has meant that each site could really support a full-time coordinator with this study if they were in between studies in other clinical trials that they did.

And so the sites have come to really rely on this kind of flexibility in the program to not only establish but to keep alive the programs at their home institution.

We've also learned about how important stakeholder input is. I was glad to hear that and to see that families spoke first on the first day. We really have used and leveraged their involvement and partnered with them to design these trials. They really do sign off on -- the parents do sign off on the protocols and the consent forms before we put them into place.

And we do that with parents who are

very, very strong advocates. And we also do that with parents who are maybe a little more skeptical of clinical research and skeptical of some of our efforts but have children with the various disease states and they're willing to speak with us.

Because we find that, although, sometimes we disagree with our greatest skeptics, even when we do, we find that we can learn a considerable amount from them if we'll just listen carefully.

And then the usual professional societies, the National -- and the National Institute of Health, the FDA. EMMES is one of our partnering coordinating center -- data coordinating center efforts, investigators in the sites.

The other lesson learned is this is -- platform trials is not a trial designed for a widget approach. And I can't overemphasize enough. If you're going to be doing a platform trial or trials to partner with somebody who has done a couple of these before.

Because I can personally attest the

number of mistakes that I have personally made across these protocols. It's stunning and time after time, we'll make mistakes in these protocols. And really for junior investigators it's not -- we're defined really not by what our great ideas are, but really how we respond to the mistakes we make and to the adversity in front of us in our research careers.

For industry and NIH more broadly, I hear sometimes about platform trials that have included two, three, or four molecules; and really in our experience, at ten molecules -- at five molecules, efficiency starts to -- you start to gain traction. Less than kind of five questions or diseases or molecules, it's tough to gain efficiency until you get to five.

And really, this really starts to pay off for the funders and the sponsors and the folks involved when we get to 20 or so questions within a protocol. And the flexibility of sponsors and agencies and companies and folks funding this and the stakeholders involved is really central because

sometimes you'll have 20 molecules or 20 questions within a platform trial and some of those are just more popular than others.

And that is a non-trivial risk when you're moving together is that sometimes some questions are answered much more quickly than others.

Next slide, please.

Flexibility is really the hallmark of a successful design and execution of a platform trial And we -- when we designed some of our opportunistic protocols, those are less the PKPD studies. Those are not the so-called -- those are not so much safety studies and efficacy studies, but really this is just getting exposure data.

In those trials, variations in PK based on subgroup. For example, those with obesity are looking at drug-drug interactions. The strength of the platform design is to fill in some critical knowledge gaps that you simply just would not undertake in a study by itself.

And if you apply this to neonatology,

there's some illnesses that are, gosh, common enough in neonates to go ahead and get the trial done. But there's others where if we don't cobble these together, we're really -- they're going to be super challenging to answer. That's also true in the rare disease state in our experience.

And so, flexibility across the protocol to account for the fact that you've got different diseases or that you've got different molecules. And when we looked at, for example, four anti-epileptics in a PKPD and safety study and some -- and look -- and also looked at some efficacy, they had such wide variations in PK properties that we really had to make the windows around sampling collections and events very, very flexible.

And for industry, you know, flexibility and compromise around protocol details and sampling schemes and balancing the sites and the diseases and other partners is going to be key. We found, you know, this was especially true in ACTIV-1. What was -- we needed for the companies involved to really

work together and they did an amazing job to work together around flexibility and compromise around a lot of the details.

Go ahead. Next slide, please.

So the lessons from BPCA are uniquely positioned to innovate in clinical trials, and these lessons can be used not to just molecules but to other care questions.

Now, I'm not going to go through this example specifically around traumatic brain injury, but we've started to look at reverse engineering some of these studies. And so we would start with the professional guidance document, whether it's osteomyelitis or traumatic brain injury or neonatal HIE.

And they usually have about 20 recommendations in them and they're usually -- almost all the recommendations are very low quality of evidence and we get the investigators to be willing to first randomize at the site level because children get sick at night; and you don't want to fail, and you

often don't have your study coordinator working nights and weekends.

And then we stack subsequent interventions with therapeutics with different questions at different times. So if you're, for example, admitted with a traumatic brain injury at three o'clock in the morning, you're randomized at the site base for nutrition because folks are willing to do that in a site randomization setting.

And then at the individual level you can randomize for things like, do you want to use various molecules around intracerebral pressure monitoring, with the long-term goal to answer dozens of trial questions within each trial.

For here, an HIE, you might look at a randomized by site for neonatal HIE question with a different five or ten different therapeutics and kind of a Phase 2a approach, where you're looking for just hint of efficacy in a couple of dozen babies and then prune molecules that don't work.

Next slide, please.

I think that I'm at 15 minutes. I'll just say this real briefly. We have used real-world evidence to link them to our platform trials. So we partner with pediatrics on this.

The pediatrics, which has MedNX, is a data warehouse, and it's got about a hundred thousand babies per year. The neonatologist in the crowd will know of the -- these data; and there are times where we are able to push through some of the information from our trials and link them to outcomes in the pediatrics database.

Sometimes we really cannot do this. The granularity or the quality of the data in that particular data warehouse won't answer those questions, but sometimes we're able to do that and we are -- and we have done that successfully.

And an example of that is the exposure seizure risk linked to ampicillin, and I'm grateful to the relevant FDA division to really work through some of that with us -- that was the anti-infectives division -- for working through some of that with us.

Because the precision of the real-world evidence has some downside and you -- you're just going to need to be able to work through that if you link real-world evidence to your platform trials.

And with that, I'll thank you for putting up with me and for putting up with me remotely.

DR. MASSARO: Thank you so much, Danny. We are going to keep moving, and it's my pleasure to welcome Michelle Campbell from our Office of Neuroscience in CDER, and she's going to close out this session with discussion of outcome assessments, which we've heard a lot about and a lot of questions about. So we're looking forward to her perspectives here.

DR. CAMPBELL: Thank you, An.

Good morning, everyone. And I am your bookend to your morning sessions and actually hopefully you'll see a theme of how they all fit together.

And also, magically, I am also speaking

right now at a PSP PFDD meeting. I prerecorded those remarks to be here today.

So, I want to spend some time talking about lessons learned from a rare disease in our pediatric -- particularly in our pediatric side of rare disease. And how is that application for neonates?

So, we always have to go back to what is our job as reviewers, and we have to look for clinical benefit in that treatment. And so what is that defined as? And that's the positive clinically meaningful effect of an intervention. So an improvement in how someone feels or functions and survives. And so that is what we're aiming for, ultimately, when we seek a treatment.

It's important to note that in a lot of our rare diseases, a aspect is staying stable or slowly progressing is meaningful; right? And so that is one aspect that is important, and we need to be able to describe this information into a label so a physician can have that conversation with a family

when making a treatment decision.

But we often are asked what do we think about every day as reviewers when we are reviewing study protocols that come in, when we're providing advice to a sponsor on their development plan.

So, we're looking at from an efficacy standpoint, is that, is there clinical benefits and is this benefit meaningful to patients?

Well, when we're a neonate, that's going to be a little hard for us to kind of figure out. Unfortunately, we cannot directly ask them, right? And so we have to leverage some of our tools that we would in maybe other diseases of how do we handle this to be able to show that this is meaningful.

We know that statistical significance alone does not always translate to clinical meaningfulness. And oftentimes you may have had a really great trial design; you've come in, you've talked to Becky and her team throughout the IND process, but the treatment had a really modest result.

And so we have to think about, well is that -- even though there's something happening, is that meaningful? And so we're really interested in looking at the within patient meaningfulness. What is happening there at the patient level?

Another piece of this puzzle when we think about our trial design is, what -- why does the type of therapy you're studying in your trial matter? And that is going to matter in how we evaluate meaningfulness and how we think about what are the appropriate endpoints that we want to capture that data to demonstrate clinical benefit.

So, if we are looking at a symptomatic therapy, a reduction in symptoms may be the desired endpoint that we want to consider, right? That may be the goal.

And so that approach to how long that trial needs to be, the -- what are the endpoint selections, what do we need to do, will be much different if we're looking at a therapy that is targeting the underlying pathophysiology of the

disease, right? Or the biology disease, right? Where we were hoping to slow progression or keep someone in an current state a lot longer is the desired effect, right?

And so it is really fundamental that we understand what do we think the drug or biologic is going to do when it is introduced into the patient.

So, this is our reality when it comes to rare disease drug development, when it comes to pediatrics, as well, is when in our rare disease populations we have heterogeneity of symptoms. And I like to say that should not be our barrier. It's -- we have to accept it and we have to work with it. And how do we do that in a thoughtful way?

We have severity. We may have different types when symptoms may emerge over the course. So, if we have an infantile version, maybe the more severe population versus a juvenile or late-onset version. So, that's going to look very different in how I'm going to approach a trial design and an endpoint approach.

And so we really need to make sure we understand a good natural history, which is always hard, and in neonates, that's even an interesting more challenge, right? Because we may not have per se, immediately what that person's trajectory is going to be, right?

That child, the infant's trajectory is going to be -- as I'm sure as the neonatologists in the room are trying to determine -- what are we working with, right? We have to make decisions now to treat what we see, but is this a disease that we think we need to watch and intervene early because we have an available treatment? Or is this something that we may be able to respond and the infant can overcome from the NICU stay?

We know that clinical outcome assessments and endpoints are -- can be poorly designed and they don't have the precision we need, but we can work with that, right? But we have to think about again, what is the appropriateness and what do we have to work with?

We know that laboratory tests and biomarkers are not always validated or standardized for the utility and needs of a clinical trial.

We know that sometimes our trials may be too short to actually show a change, right? And that we know this because of our sample size that our trials are typically going to be underpowered.

And this is something is where you -- when we work with our statistical colleagues in thinking about, and we hear often, we only powered for the primary and not the rest of the endpoint hierarchy. And so how do we balance that in the appropriate selection of analyses that need to occur?

So, this is our reality, and we are here to try to work together of how do we move forward with this.

So, in pediatric drug development, we have a couple intersections, right? So, we're balancing -- and I would say this is what is probably happening in the neonatal side is -- are we going to have a typical developing child trajectory, or are we

in a trajectory of developmental delay -- right? -- because of underlying diagnoses that we may still be trying to determine in the neonate stage and, you know, into early childhood as we have to rule out things. Because if it's not genetic and it's something else, we may have to see what the symptom progression looks like.

And then is there other comorbidities in the play? And so we have to kind of balance all of these things to kind of find that right target of what are we studying, and what are we measuring, and how can we accurately measure those concepts, right? And that's really important is, do we have the right way to actually measure what's important?

So, I borrowed this slide from a former FDA colleague who's now in industry about how do we really think about assessing benefit? And why I'm focusing on benefit is because we, if we think about it that way, we can work backwards on -- in terms of how do I assess and measure these concepts.

And so we really should be leveraging

our whole host of an endpoint hierarchy with your primary and secondary endpoints. And they should really cross the broadest range of the spectrum of your patient population and the patient you plan on including in your trial.

Because we would like to take as many patients that we can because we really do need that sample. We really want to measure outcomes that are reflective, oh, we think will change or stabilize. Again, what is my treatment going to do within that duration of the trial?

And that's really where trial design and the things that Becky talked about earlier today with some of those innovative approaches where that length of trial is really important. Does a shorter trial make sense? Do we need a longer duration trial? What does that look like?

I'm a big proponent -- some of you guys in this room have heard me talk about this -- is that we need to use multiple clinical outcome assessment types throughout the clinical trial. So, it shouldn't

just be the sole clinician reported outcome. We should be looking at caregiver report when we can into our trials. There's -- are there other outcome assessments such as performance outcome measures that may work.

And so we should really try to get that breadth of information in there. Is the use of digital health technology a way that can capture informative data, right? I think that's an area that we are continuing to explore. How can we apply that? Does it make sense for this population and for this trial design? It may.

And so we are very much open to that, and we want to have those discussions of what that would look like. And I think we've had some really great examples of some potentials of what that could look like today.

It's also very good and informative to us -- and I would say we're probably asking for more of it these days because we've learned how informative it is -- is qualitative insights from caregivers and

clinicians, particularly on when we're looking at changes. What is a parent seeing that's occurring right at home? And how do we help us understand what this quantitative data is telling us from the trial results?

Kind of gives us a better explanation in a person's world and viewpoint in their words of that lived experience that we're -- that a clinician may not see in that snapshot of that study trial visit, right? But what is really happening every day?

So, we have some options to think about for outcomes, and I'm using "outcomes" in the more bigger way of outcomes in neonates and rare diseases.

And I -- and for someone who is a measurement scientist, I'm going to mention biomarkers for a reason. Because we need to think about both biomarkers and COAs simultaneously when we're thinking about neonates and in rare disease because we don't have a lot of opportunities for multiple trials in these populations. And so we should be leveraging a breadth of data collection opportunities.

So a biomarker has the potential to support and inform efficacy, and we have examples for that. It's important that you come and have those discussions with that specific therapeutic review division on what may be needed, what data and evidence needs to be generated to support this.

So, I don't want to think that we're forgetting that, but a biomarker could be extremely informative in a way to help support the overall trials data.

We do have different clinical outcome assessment types, and I've highlighted the ones that I think make the most sense in this population. I have left off a patient reported outcome because it doesn't make sense.

If I was in an adult population, you know you're going to hear me talk about that. Or if I'm in a rare disease where I don't have an intellectual disability happening and I can get that report, I'm going to ask for that.

But for what we're talking about today,

we're probably going to be leveraging our observer, reporter, or caregiver, our clinicians, and if a performance outcome measure works. It depends on that age range we're looking at.

And, again, thinking of a digital health technology as an area of opportunity to collect that data to support that trial endpoint. So really pulling from the advancements in science and technologies that we're seeing with the complimentary of some of our more traditional things with clinical outcome assessments.

So, we do have options. You are not limited. We just have to think about them in a thoughtful way of what best fits for your trial.

So, this is a scary roadmap. I know it is. I know it is, and I can get away with saying that, but I want to put this in words for you guys.

So, this is from the famed PFDD guidance series, affectionately, Guidance 3, which is this, how do we actually select and identify how we're going to capture what we're hearing and learning about a

disease and condition for trial? How do we collect that data with an outcome assessment to support that trial endpoint?

And I want to highlight really the far left. These are foundational principles. We need to have the perspectives of all key stakeholders. So parents, caregivers, clinicians. We need to have a -- if we can get as much of an understanding of natural history, which I do know that's limited sometimes, but what do we know about the disease? And really having an understanding about the patient population to today's --

And we absolutely understand that science is evolving as we're running these programs. So we are also learning at the same time and we need to make decisions sometimes based on today's information, and we know that it could change during the duration.

And from taking that information and understanding the disease is, what are the things that we can measure? What are the things that we can

measure in a trial in a reliable way?

And when we can do these left, the far-left aspects, that will then help us in figuring and determining what's the best way to measure those concepts.

And that's where we can come in and help when you come in and ask for advice from us. Because we can also think, too, about what you have told us. But we -- what we really need is a good understanding of disease and what are the concepts and what are the -- that we want to measure that'd be interesting.

Because then there we can direct that best advice on how should we measure these things; and then maybe we're thinking outside the box and not using something that everyone says, well, we should do it only this way. And maybe we know from other experiences that there may be a better way to actually measure that. And so you should come and ask us about that.

So, I want to share an example with you

that I think it was -- I went and rallied the troops in neurology and I said, "I think I want to mention SMA as an example" because it was my closest I could get to maybe neonates/infantile aspect as an example, and everyone thought it was a good example.

And so -- and this is, obviously, a couple programs that we are aware of where we've had success, where we now have three approved therapies in the last decade in a disease that didn't have any.

So, SMA is a autosomal recessive disease of the survival motor neuron that causes motor neuron loss in the brain stem and spinal cord leading to weakness and muscle atrophy.

The infantile onset, or Type 1, is fatal by age 2 with -- from respiratory failure and infection. And we have three now approved therapies, two from CDER, nusinersen and risdiplam and then a gene therapy from our CBER colleagues.

So why am I using this as an example? Because I think people sometimes get bogged down when they're thinking about endpoints. That it has to be

really, really complicated; and it doesn't have to be complicated. We can really go simple if it makes sense.

And in this case, we understood the disease. It was fatal and that motor and developmental milestones were not met, right? And so how can we leverage that information in informing a trial design and endpoint selection?

So, for nusinersen, they actually did a randomized double-blinded control study of 82 patients. And their endpoint was the proportion of responders with improvement in the motor milestones in Section 2 of the Hammersmith Infant Neurological Exam.

And so this also shows that we did do a randomized placebo-controlled trial in a sense. And we focused on something -- you know, in the complexity of how we can measure things, something that was identifiable that you could easily measure, which was the motor milestones.

This is directly from the label, and this shows how there was the improvement in patients

in the infantile onset group from the motor milestones. They were achieving them; the control patients did not. And then there were some other motor milestone analyses that were done.

So, it worked, and it's a simple -- it was a very simple thing and it made sense with that disease.

The second example is risdiplam, which was an open-label, two-part study with 62 patients. And this did leverage what we knew with clinical practice. The clinical diagnosis and course of the disease was leveraged in the natural history type aspect of the open labelness.

So, the part 1 was a dose finding and part 2 was the efficacy piece. The endpoint was the ability to sit without support for at least five seconds.

And this was actually came from a specific item from Bayley test. And this shows how patients were successful, really had a -- the drug really worked. So we were able to overcome some of

our concerns with an open-label study.

But I wanted to show these as we don't have to get too complex, but it has to make sense, right? And in this case, we could justify this type of endpoint in the way to capture it because we did have that -- have a good understanding of the clinical course of the disease, and that was really important.

So, I would be remiss if I don't mention guidances and I -- ironically, we've all are going to mention different guidances, which is really great because that is where we're putting our current thinking; and they -- these, our guidances, should not be read as a standalone document but they -- we are often referencing either other guidances or there's other ones that kind of go together to kind of give a big picture of advice.

So, this is one that actually was stemmed from OPT and while it -- the title has to do with long-term safety considerations, there's actually some really good sections in there on endpoints, particularly neurodevelopmental endpoints and

considerations that would apply into the efficacy standpoint. And so -- that are some -- I would reference that as a good place to start when it comes to neonates because we really thought about this and what that would look like.

We have a rare disease guidances from considerations to drug development to natural history studies. And so those are always a good place.

We have our patient-focused drug development guidance series, which is a four-part series about how do we get comprehensive input from key stakeholders and from families all the way to how do we create that clinical trial endpoint.

I will let you know with this guidance series, the first two were actually written more towards patient groups in that flavor, and the last two are a little bit more technical in that they were geared a little bit more for industry for when they have to come talk to us.

So, if you get to the last two and you're like, "Ooh, this may cure my insomnia," that is

okay. It is a little bit more technical, but it has good information; and there are folks who actually know what that mean -- what -- how to implement that information.

But it has really good information, and I do know that patient groups have read these and are trying to apply these to the work they're doing because we are seeing that every day.

So final thoughts. In neurology, our diseases are often heterogeneous within the person and between patients, within the disease lifecycle. Natural history studies are important in understanding disease progression.

Please include all stakeholders in your work when you're selecting and designing your trials. And really, I think sometimes -- and I think we are getting better at this because I do remember I was a part -- I don't know if Danny's still online -- of a very early BPCA trial as a research coordinator, and I definitely know parents were not involved in that trial design.

And I talk about that as an example of "Man" -- because this was before patient-focused drug development even started -- "What a missed opportunity." So I'm very glad to hear that it is happening now because our patient and caregivers really can give us a great insight of what is happening at home.

So, plan your measurement strategy to include all potential patients that may be eligible into your trial and you need to understand their capabilities.

So, when we see someone put in five performance outcome measures, but there's a high level of intellectual disability, I'm going to scratch my head when I give advice because I am concerned we're not going to be able to get complete data then, right? There may be a lot of missing data because instructions cannot be followed.

You know, a person may be fatigued because we have all these endurance-based tests and did you give enough rest? Did we make sure we go back

to as much of a baseline as possible?

So, we really need to think about those considerations when we are selecting something, not the, "While we have them there, let's do these 20 things because they're at the site," but how does this make sense to my trial and the data that I need to support my evidence?

Really use your endpoint hierarchy to its potential. And this is where we talk with our statistical colleagues. We bring Becky and her team in to talk about the trial design and the endpoint hierarchy and how is this informative and what can we leverage?

Also, we may want to think about additional evidence and that's through our qualitative efforts for thoughts for meaningful change because we do have small sample sizes and so some of our statistical approaches may be then become limited, which is why you come talk to us early so we can think about how do we handle those small sample sizes and getting the data we need.

Again, here's a list of resources that we have and I thank you.

DR. MASSARO: Thank you so much. That was wonderful. I know that we are at break time, so if folks have questions, we can certainly find -- and also continue to put things in the Q and A, and we will try to get answers back for folks joining us online.

We are going to shorten our break a little bit, but try to reconvene sharp at 10:45, and we will head into the next session. So thank you.

(Off the record.)

DR. MASSARO: So it's my pleasure to kind of introduce our moderator for our next session, Shannon Hamrick, who is a neonatologist who works with us in the Office of Pediatric Therapeutics; and she is going to lead this panel discussion with our esteemed panelists here. And we have some that are online. So I'll turn it over to Shannon.

DR. HAMRICK: Thank you, An. And thank you all for sticking it out here today in chilly D.C.

So, this panel we're going to be discussing how to leverage networks and existing consortium and centers of excellence to be able to optimize how to operationalize trials, harmonize trials.

And we're going to try to keep it a really practical session. So, this is going to be a different format. We have three of the participants virtual, and then, of course, three of the panelists here in the room.

And so I'll just do brief introductions, but, you know, as the panelists are speaking, if there's anything you'd like to add to your introduction in terms of the role that your organization does, please feel free to do so.

But virtually, first we have Dr. Rachel Greenberg, who is a neonatologist. She's here representing the Pediatric Trials Network, part of the Duke Clinical Research Institute.

We have Gus Schmidt, who is also a neonatologist, and he is here in his role as a Program

Officer for the Neonatal Research Network, part of the NICHD.

We have in the room Dr. Klaus Romero, and he is here in his role as CEO of the Critical Path Institute.

I have Deb Regier here. She is a geneticist, and she is here on behalf -- she's the Director of RareCap, and she's going to explain that organization to us.

We are lucky to have Dr. Ralph Bax virtually participating, and he's the Head of Pediatrics for the European Medicine Agency.

And then we have my colleague Sarah Zaidi here. She's a pediatric pulmonologist, and she's going to be speaking on behalf of the FDA.

And in particular she leads the Pediatric Cluster, which is an international forum for discussion between FDA and EMA and PMDA, Health Canada, Swissmedic, Australia, if there's anybody else I've forgotten. So, Sarah will be speaking in that role.

So, the first question that I have, I'm going to direct towards two of our virtual panelists; and I'd like to direct this to the Clinical Trials Network representatives here, so Rachel and Gus.

And the question is whether, again, with the theme of staying practical, if you could provide examples of best practices for harmonization for your clinical trials network that you think have worked well. And I'll let Rachel start.

DR. GREENBERG: Thank you so much for the opportunity to be here and be on this panel. And as it was mentioned, I'm a neonatologist and I'm one of the Network Leaders for the Clinical Coordinating Center at DCRI, Duke Clinical Research Institute, along with Danny Benjamin, who you heard from earlier for the Pediatric Trials Network. And I'm also the Chair of the PTN Steering Committee.

So just a little bit more background on the PTN just in case anyone missed the previous session. The PTN provides an infrastructure for investigators to conduct trials that improve pediatric

labeling and, obviously, the ultimate goal of improving child health. And we're sponsored by NICHD as a result of the Best Pharmaceuticals for Children Act legislation.

PTN started back in 2010, was renewed in 2018 and 2025. And because so many drugs and devices in children are used off-label, PTN's main goal is to perform studies in off-patent therapeutics that improve dosing, safety information, and labeling.

So, for this work, our experience, it's led to submission of data for more than 30 products to FDA and 26 labeling changes. And many of these drugs and these labeling changes were focused on neonates and the rare diseases that occur in neonates or common diseases in neonates that are overall rare in the general populations like infections, necrotizing enterocolitis, lung disease.

So, just to get to your question then, after that background, we've learned through this experience that harmonization within a network like PTN is really essential. So, as a network you can

think about harmonizing with others, but first you got to make sure, I think, that you're consistent within your own network.

And the -- and it's really important for the PTN because our process of getting an actual change to the FDA label in drugs is a many-years-long process.

We've seen examples -- we've had examples where it's taken over 10 years between the time a study concept is proposed. And by the time we've negotiated the trial design with FDA, done the trial, assembled and analyzed the data, submitted the data, responded to multiple rounds of questions from review divisions, then the label change comes in.

So, it's important to get the trials right and get the right outcomes, harmonization, rather than reinventing the wheel each time. We've seemed to learn what elements are important to each trial and then we can harmonize with what's worked previously with other trials.

So, to get to some examples, Danny

Benjamin mentioned earlier, the breast milk trial that we do. It's more of a master protocol, so we're performing the study in the same way for dozens of molecules. So, this has a number of advantages. It works well for sites who know what to expect to perform this study, and the FDA so that they can, you all know how to evaluate the data when we submit it.

And then we use what we've learned in that breast milk master protocol study to do another separate study in a different setting.

So, we enrolled mothers and infants to study breast milk in Botswana, and we collaborated with researchers from another institution who had a research site based in the country to develop a protocol that used many similar elements to our PTN master protocol breast milk study, but also conformed to the needs of a different setting.

And so by harmonizing elements of study procedures, definitions, and outcomes we're able to expedite our analysis and the interpretation of results for the other -- the Botswana study.

Another example I can give of within network harmonization is within several of our neonatal protocols. So not all -- within PTN, not all of our studies are focused on neonates. As a neonatologist, clinically, I'm very interested in the neonatal protocols, but we -- and so we've done a number of those that have focused on a common outcome, bronchopulmonary dysplasia or BPD.

So, we had a study of furosemide, which was focused on infants in the NICU who were at risk for BPD. And that study finished a little over five years ago and resulted in a label update that is related to neonates.

And in that study, we assessed lung disease or BPD and BPD risk using definitions and calculators that were developed using data from the Neonatal Research Network. And we used safety parameters for trial entry criteria and adverse events for that study.

We also then performed another study that was focused on a similar population, hospitalized

infants who are at risk for chronic lung disease. This was the sildenafil study that finished up just last year and used a lot of these same parameters, which I think will facilitate FDA review when we submit the data.

So, it's been -- it's really important to harmonize trials within a network when you're performing multiple studies. But I think your question is also, you know, really focus, how are we harmonizing outside the network with what's being done outside the network?

So, for the neonatal studies I mentioned, we used BPD definitions that aligned with the current consensus at the time. So the NRN definition was what was often being used.

I will say that changes in what definitions are for outcomes are commonly being used in the immuno research community definitely affects our ability to stay harmonized with current work since our work, as I mentioned, takes a long time to come to completion.

So, over a course of 10 to 15 years, maybe science gets better, people start using different outcomes and definitions.

So, this does make, I think, harmonization a challenge, particularly when you're playing the long game with a protocol that's going to be providing data for FDA. But this is a focus for us. We've made a lot of efforts to work and harmonize with other networks.

I gave the example of the Botswana study where we translated our work within PTN to a different setting in order to study drugs that were more commonly -- or more consistently used in that setting and population.

We also have put together data for a label change for fluconazole using -- in infants, using preliminary data that was generated through the Neonatal Research Network, a network called the Pediatric Pharmacology Research Units, or PPRU, that preceded PTN, and PTN.

So consistency across populations

enrolled, the outcomes assessed, et cetera, were needed. It was really important to design our PTN studies on fluconazole with these previous data in mind, knowing we were going to submit all of this body of data to the Agency.

As a network, PTN continues to be interested in partnering with other networks and harmonizing our studies with these networks in order to ensure that the best quality data related to drugs are collected and ultimately used toward label changes, which is one of our main missions.

For example, we worked with the INCLUDE program to produce a protocol for a randomized trial for patients with Down syndrome. And it was really important to ensure that we were using outcomes and, in that setting, including patient reported outcomes in that population; that we're consistent with what was being used in other trials and studies in this population.

A few years ago we submitted a proposal to do a prospective study on postnatally acquired

cytomegalovirus in infants, and PTN would have been responsible for the therapeutic focus piece of that protocol. We worked very closely with the NRN to develop the plan and protocol for that effort.

And that was made possible really because of overlap of investigators within the different networks and knowing what is going on in one network and what might be of interest to another network. So that was a really, I think, good piece of collaboration and example of harmonization of strategy and ultimately the science that we wanted to do.

But ultimately, we didn't receive funding for that proposal, but that's an example of looking for opportunities.

We continue to look for opportunities for collaboration and harmonization and we really -- I really think that the -- in the infrastructure and knowledge of how to study therapeutics -- which is really PTN's greatest strengths -- in different populations, can be leveraged as we work with other networks to study neonates.

So that -- that's my answer. Thanks.

DR. HAMRICK: Thank you, Rachel. So many good points there.

Gus, we'd love to hear from you, your thoughts on the topic.

DR. SCHMIDT: Sure. Thank you for the opportunity to discuss. I wish I could be there in person to meet all the colleagues and have this discussion.

But for this topic, I wanted to share a couple of different ways that we've experienced harmonization in the neonatal network because they illustrate different pathways through each that happen.

And the first one was one that was not really targeted at randomization and -- but became a powerful tool in a framework that we, in the NRN, we -- is used, which is our Generic Database.

So that was initially built as a registry, a way to collect population level data on all infants that are extreme preterm in our network

centers. But that database over the years became a core data infrastructure that can be used across multiple trials while maintaining common data elements.

So, instead of building new data collection systems from scratch for each study, we have a framework of core data elements that is consistent across all our studies. And echoing what Rachel just mentioned, we were able to build internal consistency by building the GDB, the Generic Database.

And, again, the Generic Database is used not only across our clinical trials; they're used for all extreme preterm infants born in the network centers, whether they are -- the babies are enrolled in trials or not.

So, we are collecting standardized data on all these infants, which means that we have comparable data, both for trial participants and nonparticipants, which allow us to plan better trials by having a really extensive data on the population of interest, understanding generalizability of our

trials, and also understanding selection bias in our trials.

We can answer questions on the incidence of conditions of procedures and characteristics of our population that may be relevant to plan to specific trials and understanding whether the babies that were included in that trial are really representative of the babies that we're trying to help that represent our population.

Our Generic Database also gives us very important operational benefit. Our investigators, the research staff, that are at the centers are very familiar with GDB forms and the data elements. And over the years, they have the developed ways of collecting this data accurately and efficiently because they're using the GDP on their daily work.

So, when we launch a new trial, we're not training people on the entirely new system. We're adding trial specific forms to a foundation that is already known, which reduces the startup time, reduces error, and reduces the burden on the site staff as

well.

And this, our Generic Database, covers maternal history, delivery information, clinical data during the NICU stay, procedures, and discharge information.

And because this is collected informally across trials and across all infants really allows us all those benefits that I have discussed, and we can compare enrollment patterns across centers, across trials. We can look at temporal trends and outcomes independent of any trial, which has been an important contribution of the NRN to the field of neonatology.

And when we are designing a new trial, we already know what data will be available, which help us design more specific studies.

And a natural extension of the GDB as an extension, is our follow-up study. Our -- as it was discussed yesterday in -- neonatal trials are almost always interested in long-term outcomes even if they're not the primary outcomes.

So, the NRN has developed the very standardized protocol that specified the timing of assessment, the instruments to be used, and how outcomes should be classified.

And the NRN has really invested heavily training with -- we have a continuous recertification process for the research staff that administer those assessment tools so that the data is reliable and very consistent across all centers.

And like the GDB, follow-up is not limited to trials, but all babies at high risk of long-term impairment are included.

And the impact of GDB and follow-up has extended beyond the network towards harmonization. We receive requests from investigators outside the network for manual forms for both GDB and follow-up so that they can implement similar forms and similar data elements in their own trials.

And this happened organically because using well-established or tested forms is much easier for an investigator than creating new ones from

scratch.

And another way through which we -- we've been applying harmonization, obviously, a more intentional harmonization process. And one example is our reporting of serious adverse events.

We had a deliberate decision to harmonize our safety reporting across trials, and we decided to adopt the International Neonatal Consortium Reporting framework.

And this has really been an important step forward because the adverse event reporting neonates has historically been very challenging. What -- what's an adverse event in a baby that was born at 23 weeks gestation, which is very likely to develop so many complications and morbidities during their hospital stay and what -- so what's a true adverse event related to an intervention versus what's a complication from prematurity?

So, the -- this -- the INC framework really helps us with a standardized approach, categorizing reporting adverse events that account for

the characteristics of our population. And this is being implemented across all our network trials, which means that we have consistent definition grading and attribution criteria.

This is relative -- for the length of the network has existed, this is relatively new for us, but it will allow us to compare safety profiles across different interventions.

And most importantly, because this is a framework adopted by other groups, our data becomes comparable. Our safety data becomes comparable to other neonatal trials happening outside the network and really expands the potential for safety analysis and understanding rare adverse events that no single trial will be powered to detect.

So, what we can -- I think we can take away from this NRN experience is that when you build an infrastructure that serves multiple purposes and is sustainable beyond a single study, it really helps reduce the burden of adoption and facilitate harmonization and data collection and inform and

execute better studies.

DR. HAMRICK: Thank you so much, Gus. And I just have one clarifying question for you, which is, if you can speak to whether the data in the GDB is open to other investigator -- non-network investigators or investigator sponsors?

DR. SCHMIDT: Of course. So currently we are in a transition process, so the data is right now is available upon the request. We have a process through which investigators can request our data through our network website.

In the future, now that we're transitioning to a single IRB model, we will -- the data will be available through the DASH, N-DASH repository, which is the -- and which is the repository -- data repository that NICHD uses for all its trials. So that will be readily available for investigators that are -- that have access to N-DASH.

DR. HAMRICK: Great. Thank you so much. So, we'll move along to the next question, which is essentially the same thing, but for the regulatory

organizations that are here.

So, to hear from EMA and FDA about, with respect to multinational trials, what kind of advice you've given or considerations that you've given to sponsors to aid with harmonization across countries, which is, you know, quite tricky.

So, I'll let Ralph go first since we're on the theme of virtual participants, if you don't mind. And then we'll hear from Sarah after that.

DR. BAX: Yes. Hello. Thank you for the opportunity to be joining you even if it's only virtually. I would have really appreciated to myself being there to have these discussions.

I just wanted to add to -- as an introduction, that I'm also trained as an neonatologist and worked 15 years in this area, so -- before for joining the Agencies. So, I still know who I'm working for and my colleagues in our pediatric team have to put up with a certain bias I have.

And this leads me also to the activities we are specifically doing with

international regulatory bodies and mainly also with our FDA colleagues, having being the first in the overall to developing a pediatric legislation. We learned from them and followed about a decade later.

And Sarah will be much more experienced in describing our activities, but it is a very important platform for us to discuss perhaps more alignment on our side to then push for harmonization of global development, specifically in areas such as neonatology or rare diseases where we need to have global trials.

So, the Cluster is one area, and potentially we have to discuss how to also learn from other therapeutic areas for our Cluster and to improve perhaps our discussions also around neonatology.

So it -- another point I wanted to make is that, obviously, we are supporting also harmonization on the site level. So, parts of our regulation is also on information transparency and supporting infrastructure. And here we are also learning from our discussions at the Cluster and at

many interventions we have and communication we have in multi-stakeholder meetings with our U.S. colleagues and other international colleagues.

Europe is still very fragmented and whether it's standard of care in neonatology, whether it's devices available in the various clinical settings. And here we are really -- whether it is data collection -- and all this we try to gather in our -- in Enpr-EMA Network, which is then closely connected also to discussions with our U.S. colleagues.

But for more details on the Cluster, I will hand over to Sarah.

DR. ZAIDI: Should I just go ahead, Shannon? Okay.

Thank you, Ralph. I'm very grateful that Ralph set us up and gave us this framework.

I guess I should start by explaining what the Pediatric Cluster is. FDA and other international regulatory agencies, quite often it's EMA, have a mechanism by which to, they can discuss

confidential information that's related to many, many topics. I think there's almost 30-plus Clusters at this point.

The Pediatric Cluster was stood up in 2007 to discuss issues related to pediatric drug development applications that were under review at both Agencies. At this time we're not having extensive discussions about devices, but maybe that's an area of growth.

And the way it works is that, you know, as Shannon said, it's not just EMA, there is a Australia, Japan, Health Canada, and recently Swissmedic was added thanks to our Program Manager, G.T. Wharton.

You know, anybody who has an issue with a review that they're doing for a pediatric application can nominate this topic for discussion. We meet almost monthly and we can have sort of ad hoc meetings to facilitate tighter timelines. And these -- this forum is then -- it's a regulator-only forum, covered by confidentiality commitments. And

it's a place where you can -- it's kind of like the equivalent of the safe-space idea.

It's a safe space for regulators to come together and really just like honestly say, hey, this is what we're thinking. This is what our issue is. Maybe we have some flexibility here. Maybe we can have some wiggle room and discuss things.

I think, you know, for pediatrics in general, there's a lot of rare disease overlap, as has been said earlier today, and neonatology as well. So it's not a neonatal-specific cluster, but we -- and FDA, like, we do have the neonatal consult group that somebody was talking about yesterday. I think it was Melissa.

And then we have our each individual review divisions within CDER or CBER that actually review neonatal applications. And the Pediatric Cluster and OPT is a place where we can pull all that together and have those discussions.

So I just briefly -- Shannon asked us to talk about practical things -- want to mention that

for, you know, things that we've done already and things that are helpful from the standpoint of the regulators when we're getting together to talk about these things.

I think the first thing I'm going to say is that I've been doing this for about five years now. I'm really impressed with how dedicated everybody is. Everybody really wants to, you know, just get to the best place possible to make these drug development programs work. So, there's a lot of really, really positive intention there.

I think with early pediatric submissions, early engagement of the regulatory agencies, sponsor transparency between FDA and EMA, all these things are things that sponsors can do to help us come to an earlier alignment on issues and help to come up with a pediatric drug development plan that's going to work for a rare population where the drug development is often global.

And then examples of areas that we've reached alignment at through the Pediatric Cluster

include just like this broad topic pediatric development plan. What should the timing be of the pediatric development plan? How far along should the adult program be before we start requiring pediatric studies?

What kind of borrowing can we do? Can we extrapolate? How similar is the disease? Is there a disease correlate? What kind of comparator -- that's also a big thing that we talk about -- would be regulatorily acceptable as well as feasible and practical?

In the oncology space, as Ralph had mentioned earlier, we have a lot of collaboration even outside of the Cluster. So then when we come to the Cluster, we see very mature discussions about well, could we tolerate a single label -- sorry -- a single-arm open-label study, or do we really need a comparator that's, like, you know, double-blind placebo controlled, or can we look at historical comparator, or can we look at a patient as their own comparator?

So, we have these discussions, and it's helpful when there's also other platforms where the, you know, scientific thoughts are being matured.

The other thing that -- other things that we talk about, as was mentioned earlier today, are endpoints, tools like patient-reported outcome measures, which as somebody said earlier and neonatology would be caregiver-outcome measures or clinician-reported outcome measures. You know, what kind of biomarkers seem like they could work? What degree of validation do they need to have before we can accept them from a regulatory standpoint?

So, these are kind of practical things that we've fleshed out and worked out at the Pediatric Cluster to help with providing alignment and harmonization from a regulatory standpoint on some of the global pediatric drug development plans that we've had discussed there.

And I'll stop there and hand it back over to you. I hope I didn't take too long.

DR. HAMRICK: No, not at all. That was

perfect. And I was just going to ask in your experience in the Cluster, and Ralph's as well, is -- has it, you know, what percentage of the time roughly do you reach alignment with the other regulatory agencies?

DR. ZAIDI: Oh. So this is a really hot-button question. This is very provocative, Shannon.

It's a really hard thing to measure alignment, and we've been through a bunch of different positions about that. And I think, you know, we've had this discussion at the Pediatric Cluster. To Ralph, I'd be very interested to hear your input.

But I think we've -- we kind of have come to a place where we realize that there are things that we can align on right now in this discussion, and there's things that we can align on in a few years, five years, ten years. And we need to hold workshops or we need to get together in other formats because the level of complexity, it just doesn't lend itself to a 20- to 25-minute discussion at the pediatric

cluster.

I would say that we have -- we say that we've reached alignment a lot. Like most of the time, our thinking is mostly aligned, but how does that translate to, like, specific advice that we give?

We're not giving identical advice. But there's a high degree of motivation both on EMA's part and FDA's part and any of the other regulatory agencies that have brought topics to us like Japan, PMDA. There's a lot of motivation to reach a place where something can work for both of us.

So, I have seen a lot of times where people are like, well -- I'll just give a really easy example. "Well, you know, we thought that we really shouldn't go below an age of, like, 8 years, but I hear you. You're saying 6 years, that works for your experience. Okay. If they submit 6-year-old data, we're not going to have a problem with that. Like, we'll take that."

So that's just a little example and I'll turn it to Ralph.

DR. BAX: Yeah. I -- I'm aligned. Yes. It's -- I mean, we have to bear in mind that we have different legislative backgrounds and also scientific potentially, you know, how phenotypes and conditions and local issues, which we might have to take into account, clinical standard of care sometimes.

You know, one geographical area might be more -- doing more aggressive clinical monitoring, taking biopsies, whereas the others are more relaxed and would be content with just imaging and things like that.

So, but I would say even then we will find a solution. Even then it will be complimentary. So, we will -- it will not lead to duplication of studies, but potentially you have to address some requests for that part of the world and others for the other part of the world.

So, overall, I believe it -- we are really here on a good way; and as Sarah said, if there are bigger discrepancies -- and often it's based, you

know, we can't just -- it's based on this background or try to explain -- I try to explain, then we indeed need a multi-stakeholder meeting and more scientific discussions to then come and to reflect them also than in regulatory decisions.

Thank you.

DR. HAMRICK: Thank you both. Those answers were full of hope, and I liked -- I like to hear that.

Well, I'm very interested to hear from our next two panelists. So, we're going to hear from the public-private partnership aspect with Klaus and C-Path and then facilitating organizations like Debra's RareCap.

And so the question for them is, if you could just describe the resources or the tools that you've developed in your organization and how that can help facilitate conduct of rare disease or neonatal trials.

So I'll let Debra go first if that's all right.

DR. REGIER: I'm happy to. So I'm going to be the one up here who spends most of their time as a clinician in the trenches a bit. And I quickly realized that if I look around this room and everyone on screen, 24 of you likely have a rare disease. Whether you know it or not, that's your decision.

And in our hospitals, in a pediatric hospital, about 40 percent of our inpatients have a rare disease. That means we have a workforce issue because there's not enough providers that know enough about rare diseases to provide the intricacies for rare disease.

Now, before I came here, I did a little bit of NICU research. Guess what? You have a workforce issue, too. We all agree on this. There's issues with having to have a level of expertise to even create what is the standard of care. And you have to have the workforce that understands that intricacies to figure out what the standard of care even is.

So, how do we approach this when we know pediatrics and rare disease and neonatology are all on the struggle bus right now for workforce? And let's be honest, it's going to get worse. So, how do I give hope like the last two people did into the future?

And I said, okay, we need to think about education. We need to think about how do we do this in a proactive way. How do we get ahead of this now?

And that's where a lot of my work comes from. I'll be blunt. I'm not a clinical trialist. I do educational outcomes research. I try to figure out how do we educate so that the next clinical trialist has what they need to be successful. I'm not the one doing it. I'm the one helping them do it.

I could be one clinical trialist or I could help a hundred. So, I decided to try helping a hundred. It's crazy, right? But it's fun.

So, what did we do? We said, okay, we need to figure out what is the standard of care; and can people in the trenches even do the standard of

care? How can we have a natural history if the standard of care isn't consistent? So that was one of our first issues.

And then we said, how do we help the people that are the experts interact on that standard of care if you only have one or two patients at each location and only one or two patients at each specialist at each location?

So, we had this crazy idea called RareCap, and it was this crazy concept where we all sat in a room and I would, as the educator said, I want to make sure we can educate through this. And Marshall Summar said, I, as the clinical trialist want to do clinical trials through this. And we all sat down and said, how do we do all of these things at once on one platform?

And that's where RareCap came from. It is this platform; it is hosted through REDCap at Vanderbilt. That's why it's called RareCap. We're not that creative.

And it is an up-and-running tool both

to help front-end clinicians with what is standard of care for rare and ultra-rare disorders. We currently have about 150 ultra-rare disorders on there. What is a standard of care for KBG syndrome? You guys have probably never even heard of KBG syndrome.

So, if you are in the emergency room staffing it and someone walks in, what do you do? It's a quick QR code that families can share saying this is down and dirty information on KBG syndrome. Specific medications that, yes, they're off-label, but it's all we've got.

The cool thing is if you have something on-label, it's also there because guess what? Your emergency room's never heard of those drugs either, right? And it's great if you can at least say this med is for this disease, and here's a link to how it's used or here's a link to something helpful for those frontline providers.

So why am I sitting in front of you? Well, what we realized was we had this great chat function, where people could log in as specialists and

say, "Actually, I don't agree with this protocol. We had bad outcomes with this med" or "We had good outcomes with this med" or "That dose is wrong."

And it kind of blew our minds being, like, wait a minute, in real time we can collect data. In real time, we can update these protocols, and in real time we can actually maybe do something crazy and move things forward.

So that's how it's evolved into this platform where we have the front-facing emergency medical treatment side of it, and we have the back end because of how it was all set up with Vanderbilt and RareCap, that we can have these chats happening behind the scenes.

So, you should see some of the dieticians that chat. Wow, they're -- wow. They got opinions. But it's great because it creates a venue where they can all have these conversations around what the protocols are and how they need to be updated or changed.

So why do -- why am I sitting here in

front of you? It's this idea of this is not federally funded work. This was funded by an educational grant from a for-profit pharmaceutical company who said, "We'll give you educational money." And I said, "Thank you. I will use educational money and we'll have a nice side product."

So, this idea of how do we use all of our resources together? Because rare is common, right? So how do we, you know, neonatology, guess what guys? Welcome to the rare world. You're rare. So just join us. Be in the mud with us. It's a great mud puddle. We have a really good time. So we're excited to have you with us.

And I laugh because I'm having flashbacks because I had a baby with An Massaro and Sarah Zaidi in the NICU. I remember this baby and I remember you said, "We've never done it that way before, but we should try it because we got nothing else."

And, An, you looked at me and said, "I've never used that much fluid on a baby ever. But

we don't have a choice. Let's do it."

So, this idea of doing things we've never done before in a different way because we don't have another choice, that -- that's 2026. That's where we are in rare. And to be blunt, that's where we are in neonatology too, I think.

DR. HAMRICK: Thank you, Debra. That was -- I love the idea of RareCap and especially it ties into practicality, right?

All right. Klaus.

DR. ROMERO: Okay. It's 2026. I want to build on that because I want to start by acknowledging anniversaries. FDA is having its 120th anniversary this year, and I think this is the time to really start moving the needle.

Another anniversary that took place two years ago in 2024, it was the 20th anniversary of the Critical Path Initiative document. That document has been updated, but even the original form of that document is so valid today as it was in 2004.

The FDA came out to the world and they

said, look everyone, this is not working. We have the mission. You have the mission to regulate the products. Industry has the mission to develop the products. Whose mission is it to make the process efficient for everyone? It can't be just an add-on to the FDA agreement. Individual companies shouldn't be taxed with trying to do that on their own.

So why don't we create public-private partnerships to work together and make the process efficient for everyone.

In 2005, we were established, the Critical Path Institute. It's in our mission to help FDA materialize the vision of the Critical Path Initiative. So with that, we launched on creating these public-private partnerships.

Something that was mentioned during the talks in the previous session was the endless song of either, "This cannot be done," "This cannot be done here," or "This has already been done." In 20 years of our existence, we've heard that song. We cover about 38 therapeutic areas. We've heard that song 38

times whenever we've gotten into such an area.

We certainly heard it when, actually, FDA approached us to create what Kanwaljit leads, which is the International Neonatal Consortium.

So, what have we been up to? Bringing everyone together into a neutral environment that has the legal infrastructure, the scientific infrastructure, and the regulatory infrastructure so that companies and regulators and patient advocacy groups can come together. And we diagnose what the actual unmet need is.

And this is a call to action for this group today. It's great that we have J&J. It's great that we have ReAlta, but we stand to bring in even more industry representation, especially because of the end of that title, Rare Disease Clinical Trials.

You said it best. Number one, neonate drug development is part of rare diseases. But, number two, rare diseases are not rare.

And so as part of connecting the dots, one of the biggest accomplishments of the neonatal

field has been the establishment of this database that has more than 300,000 individual patient records from hospital networks in the U.S., Canada, the U.K., other European countries, and Japan that we have put together into our data and analytics platform.

More than 300,000 individual records that have led to what Kanwaljit was presenting, understanding lab values, understanding disease progression for bronchopulmonary dysplasia.

The non-rare space keeps coming to us to learn how that was done. Michelle Campbell was mentioning neurodegeneration, what she leads within the Office of Neuroscience.

The Alzheimer's community and the Parkinson's community are applying all the learnings from the neonatal space to augment their rare -- their real-world databases. That's some major accomplishments, and we should be talking more about those victories that everybody's learning from the neonatal space.

But let's flip it. With Michelle, we

have a consortium that is dedicated in -- on Alzheimer's disease, and we've learned a lot about modeling trajectories of disease progression, variability, placebo effects, magnitude, onset, duration, variability, clinical trial simulation tools. We have disease modifying drugs for Alzheimer's disease, thanks to all that work. And we have more than 300,000 individual records in neonates.

One of the next steps -- and actually Gerri mentioned it just before we started -- we stand to generate digital twins in a -- at an industrial scale with those types of data, but not just for the sake of generating digital twins. It's for the sake of actually moving the needle in facilitating these clinical trials.

Especially because in the other session that -- where we talked about different innovative trial design methods, it's about evidence generation. Because the other piece of the statute that governs FDA is that the FDA is supposed to make decisions about the approval of medical products based on

well-designed scientific investigations.

I challenge anyone to just try to find the term randomized clinical trial in the statute. It's not there. And there's a reason for it not to be there because it's all about the evidence.

We're taught in regulatory science that there's four pillars for the approval of medical products. What's the clinical context? What's the totality of evidence? Full evidence, depending on if you love or not the term "totality of evidence." What's the remaining uncertainty? And what are the regulatory pathways?

Those four things apply every single time. So, depending on the context, you can generate a plan to generate evidence that can actually support decision-making.

You can understand what's the residual variability, and then you can decide if, from a public health stewardship standpoint, you can live with that remaining uncertainty and then define the regulatory pathway. It has been done. It is doable.

And the last piece is that we shouldn't be separating neonatology from rare diseases. And here's a big hook to bring more industry representation, ASOs, gene editing, gene therapies, all technologies that can be designed for ultra-personalized diseases where we understand the genetics.

There's a lot of investment on the part of pharma on those technologies, but because of the way we've parsed out medicine, a lot of those development groups in pharma don't have neonatologists.

They have the medical geneticists. They have the pediatric neurologist. They have, you know, you name it, for lysosomal diseases and for neurodevelopmental disorders, rare epilepsies, et cetera. The more you look at when to intervene, the earlier you need to go in the live sequence, and you go earlier and earlier and earlier up to the neonates.

A lot of those development leads in industry hear that, and they go, "Oh, my gosh. I need

to run a trial in neonates. How am I going to do that?" Well, we have a group of people here that what you guys know what to do is run trials in neonates all day long.

There's an opportunity to connect the dots there because if we offer to them that type of pathway for the expertise in not the, "Oh, this is the end of the world because I need to enroll neonates," but bring them over so that we -- I propose that we blur the lines why neonatology and the -- it's about providing the biggest benefit to people.

And if you need to intervene at the neonate stage, even if it -- if the neonates are not overtly sick at that stage, then great. Let's run how to generate the actionable evidence to have a totality of evidence discussion, understand what's the remaining uncertainty and make actionable decisions.

And then put that into context with the jurisdictions that govern every single regulatory agency. Because it -- I -- I'll tell you our experience in proposing all kinds of different drug

development tools, from biomarkers to surrogates to intermediate endpoints to new COAs, to PRO instruments, to clinical trial simulation tools, to disease progression models, to synthetic data generators, that have transformed a lot of areas.

In our experience, when we present those solutions to EMA, PMDA, or FDA, you peel the layers. We only see scientific agreement and alignment. But we cannot expect that scientific alignment to break the jurisdiction that governs each one of those agencies. We just need to adapt accordingly.

And there are ways to adapt to that. Just one example, "reasonably likely surrogate." Well, that's a great term because the statute provides FDA with the accelerator approval pathway. That doesn't exist in other places. So, we cannot be speaking about reasonably likely surrogate endpoints outside of what governs the FDA. So that -- it's just the context that is so important.

But then to close, 120 years of FDA, 22

years of the Critical Path Initiative, 21 years for us at C-Path. If we have been able to transform how drugs are developed and advanced in Alzheimer's disease, Friedreich's ataxia -- Ron is there -- Duchenne muscular dystrophy, tuberculosis, we can make this happen for neonates. And we need to move the needle. I'll leave it at that.

DR. HAMRICK: Thank you so much, Klaus. And it -- I think you bring up a great point about the restrictions that we are all governed by and, you know, perhaps the next session we'll get into this, but I think, you know, having a legislative assistant or somebody that's a direct conduit to those type of decision-makers is often needed in this room.

I have another question for the panelists, but I first wanted to see if we have any questions online or for the audience, because I know in the prior sessions, we haven't been able to get to those very often.

I am keeping track of time. I know everybody is eager to eat lunch soon. So let me see

what questions may come our way.

DR. MASSARO: Sure. There was one question I think would be quick for Gus if -- about whether genomic data will be included in the NRN database for use in risk stratification of infants using known pharmacogenomic variants in newborn drug studies? That was from Sash [ph] Kol [ph].

DR. SCHMIDT: Sure. Sure. Thanks, An. Currently, we don't routinely collect and do genomics analysis in the network, that we have a lot of interest, that we have a group of our investigators that actively look at incorporating genomics into studies.

Any future studies that involve genomics, the data will be available per NIH policy. So right now we don't have that. I think we all agree that that's a very important aspect of trials that we have to integrate, and we're working on that and it will be available when we do that in a study.

DR. HAMRICK: Gerri.

DR. BAER: Hi. Gerri Baer, FDA, CDER.

This question could be for any of the panelists. Debra spoke a little bit about practice variability and standard of care in rare diseases. And we know that there's a lot of practice variability in neonatology.

From a regulatory and scientific perspective, we always prefer some homogeneity in the trials so that we can, you know, detect if there's a signal for whatever we're testing. So, you know, we want homogeneity.

We, you know, one of the most frustrating experiences I've had as a regulator is looking at results of a trial and, you know, being told by a company and academic investigators that there was nothing they could do to harmonize the -- in this example, the clinicians weaning the ventilator support or the respiratory support. That that just couldn't be sort of harmonized.

And maybe it can't, but, you know, so this is what we hear from other stakeholders, like industry and clinical investigators, that it's

impossible to harmonize standards of care, to harmonize, you know, protocols; and maybe it's not feasible. Maybe it's not aligned with real-world practice, but that, you know, continues to introduce a lot of noise.

So, I'm wondering if anyone on the panel could speak to their experiences, kind of balancing these tensions. Do you have any good examples of how we can balance the tensions between feasibility and scientific clarity?

DR. ROMERO: Thank you, Gerri. That -- fantastic point. So I would challenge the notion that what we need is homogeneity. What we need is to understand what are the sources of heterogeneity

We were able to put together -- so in our data and analytics platform, we have close to 750,000 records from clinical trials from pharma that have been shared with us across 20-plus indications.

We've got the real-world data example from neonates. We've got the observational study examples in a number of indications from universities.

We put all those data together. Those are not buckets of data that cannot speak to each other. We make them talk to each other.

When we developed the first regulatory-endorsed clinical trial simulation tool, which was for Alzheimer's disease, we started with a database that was 2,200 patients, something like that. Now that database is more than 100,000 individuals.

We started with nine trials, 2,000-plus people. The level of heterogeneity across each one of those trials in some of the key variables, including the endpoints, was significant. And that was just a reality of the situation. When we integrate the data and we started generating those quantitative solutions, we were very transparent about the heterogeneity.

And there are a lot of methods for how to account for the individual variability that comes from each one of those trials. And these are highly, highly curated Phase 2 and Phase 3 trials that support regulatory submissions. That just gets amplified the

more you go into the real world.

But what we truly need -- I think that's one of the advantages of initiatives like RareCap -- is that you're able to -- we're not going to be dictating to people what they should do --

DR. REGIER: Just want to know what they do.

DR. ROMERO: -- but it's for them to document exactly what they do. That's exactly it.

Because that is what allows you to identify what are the sources of variability and quantify those sources of variability and then determine, okay, with the residual uncertainty, can I live with that in this context, or not? That's really where the money is going to be because that's what informs regulatory decisions.

Just -- there's an analysis that is going to be published later this year, but the same level of residual uncertainty between Type 1 diabetes prevention trials and Parkinson's trials, it -- as a quantity is pretty much the same, but the consequence

is very different because you can live with that residual uncertainty in Type 1 diabetes prevention way more than you can in Parkinson's disease. So the context really, really matters.

So that's been our experience area. I hope that answers that question.

DR. HAMRICK: Thank you. I think Gus has a comment.

DR. SCHMIDT: Yeah. If I could add to that. In -- with every trial within NRN, we are faced with a variability in practicing neonatology and whether that the interventions for the trial are feasible at the different sites. With 15 sites, we probably have 15 different ways of doing things often.

And I think the balance is a -- to achieve the balance is an ongoing discussion with the trial, and defining what the procedures are and trying to make it real applicable to the real world and to real practice that will be -- the results will be generalizable and balancing the biological reasoning and the -- of the intervention.

So, it's an ongoing balance with every single research question that we have, so that we can adapt and develop, actually develop, a trial in a way that will respect those differences, but still be able to get a meaningful answer to the question that we have.

And although we always reject the variability, we -- there's also a lot to learn within the variability. And in the network, we had the benchmarking study for BPD that looked at variations in care practice across all the centers and from that derived the best care practices that were later implemented to reduce the incidence of BPD.

So, there is something to be learned from the variability at the different centers in -- that practice, that take care of the population.

DR. HAMRICK: Great point. Thank you.

An, do we have other online questions?

DR. MASSARO: There's another question for Klaus. What can neonatal drug development community learn from other patient communities like

adult neuroscience. They've already done long ago some of what we were hoping to do in the neonatal space, biomarkers, surrogate endpoints, et cetera, so.

DR. ROMERO: Well, yeah, a ton. And thank you for that question. I mean, this is why I want to make sure that we de-silo things and that we don't get into this echo chamber of neonatology with neonatologists talking about neonatology with neonatologists.

That's great. And that -- and those spaces need to continue to exist just like in my field of internal medicine for adults and clinical pharmacology. We have our own echo chambers, and we nerd out on those echo chambers. But we need to get out of those, and we need to be speaking to the other disciplines and the decision-makers.

Importantly, the -- speaking about variability. A lot of those trials and other diseases are trials that span a very different timescale. The NICU context provides an amazing opportunity because a timescale is really, really compressed.

Alzheimer's, Parkinson's, rheumatoid arthritis, lupus, those timescales for those trials are insanely long. But you can run a trial for 15 years.

You need to have a notion of how to run a trial for one, two years and understand what's going to happen way later in life. We stand to have a really great impact in thinking in those terms in neonatology and the advantage that a short time span provides. That's one.

The second, the identification of the sources of variability and capturing those in a meaningful way as we collect real-world data and do observational studies and we do natural history studies.

I want to call on something that Ron was instrumental in making happen. He leads the Friedreich's ataxia community, and they invested on making sure that the data and the registry, the natural history data that they collected, was well thought out from the very beginning.

And when we partnered, we made sure that even to his credit, he had to go and reconsent some people to get some things realigned. But what that led to was, number one, the largest integrated database in Friedreich's ataxia, which we have the privilege to host.

But then importantly, a really cool example of what led to the first approval of the first disease modifying medication for Friedreich's ataxia by leveraging external controls based on the data.

That's a beautiful learning case for neonatology, but also what Kanwaljit was showing. This whole notion of what are the lab standard values in the NICU, you know, open question.

Well, what a fantastic opportunity to apply some really cutting-edge methods to figure that out because then my hope/prediction is that dosing methods that we end up developing to figure out the lab value constants in neonatology will prove the future for how to prove other types of lab value standards outside of neonatology that just prove to be

way more innovative than what we have today.

Just look at the story of cholesterol, clearly a sobering story of what -- in not having the lab values today is actually one of the best opportunities we have to do innovation, move the needle, and provide learnings to other fields. I hope that helps.

DR. HAMRICK: Thank you so much. I'm going to -- I -- we only have about ten more minutes, so I'm going to just do sort of a rapid question for the panelists here.

And I'll start this with the clinical trialists virtually. But when you've been involved in the conduct of a clinical trial, I would love to hear an example and of, you know, a specific challenge that you've had and then how you were able to address it.

And this can be something very simple, or this could be something complex, but if I could just hear an example from you two and if we have time, we'll move it open up to the other panelists. So we'll start with Rachel.

DR. GREENBERG: Thanks. I guess clinical trials are super easy, so we never see any challenges, right? It's hard to pick, right?

I do -- in thinking about your question, one thing that comes to mind is, I think, a lot of the challenges. You know, recruitment is always a challenge and keeping sites engaged and able to do the work, it can be a challenge.

One -- and is difficult, I think, in these times, I think, the -- to keep -- to have the resources at the site level to continue to have that, to continue maintain the expertise for people who know how to engage patients and parents and to just keep the operations going.

And so I think one -- and in our network, we don't have a substantial -- it -- it's really an open network. So there's not a -- sort of a base amount that sites get to participate.

Much of our network operations is based on cavitation and how much they enroll. So, one thing, one strategy, that we've used to address the challenge

of being able to support sites to continue to enroll in between trials, or when a trial is up and going, how do -- before you enroll, how do you get things started -- is by using the more master protocol studies or having a sort of a study that can be ongoing and that is flexible to be able to address multiple molecules or multiple problems that can be ongoing, so that sites kind of maintain an engagement and are able to continue their operations while they're waiting in between trials or while, you know, it's not possible to enroll in one trial, they have an opportunity to be still participating and engaged.

So, you know, I know other networks have studies or things -- kind of a basic study that can be used to, in this way, not only is it generating important information, but it serves an important function in the network.

For our network, that would be some of the platform trials that Danny Benjamin was mentioning, our opportunistic pharmacokinetic study or a breast milk study, where sites can be working on --

there's always new molecules that we're bringing into those studies.

And I think that's one way to kind of, to address that more logistical operational challenge, which, you know, is separate, I think, from a lot of the other challenges that have been discussed in terms of how do you design the trial, you know, the right outcomes and harmonization. But I think that is a real operational issue.

DR. HAMRICK: Thank you, Rachel. Very clever.

Gus.

DR. SCHMIDT: Sure. Thank you. Yesterday during the panel discussion, I think there were a lot of great discussion around the issues of consenting neonatology, which can be challenging, especially related to the acuity and the time limited amount of time that we have to often to consent to those families that are in a fragile situation with a critically ill infant.

And we've adopted different approaches

such as antenatal consents, which requires a lot of extra effort because unfortunately we cannot predict which babies will deliver early or within the time frame for the trial. But that's an approach that we've adopted to improve consent and increase recruitment to our studies.

Another challenge in neonatology that we've alluded to in the discussions and, unfortunately, we have not been able to solve yet, is the precision of our disease definitions. Especially if we think about BPD or necrotizing enterocolitis, those definitions are awfully imprecise.

And although our network and others we have adopted the specific definitions for those conditions and we've been able to achieve internal consistency, which is valuable, those definitions are still imperfect. And they may not always capture all the clinical important cases or the detail, the phenotypes within the diseases, that may have important short and long-term implications.

So, this is -- this creates a problem

for trial harmonization. It creates a problem to identifying clinical and meaningful outcomes within that disease. In the recruitment of patients, we're talking about diseases that are already rare and also if you look at subphenotypes of those diseases, those become even less common.

And part of the challenge is biological because those diseases exist on a spectrum. They have multiple phenotypes, and we can drop categorical boundaries, but those are really continuous variations of the same disease.

And on the practical side, we also need definitions that can be applied in the real-world settings. So we -- if we have a perfect definition, but that cannot be easily applied, that's not going to be helpful. So, it's a -- it's an ongoing balance of defining diseases in a way that we can be practical but also clinical and meaningful. And that's, I think, is a big challenge for trials in neonatology.

DR. HAMRICK: Thank you. So, yes, exactly right. And we need definitions that also

include the family perspective and what is meaningful to them.

Debra, did you have a comment, too?

DR. REGIER: So, I think one other piece of this that I think we forget is the moral dilemma or distress, whichever term you want to use, of being at the bedside with a patient and saying, how do I prioritize this patient but also realize I want to be involved in research to prioritize the next patient.

And I think that's a lot of where this dilemma and harmonization issue comes from, of I want to wean this vent because this baby's in front of me right now and I think I should wean the vent. And that didn't follow the protocol.

And I think until we kind of come out and say, this is going to be hard and we need to acknowledge that and we need to acknowledge that, you know, the families are in this with us. And it -- it's hard both sides of it.

And I don't know about anyone else in the room, but when I saw the SMA trial, my soul still

hurts every time I see those placebo kids. I almost want to cry that a third of the kids got the placebo in the SMA trial. And in my heart that just hurts; right?

And I know I'm looking at moms in the room. It hurts that a third of the kids got the placebo. And I think that's the real world, really, is how do we think outside the box so that we can still get the approval and yet either realize we're going to have this moral distress and this, you know, whatever we want to call it in response to this way we do research or we need to find new methods to do research in different ways.

DR. HAMRICK: Excellent comment. I think unless anybody else has something that they really would like to share, I think we can wrap it up on that note. Great.

DR. MASSARO: Thank you everyone for a wonderful morning. We are going to take a lunch break- well deserved by everybody. We'll have an hour and we'll reconvene at one o'clock. Thank you.

(Off the record.)

DR. MASSARO: We are going to go ahead and get started with our two panels this afternoon. This first panel is with our regulators from both FDA here in the room, and we have Ralph Bax back with us online from EMA.

So, in this discussion we'll be talking about the various programs and pathways and options we have for facilitating neonatal and rare disease drug development.

And our moderator is Cynthia Rothblum, and I'll let her -- Rothblum-Oviatt -- sorry. I'll let her introduce the panelists.

DR. ROTHBLUM-OVIATT: Thank you. So welcome back from lunch and welcome to Session 4, which is entitled Regulatory Landscape and Future Directions for Neonatal and Rare Disease Drug Development.

So we're going to start that session with this panel on the regulatory perspective, how expedited programs, incentive pathways, and other

regulatory initiatives can be leveraged for neonatal and rare disease drug development.

So as An said, I'm Cynthia Rothblum-Oviatt. I'm a Science Policy Analyst with the FDA Center for Drug Evaluation Research, or CDER, Rare Diseases team.

And for this panel I'm going to be joined by colleagues from both the European Medicines Agency, EMA, as well as the FDA.

And just to give you a little structure for our hour. Each panelist is going to introduce themselves and then briefly present some regulatory programs, pathways, initiatives that may be leveraged for neonatal and rare disease drug development.

Then we'll have some moderated discussion, Q and A, and we'll open it up from -- I do want to open it up for questions from the audience.

So, I'm happy to say that Ralph Bax is back with us for our panel.

And, Ralph, can you get us started with just a brief intro for yourself again for those who

might not have been at the last session and the info you'd like to share from EMA.

DR. BAX: Yes. I hope you all had a good lunch. It's evening here and best wishes from Amsterdam.

Yes. I'm Head of the Paediatric Medicines Office at the European Medicines Agency. I'm a trained pediatrician/neonatologist and joined already many years ago -- right? -- the pediatric team.

And here just wanted to highlight some programs or, let's say, the usual steps actually leading to marketing authorization and perhaps also then emphasizing on some take-home messages what we are mainly looking for.

So I try to make this boring topic a bit, at least a bit colorful, and separated it to Early Interaction, Foundation, Development Support, Acceleration, Marketing Authorization. What I didn't cover is the clinical trial application and clinical trial regulation because the specificity in Europe is

that this is done at national level, whereas it is coordinated at EMA using specific IT systems.

But we are also involving us more and more in aspects of how to perform clinical trials. So we recently had a workshop for assessors, for example, for pediatric clinical trials, getting them together because that was a little bit missing in our setup in Europe, getting them together as experts and discussing this important topic.

So this leads me to this early interaction where I have listed some points, innovation task force, academia briefings, and office for small or medium enterprises. And, in general, the importance of pre-submission meetings.

So, the ITF, so-called ITF meetings, they are very early and informal. So here developers would have a chance to come for a very informal dialogue to confront regulators of what is happening and start a dialogue specifically on innovative and complex developments.

It might still be underused, but, you

know, it is really a start of a journey and encouraged. And the same is actually for academic colleagues.

So, when I was at a -- one of the neonatal meetings in Europe last year, I was confronted with a situation that still a lot of clinicians and researchers perhaps lack understanding of the roles of regulators. So, apparently, we haven't done an optimal job yet. And that was specifically also in the neonatal field.

And that is why EMA is also supporting initiative by the -- which was kicked off -- and that was the so-called Lancet Commission on Neonatology, where actually clinicians, neonatologists, came together and have set up a policy paper to improve the situation of neonatology.

It starts even with the actual clinical setting and setting as a specialty across Europe. But then also touching upon drug development, which, obviously, is important also for us. Important for us also that the infrastructure as such and also the

clinical setting is strengthened in Europe.

So here we offer for academic colleagues to come to the Agency and to explain their goals and get a first insight and guidance, actually, where to go to next.

Similarly, the SME office, this is more established for, as I said, for more small enterprises, biotech companies, which, obviously, also dominate potentially the scene in neonatal drug development.

The foundation from a pediatric and orphan perspective is indeed the orphan designation and the pediatric regulation framework. So in Europe this is, often products are not exempt from the pediatric opportunities or requirements and obligations. And, therefore -- and these open up again as you know, other regulatory pathways like protocol assistance, scientific advice for orphan products, orphan-designated products.

And the pediatric investigation plan is mandatory for nearly all new products, even if they

might be developed for adults. And that is often seen as a hurdle because it is mandatory. It is binding. It can be changed via modifications. But this is, again, additional work and developers are indeed committing to this plan.

We see it more as an opportunity, as an opportunity, for example, to submit to FDA and to EMA the respective development plans at the same time, in order to get -- right? -- early, as it is foreseen, sort of pediatric scientific advice.

So, a scientific advice which covers the complete development of a product. So from nonclinical to formulation to clinical trials to methodologies, like, use of extrapolation, modeling and simulation and so on.

Realizing the hurdles and realizing that often we had to design plans which -- where not sufficient evidence was even available for planning purposes, we, last year, initiated this project pilot of a stepwise PIP, where in specific exceptional circumstances the developer can submit a plan even if

not all elements are yet known.

And this applies -- so we -- this is -- has been very much welcome. And first, you know, analysis about the submissions showed indeed that they are mainly pediatric-only conditions and mainly rare diseases where this approach has been applied for.

So it will most likely also be included in the future new pharma legislation where we are awaiting the text still.

The next column, as I mentioned, scientific advice. This is a bit also with the PIP a bit can be backwards-forward. So if, for example, specific methodological aspects need to be advised on, this would be mainly the area where one would go to. Pediatric-only scientific advice is also free of charge.

And then you can see also the initiatives of PRIME and accelerated assessment. So PRIME means mainly that the applicant gets a specific regulatory support, continuous regulatory support.

The problem is a little bit that it is

selective, that you need to show that you're covering an unmet need, and that there is a high potential that this can be met by this specific development.

So biologic plausibility, so often it is also -- it is an opportunity, but it is not guaranteed, so to say, in your planning that you will be awarded this scheme.

For the accelerated assessment, this is a reduction again of assessment time. This was mainly -- here, again, it's major public health issues to be addressed. So, an example would be, for example, the COVID-19 situation where this was used. So a complete package is needed. It needs to be ready and in order to apply for such an approach.

And, finally, conditional marketing authorization and marketing authorization under exceptional circumstances. So, the first would apply if it would be not beneficial to postpone further marketing authorization and waiting for additional data and thereby then requesting them on an ongoing basis.

So, there is an annual review, and it is used rather often also in the rare and neonatal space, where the marketing authorization and exceptional circumstances is more a situation where actually the full evidence might never be expected, so in ultra, ultra-rare diseases.

But this is then also expressed on the label and limitations could be in Europe with respect to HTA and payer decisions which then follow downstream.

And finally, the pediatric use marketing authorization. This is applicable for off-patent medicines. This is a scheme which has not been -- has not reached the success the legislator had hoped for.

Apparently, the protection is not sufficient and, again, often under this scheme, pediatric formulations, for example, are being developed. And then we have faced the situation that these indeed have been authorized, have been developed, and face problems with payment.

So, then hospitals would not be able -- reimbursement would not necessarily be able, so hospitals would perhaps further rely rather on extra contemporaneous formulations than using one which has been specifically authorized for use in the pediatric population.

I have missed here not only the clinical trials but also a column before the early interaction or extending the early interaction and then also one on the right-hand side for the future.

So on -- so for early interaction, here, I would include all the activities we have been referring to also in our previous session: working together with networks, supporting networks, supporting infrastructure, PPIs where increasingly now all relevant stakeholders, multi-stakeholder meetings, where all stakeholders are collaborating.

Also patients, patient representatives, in neonatology perhaps more, which ensures our way because regulators also need to learn. We all need to learn from each other -- to ensure that the evidence

is sufficient because without sufficient evidence all these other schemes wouldn't work.

And on the right, looking into the future, I already mentioned the NPL. Here we are awaiting the text, but potentially it could also include a mode of action approach for PIPs which might be interesting looking at developments for adult conditions where they might not exist in children and also in neonates. But where the mode of action might be interesting to look into and then potentially develop for a -- for the same mode of action but a different more relevant condition in children.

Another point is the biotech act, which will also improve and enhance investment into the clinical trial landscape. That is, obviously, not a regulatory pathway but also a policy which is intended to support the whole development landscape in pediatrics and neonatology.

And that was my fast review of some schemes we offer. Thank you.

DR. ROTHBLUM-OVIATT: Many thanks,

Ralph, for sharing all that great information on pathways offered by the EMA and for your perspectives in weaving in neonatology and rare disease.

Janet, would you like to kick us off with a brief intro of yourself and for the FDA?

DR. MAYNARD: Thank you very much, Cynthia.

So I am Janet Maynard. I am the Director of the Office of Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine. I'm a rheumatologist by training, which I mentioned because in rheumatology we've seen so much important therapeutic development.

And as a rheumatologist I think it just sort of helps emphasize sort of a theme that we are hearing today, which is having safe and effective treatment options available for patients and sort of intervening early in a condition is so important so that we can really help change the trajectory of the disease.

But today I'm going to be focusing on

FDA's expedited programs for serious conditions, and I will be presenting this with Dr. Najat Bouchkouj. And we thought it was important to sort of split up and present this together because it really highlights the synergy and collaboration between the Center for Drug Evaluation and Research and the Center for Biologic Evaluation and Research because these programs are really relevant to both Centers and to the development of both drugs and biologics.

So, FDA's expedited programs are really intended to facilitate and expedite the development and review of drugs and biologics that are for serious or life-threatening conditions that address unmet needs.

So, the first program I wanted to mention is Priority Review. So Priority Review offers a shorter review clock of -- for marketing applications. And in a Priority Review, this is for applications where if approved, the drug could be a significant improvement in safety or effectiveness over existing therapies.

And the second expedited program I wanted to mention is Accelerated Approval. And we've heard some mentions of that over the last two days. So this is when there's an approval based on an effect on a surrogate endpoint or an intermediate clinical endpoint that's reasonably likely to predict clinical benefit.

And it's important to note that these drugs provide a meaningful advantage over existing therapies, and that FDA requires post-approval confirmatory trials to verify these clinical benefits.

The third program is Fast Track Designation, and this is when nonclinical or clinical data demonstrate the potential to address unmet medical need. And it offers actions to expedite the development and review of a product, such as having meetings with FDA.

There's also the option for Ruling Review and eligibility for Priority Review if the criteria are met.

And the fourth program I'd like to

highlight is Breakthrough Therapy Designation. And this is when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint over available therapies.

And Breakthrough Therapy Designation offers intense guidance and organizational commitment, the option for Rolling Review, and other important actions that really help expedite the review of products.

So those are the four programs that I wanted to highlight; and now I'm going to hand it over to my colleague Najat from CBER to take it over to emphasize some additional expedited programs.

DR. BOUCHKOUJ: Thank you, Janet.

So as mentioned, my name is Najat Bouchkouj, and I am the Associate Director for Pediatrics within the Office of Therapeutic Products at the Center for Biologics, CBER. I am a pediatric hematologist/oncologist by training, and I've been in the FDA since 2016.

So I'll be happy to just build upon the programs, the expedited programs, that Janet had just mentioned and discuss a program that's specific to CBER, which is called the Regenerative Medicine Advanced Therapy designation or RMAT designation.

And this is a program that is designated for regenerative medicines, which includes cell and gene therapies. The products must be regenerative medicine that provide preliminary clinical evidence indicating the potential to address an unmet medical need.

The statute addresses flexible approaches in the post-approval setting in terms of how to satisfy post-marketing applications. The program does include all of the features that the Fast Track and Breakthrough Designations have.

Can you hit next, please?

So next, I would like to discuss some of the programs that support rare disease drug developments, including neonates in small populations.

So, the first is the Rare Disease

Endpoint Advanced pilot program, or the RDEA, which is a collaborative mechanism for sponsors to work with us, the FDA, on establishing novel efficacy endpoint developments.

The sponsors can have up to four meetings with the FDA. It advances rare disease drug development programs in general.

The second program I wanted to highlight is the Support for Clinical Trials Advancing Rare Disease Therapeutics, or the START pilot program, which is designed for CBER and CDER products together. And it provides additional support mechanisms for rare disease drug developments, interactions with the Agency.

The selected participants must have access to frequent and advise FDA staff from the -- within the FDA and address several issues during the development program. It can range from identifying the correct patient population, leveraging clinical and other nonclinical information and product characteristics in terms of furthering the -- these

programs.

And then the last that I wanted to mention is the Rare Disease Evidence Principles or RDEP, which is also another program that facilitates approval of drugs and biologics for rare diseases with very small patient population.

It does address -- addresses conditions that have significant unmet medical need as mentioned with the other programs. And this one is for diseases that have known genetic defects, that is the major driver of the pathophysiology of the disease.

So I'll just end here, and I don't know if, Cynthia, you have any questions for us?

DR. ROTHBLUM-OVIATT: Not at the moment because we're not done yet. It's coming. So thank you very much, Janet and Najat. That's great.

And Erika?

DR. TORJUSEN: Yes. Thank you so much, Cynthia. So it's great to be here. I'm really excited. I'm actually here from the Office of Orphan Products Development. So my name is Erika Torjusen,

and I oversee three of the programs here in OOPD, in the Office of the Commissioner, namely the Rare Pediatric Disease Designation Program, the Humanitarian Use Device Designation Program, and the Pediatric Device Consortia Grants Program. It's a mouthful.

But I have to say that -- so I'm a pediatrician by training. I subspecialized in allergy immunology. So, meetings like this warm my heart. So a big thank you to OPT for putting this on.

So, I have the benefit of working in the Office of Orphan Products Development. It's -- their mission is something that, you know, every day it's great to come to work because we're really trying to facilitate the development of products for rare diseases.

And as I said, I'm a pediatrician by training, so I get to work on a few programs that have some pediatric focus, which is really exciting.

So, we do have three different designation programs on this slide that are noted

here. And we also have four grant programs.

And if you could just click next. Perfect.

So those programs that are highlighted in red, actually, have some specific focus for pediatric patients, which I think is really important and great and relevant for this meeting today. So I'm going to give you a really quick overview of these programs. I know we're probably short on time so I'll go quickly.

So the first one is the Orphan Drug Designation Program. That is our largest program. We see over 700 designation requests each year. The main requirements are really looking that the product is going to be treating something that's rare.

So all of these programs, if I don't say it, they're all for things that are rare but were -- except, actually, for PDC, I apologize. I misspoke. But everything but PDC is really focused on rare diseases.

And then the other thing you need is

really scientific rationale for the product; and for those products that are designated, they're ultimately potentially eligible for tax credits, exclusivity, and potential waiver of their marketing user fee.

The next program we have is the Rare Pediatric Disease Designation Program. And, again, this meeting was well timed because the RPD Program was actually beginning to sunset, and it required -- it is not a permanent program. A lot of our programs are permanent, but the RPD Program requires reauthorization. So, we were beginning to sunset, and we were waiting to see what Congress was going to do and happily -- I believe it was Tuesday -- they just reauthorized the program.

So, it is -- yes, exactly. Very exciting. So, it is reauthorized through 2029, September 30, 2029. So that is exciting news.

So, we really learned a lot from the Orphan Drug Designation Program, and we built upon that and that's how the RPD Program really came into existence. It's -- it takes a lot of the same

paradigms but makes it pediatric focused, which is really exciting because a lot of times you see for pediatrics, we'll build a program for adults and expect it to work in kids; and it doesn't always do that.

So the RPD Program is specific for children and it's something that we actually have a joint review with the Office of Pediatric Therapeutics. So, we work collaboratively with them on this particular program.

And what's interesting is, so, yes, you do need to be rare. You need to be for a rare disease; you do need scientific rationale, but you also need to show that the disease has serious and life-threatening manifestations that primarily affect individuals from birth to 18 years of age. And application -- or for the designation requests that we receive, once they're designated, those are eligible for a Priority Review Voucher.

So they submit those requests with their marketing application. Designation does not

guarantee that you're going to be eligible for the voucher. They're separate criteria. But certainly these -- this is one of, kind of, the hallmarks that you sort of get through and then you're potentially eligible.

And I know Dr. Maynard actually already went through what a priority review is, but basically it shortens the review clock. So if they are awarded a voucher for that rare pediatric disease product application, they can use the voucher for a subsequent product. It doesn't have to be for a rare disease.

They can use it to shorten that review time from what would normally be about 10 months to about six months. So that's very exciting that this is reauthorized.

Next one is the Humanitarian Use Device Designation Program. I know we're not talking about devices very much today, but I just wanted to highlight it because the other two programs are specific for biologics and drugs.

And this is really another designation

program that's specific for devices. And we do have a specific pediatric provision, where we look at the pediatric population as a unique and distinct population. So certainly when you're looking at whether something is, in fact, rare, when you're able to really reduce the size of the population by looking only at pediatrics, that certainly can serve as an incentive to encourage pediatric medical device development.

And so for those applications, they would come in and if they're designated, they're eligible for a different marketing pathway, which is the HDE, the Humanitarian Device Exemption pathway. And that's with CDRH and CBER.

And moving on quickly to our grants program. So the Clinical Trials Grant Program, that's again focused on rare diseases, and it's our largest program really. They get a bulk of the funding out of all of our grants. So it's usually around $17 million but it can fluctuate and they're funding over 80 studies at this time.

Next is the Pediatric Device Consortia Grant Program. So that's, again, that's focused on devices. But I think what's important here is that it's a pediatric-focused program. It is a consortia, so it's not funding a clinical trial.

It -- they, Consortia, we have five different geographically dispersed sites and they provide wraparound services for innovators who are working in the pediatric space. Also conduct real-world evidence studies, provide direct device funding, connect with venture capital. So, a lot of really great movement in that space.

Next is our Natural History Grant Program. That's a smaller program but it's certainly very important, focused on the natural history of these rare diseases, hoping to inform different clinical trial designs, endpoints, et cetera.

And our newest grant program is the Rare Neurodegenerative Disease Grant Program. As the title implies, it is focused on neurodegenerative diseases, and that is one of our newest programs.

So I'm going to stop there in the interest of time, but certainly that webpage there has additional information. You can look at all of the different programs that we have if you want more detailed information. Thank you so much.

DR. ROTHBLUM-OVIATT: That's excellent. Thank you so much, Erika.

And last, but by no means least, Amy.

MS. COMSTOCK RICK: Thanks, Cynthia. As Cynthia said, Amy Comstock Rick. I'm the Director of the Rare Disease Innovation Hub, which is both CDER and CBER.

For those of you who don't know -- there are some new faces, at least to me, in the room here -- the Hub was launched in the fall of 2024, so it's about a year and a half old now.

And the mission of the Hub was, as you see on the slide, to create a focal point that will further enhance the synergy between CBER and CDER and strengthen the collaborations across FDA to accelerate development of rare disease therapies, especially

those with smaller populations.

And to put mission language sentence into support, bring it to life, the Hub really has two areas of focus.

One is to promote and enhance the synergy between CDER and CBER in collaboration and consistency. And the other is to engage in a new way with external stakeholders in a way that is separate from product development, and I -- and review.

I think that's really important that the Hub focuses at a bigger picture on consistency, collaboration, communication.

But because we don't get involved at all, and we're quite strict about this -- Janet and Najat can confirm that -- we really can have conversations one-on-one or in bigger, larger settings like this about policy or process areas that -- where there may be questions or concerns. And really there's no -- it's not tied to a particular product.

I have to say, given the excellent presentations that came before me, one question you

might have is why do you need to enhance collaboration between CDER and CBER because there's so much going on already and that's -- it's very impressive.

But -- so I'll take a moment to say that there's amazing things going on between CDER and CBER, but with the wealth of products and product categories and programs and diseases, you know, as we all know how many rare, 10,000 rare diseases, there's always room for more collaboration and more consistency.

And when the idea for the Hub was created, FDA actually had 18 rare disease programs, each of which pretty much grew up on its own, was needed to -- established to address a particular concern or problem or opportunity.

And I think the thinking at the time -- I was brought in for the Hub so was not part of these conversations -- but I certainly have been told the thinking at the time was rare disease therapy development had evolved so positively within FDA that it was at a point where we needed to think about more

aggressively linking them together in external presentations.

So that is where the Hub comes in. It's important again to emphasize that the Hub's emphasis really is on some of the smaller rare disease populations where traditionally two adequate and well-controlled investigations is infeasible if -- and if -- you know if not really quite difficult at least to be randomized.

The HUB's goals, really, goal one, is to further advance regulatory science of rare disease therapies. We've implemented that goal primarily with the launch of a program you heard about this morning, RISE workshops, Rare Disease Innovation Exploration -- no, Innovation, Science and Exploration. We had to have a pithy name like RISE and it stuck. People -- yep.

But you heard mentioned this morning the concern -- I think Allyson raised it -- about data sharing. So this is where I will give an -- same plug, our program RISE workshop, the third workshop,

is on March 30th and is on data sharing. And so we're really excited about that. That's a hybrid program. So it will be in-person opportunities in D.C. and then of course online.

The RISE workshops are intended to be scientific workshops with heavy engagement between the stakeholders and as a learning opportunity for everyone, including FDA, to bring back and see what did we learn from this, what can we do differently?

The RISE workshops in intent and design are to be -- generate information that can be acted upon. RISE workshops are well attended and it's even -- tend to be fairly evenly spaced. A heavy industry attendance, heavy FDA attendance, and stakeholder, patient, and disease organizations.

I will also add that the -- we have an open Federal Register docket to receive proposals for areas that anyone in the rare disease community thinks needs attention from a RISE workshop. We particularly encourage proposals that address issues that are common to more than one disease or class of diseases.

Just -- we're looking for ideas that may have greater applicability but not such great applicability that it's not specific. So there's that perfect sweet spot, that we've -- many people, you know, figure that out, and we've had some good topics.

The first two were external and internal controls when -- on clinical trials when the populations are particularly small. And the second one was on individualized therapies.

The Hub's second goal focuses very internally on enhancing. And based on what I said before, you know that it is truly to enhance the coordination between the medical product Centers with a particular focus on CDER and CBER.

For that goal, we have created a council where vexing, if you will -- that's my word, not what's in our agenda -- challenges can -- will bring both Centers together to have really meaty, in-depth conversations across the Centers to both learn from each -- on a particular disease or design, innovative design, but a -- something that each of

them is do -- dealing with at that time.

And to share information as well as to learn from each other with a goal, of course, of consistency. I do want to add here because consistency, which if one feels they don't have consistency, can lead to uncertainty, which is not great for therapy development.

One of the things that I've observed in the year and a half that I've been in this position is consistency. Seeming inconsistency does not always mean it isn't scientifically justified.

So perception of inconsistency, I sometimes have learned, is a need for more explanation or understanding of the topic because let's face it, the two Centers deal with different product categories and they -- the particular drug, you know, the products can be very different.

The patient population -- you're treating same disease, but the subpopulation could be very different and that what is sometimes perceived as inconsistency between the two Centers, in fact, has a

scientific justification.

So I'm going to take a moment to put in a plug for making sure that if you believe there's an inconsistency to not stop there and be frustrated, but instead to explore it either with your colleagues or reach out to FDA because we all understand that that arbitrary inconsistency is not okay with anybody.

Moving on more quickly, our third goal is to create a centralized point of contact for external partners. I will be completely honest. That language has always frustrated me a little bit because it can imply to some people sole point of contact, and that is not the intention of the Hub at all.

But that means more that -- but I didn't write it. I wasn't here yet, so. The -- but really more the -- what I talked about is trying to bridge the many rare disease programs, excellent rare disease programs across FDA.

For the purposes of this program, I'd say that what we look for, for Hub work is opportunities where we can, again, separate from a

particular product, bridge the interests of this community. I deal a lot with the external stakeholders, bridge concerns, and create opportunities for better understanding of what FDA is doing.

The Rare Disease Evidence Principles that we just mentioned earlier is actually a pretty good example of the work Hub can and might do. The Hub facilitated those conversations between CDER and CBER and the Commissioner's office and all the players around the table.

But that document is really -- it is a document that creates greater assurance to drug developers and patient/community that the authority and flexibility that FDA has within its drug review, drug and biologic reviews, will be -- will be used and considered, not necessarily guaranteeing approval, but used and considered in review, particularly in the cases as was mentioned with ultra small certain criteria populations.

Because the Agency knows that turning

their back on that population simply because it's so small and imposing what is more traditional, substantial evidence for a drug review is infeasible.

So, it really was an assurance document that what we already legally can consider in a review, we absolutely will for these smaller populations. So that's a good example of what the Hub tries to do on a day-to-day basis.

So, I will stop there and leave time for questions. I think we're actually on schedule.

DR. ROTHBLUM-OVIATT: We're doing, pretty good. Thank you.

MS. COMSTOCK RICK: Thank you.

DR. ROTHBLUM-OVIATT: That was excellent. Thanks so much.

So, at this point I do have questions for the panel, but I do want to take the opportunity to open it up to the audience now who's in person and perhaps online if anybody has any questions for the panel at this point. And if not, I will proceed with mine.

Sure.

UNIDENTIFIED SPEAKER: Are the -- those -- the RISE Workshop, like the very first one, are those notes or are those, is there any material that came out of that if we missed that?

MS. COMSTOCK RICK: Oh, sure. That -- and thank you for asking. I neglected to include that. The RISE workshops are facilitated by the Duke-Margolis Institute for Health Policy and the -- there's a summary and a video of the first RISE workshop on internal and external controls. And the summary can be found on the Duke-Margolis website as well as a link to the video.

The -- I don't know about the video for the second RISE workshop. Someone else may know whether that's up yet, but if it isn't up, it's very soon. And the -- also the written summary for that will be very soon.

I completely agree. We've all been to meetings where if you weren't there, I guess it didn't happen for you and that's right. Yeah.

DR. MASSARO: A follow-up. There was also this -- a similar question online about the March RISE workshop. So that's also on the Duke-Margolis website and the link. It was on the slide, and we'll have one at the end as well for those who are looking for that.

MS. COMSTOCK RICK: And registration is open and the word RISE, all caps, is in every title. We kind of have a contest in our team of -- for the next upcoming RISE workshops, what do we title it to get RISE in the name. It's getting harder.

UNIDENTIFIED SPEAKER: That sounds like a lot of fun. I would love to be part of that competition.

Quick question about the START Program. Has that opened up to additional indications? I know that was a small group of indications where you had to apply and have an open IND and it was limited. And we have an open IND as a non-profit to for-profit. We'd be perfect for this Program. Is there a plan to open that up again to newer indications?

DR. BOUCHKOUJ: Yeah. Maybe I can take that.

So, yes, the Program actually is open, and you are welcome to discuss with the particular division where the IND is hosted, whether it's within CBER or CDER. You can communicate with the review team and through dialogue then the, you know, the decision can be made whether it qualifies for the START or not.

UNIDENTIFIED SPEAKER: Oh, amazing.

DR. BOUCHKOUJ: But it is still open and accepting applications.

UNIDENTIFIED SPEAKER: Great.

MR. BARTEK: Just a quick follow-up on what you've all said, including our EMA colleague about collaboration between the orphan product efforts here in the Hub and the EMA's.

In terms of the kinds of flexibilities that have been manifest in both agencies in terms of pediatric inclusion at earlier and earlier stage, I'm wondering how frequent are your communications in this

dialogue so as to keep up.

We all know that the policies, the thinking here at the FDA, is pretty frequently evolving and in a very positive direction from the perspective of a rare disease advocate.

I'm wondering how frequent or do you think the collaborative efforts between the FDA and the EMA are sufficiently frequent so that the evolution takes place in both agencies at roughly the same time?

DR. ROTHBLUM-OVIATT: Ralph, did you want to address this and then maybe someone in person?

DR. BAX: I would defer to my FDA colleagues because, yes, indeed we have several clusters. We also have an Orphan Cluster. But they will be able to report much better on the frequency, how often they happen, because there's a little bit of a separation between the Pediatric Cluster and the Orphan Cluster.

But, in general, as -- at EMA, the pediatric investigation plans also cover orphan

diseases. We sort of in the pediatric space cover also this aspect, but I would defer to FDA colleagues specifically for the Orphan Cluster. Thank you.

DR. ROTHBLUM-OVIATT: Thanks, Ralph. So anybody?

DR. TORJUSEN: So, thank you for the question. I wanted to say that, you know, just on a high level, we do certainly -- and I think we even heard during the course of this meeting -- that there are various Cluster meetings that we have with the EMA. So various offices are all meeting with the EMA on a regular basis with regularly scheduled calls.

I might get the consistency off a little bit. I think it's at least monthly from what I recall. So we are having regular -- regularly scheduled meetings with the EMA to discuss issues to really make sure that we understand where they are and they understand where we are. So those collaborations are happening in real time.

MS. COMSTOCK RICK: I actually, I want to follow up, Ron, on the -- your use of the word

"evolving." My answer is not about EMA/FDA, but within the U.S. community of sponsors, patient organizations, and the regulatory agency.

I -- FDA is evolving. We heard Michelle Campbell use that word herself this morning. And another thing that I've observed in the -- because I've met with probably 75 to 100 companies since I came to FDA to hear about their concerns.

And something that has been very clear to me is that, yes, science is evolving. FDA is appropriately evolving as well. We all are evolving, we hope -- right? -- all the time. And there is a responsibility in my view for clinician sponsors to understand that FDA is, in fact, always growing and evolving.

And I hear -- to the point that I'm trying to think of what program we can do to address this -- sponsors say, "Well, you turned it down," or "You didn't like the idea five years ago," or "Well, my colleague said in another company says, 'FDA won't.'"

And I, most times when I'm out speaking, I fairly try to weave this in to say, please don't make assumptions about what the February 6, 2026, FDA will do. FDA is learning, growing, based on innovation all the time; and it's -- really hurts the rare disease community, the neonatal community, if you aren't trying as hard as FDA is to see what's next, to see what's possible and asking and telling them your novel idea and asking.

But don't make assumptions that are against where you think scientifically you can go for your patient populations because that's not doing them any good, especially when you might have missed a positive answer. That's the advocate in me.

DR. MAYNARD: And just to build on everything that's been said. I think we really, all of us up here -- I'll speak for all of us -- really appreciate these sorts of opportunities when we get to hear directly from stakeholders in the rare disease and neonatal drug development space to really understand the challenges that are being faced and we

can all work together to think of sort of potential solutions.

And as Amy mentioned, you know we're always trying to think of new ways to support drug development to ensure that we have safe and effective products available for patients.

And I know there was a specific question about START. I just wanted to clarify for CDER products, we aren't currently accepting new applicants to the START Program, but we are actively working with folks in the START Program who are already accepted.

And I'm going to turn to Cynthia if she doesn't mind offering, too, like the ARC email address for folks. Because if you have a specific question, like if you are a drug developer, you have questions about specific programs and if they are relevant to you, we really invite you to send us an email, but I'll make sure Cynthia says the correct email address if people have a question that they want -- or maybe we can put it up afterwards. Yeah. Maybe that'd be

great.

But, yes, also on the ARC and the CDER ARC website there's information and links and ways to contact us about a -- if you have a product in CDER. And we are happy to address those questions.

Or as Amy mentioned, the Hub can also serve as a central point of contact because I know sometimes it's unclear where is the best way to send your questions, should it be CDER or CBER or maybe it spans the center.

So, we're happy to try and get you to the right place and there's lots of different ways to connect with us. So thank you.

DR. ROTHBLUM-OVIATT: Thank you, Janet. So I know our, the ARC email address has a underscore in it, so it might be ARC underscore -- thank you. Thank you.

So, any other questions from -- we do have a little time so I can ask some questions of the panelists, but I just want to make sure there's nothing else from online or in person before I do.

Okay. So actually, Najat, you kind of read my mind a little bit because I did want to ask you a question, and it's kind of a two-parter.

But one of the most challenging aspects of gene therapy development is that post-approval landscape. So can you share with us about how to conduct confirmatory trials or long-term safety monitoring for a one-time treatment in a rare population.

And then the second part is, what flexible approaches is CBER considering for those post-approval requirements under programs that were mentioned like RMAT and Accelerated Approval?

DR. BOUCHKOUJ: Sure. Thanks. And that's a great question.

As we heard before and Amy just mentioned, yeah, there are certain differences between drugs and biologics. Cell and gene therapy products are unique, complex. They're not -- unlike small molecules and drugs, they involve complex manufacturing. Clinical, nonclinical data might be

different between the two.

And, therefore, in the rare disease framework -- and when we talk about pediatric populations, neonates, small populations where the standard randomized controlled trial might not be feasible -- we discuss several pathways on how you get the drug approved.

And, also, after approval -- we actually had -- we held a session back in 2023 that was mainly focused on a patient listening session, hearing from the patients themselves post-approval, what are the methods and approaches that the patient community, patient advocates, are willing to accept or -- in terms of their post-approval monitoring for efficacy or safety.

And we just recently published a guidance building up on that patient, you know, public meeting.

There are several approaches, I would say, that demonstrate regulatory flexibilities, especially that we have within our office in OTP, the

reliance on real-world evidence and real-world data to satisfy post-marketing requirements to demonstrate the durability of response, for example.

And the second approach, I would say, may -- the patient registries, they can be very helpful in providing critical information in the post-approval setting in terms of safety or efficacy follow-up post-approval.

And then most importantly, decentralized clinical trials or decentralized collection of data post-approval is very critical because it's going to retain patient follow-up post-approval, especially in the long-term follow-up where there's concerns, for example, for malignancies that can occur after cell and gene therapy trials or treatment.

So and, of course, the RMAT as we discussed before, it allows for some flexibility in the post-approval setting and discussions of what is the appropriate setting for confirmative trials and selection of specific endpoints that could be helpful

in the post-marketing setting.

I hope that answers your question -- and then I would just -- one thing I would just say that I would really advocate for early communications with the FDA.

Don't wait until the product is approved and then talk about the post-marketing requirements or what -- how can we satisfy long-term follow-ups or -- so just early communications at the stage of the IND, pre-IND, and then during the marketing application review. Those discussions are very helpful to happen early and frequent enough.

DR. ROTHBLUM-OVIATT: Janet?

DR. MAYNARD: Yeah. I just -- I really liked what Najat said, and I was just going to add that I think you highlight the importance of also having patient and caregiver input.

That that's also an important way to really expedite development, to make sure that we're really listening to patients and families about considerations related to clinical trial design and

what is meaningful; that that is really critical and is critical throughout drug development.

So, we need to really start from the very beginning when we're thinking about what a clinical trial might look like to designing what is the endpoint that we're going to focus on in a trial. And so that I think is a very important aspect of drug development.

DR. ROTHBLUM-OVIATT: Thanks, Janet. So I want to follow up, I think with both, but, Najat, did you have anything else to add about exact -- what sponsors should be thinking about their post-approval commitments in the earliest stages of development?

DR. BOUCHKOUJ: I would just reiterate that really just come and talk to us. Benefit from all of the programs that we highlighted. We have several expedited programs. We do have a lot of incentive programs that would help expediting the product developments within each office.

So come and talk to us early and often and take advantage of all of these programs that are

there.

I would also want to just highlight one approach that we often use within our Center is the reliance on extrapolation.

And there, you know, there is, as you might know, the ICH E11 guidance on extrapolation, where you can borrow some of the efficacy and safety data from certain population, whether it's adults to pediatrics or from pediatric populations from one age group to the other, which can help promoting the drug development for neonatal patients, where clinical trials or the patient population might not always be available to be included in clinical trial.

So just, you know, use that tool also of extrapolation when you design your clinical trials for approval of the products.

DR. ROTHBLUM-OVIATT: Thank you. Thank you, Najat. Good information. And we are at a hard stop, I think, unfortunately, because it is two o'clock.

Thanks to everybody on the panel.

Thank you for the organizers for having us.

DR. MASSARO: That was fantastic. Thank you all so much. We are just going to swap out our panelists here. And while those folks are coming up to the stage, I'll just introduce our next panel, which will be our kind of closeout panel with our multi-stakeholder panelists to kind of talk about their reflections on hearing the discussion over the last day and a half, lessons learned, gaps, and future directions.

So we have our esteemed moderator here, Gerri Baer, from CDER, who's also a neonatologist who will be leading this discussion.

So we'll get everyone up here and get started.

DR. BAER: Good afternoon. If folks in the room want to stand up and stretch. We are the last panel. We're not the last session. Dr. Yao will bring up the caboose with the final comments, but we're the last panel. And so folks, you know, you're probably, most of the blood is in your intestines, in

your --

So let me just do a very quick introduction of our excellent panelists. Our panel is entitled "Stakeholder Perspective: Lessons Learned, Gaps and Future Directions."

I would posit that we focus mostly on lessons learned and future directions because we know all the gaps. We've talked about all the gaps; there's gaps everywhere. So we'll hopefully be able to focus mostly on lessons learned and future directions.

So next to me is Yuliya Yasinskaya; she is a Deputy Director for the Division of Rare Disease and Medical Genetics in CDER. And she is a pediatric infectious disease physician who has been involved in a lot of pediatric drug development for products that are intended to treat bacterial, fungal, and parasitic infections, and now inborn errors of metabolism.

We have Dr. Ann Poduri, who is a researcher at Boston Children's in the -- and her research is into the genetic causes of epilepsy. She

sees patients with epilepsy and neurogenetic conditions and mentors physicians and scientists.

She also spent some time at the NIH at NINDS as a Deputy Director not too long ago. We're happy to have her.

And then next to her is Dr. Susan McCune. I asked Susie for her bio, and at the top of it she wrote "really old." I beg to differ. I mean, it's all in your mind, Susie.

Susie is a pediatrician and neonatologist who spent several decades as a clinician and researcher at D.C. Children's, Hopkins, and NIH, looking at the molecular biology of receptors in the brain during brain development and brain injury.

She also spent 18 years after that at the FDA in both OCTAP, which was some prehistoric office, OTS in CDER, and then as Director of OPT, after which time she spent several years at PPD Thermo Fisher, which is a CRO, and is currently an Executive Principal, Medical Consultant, at Scendea, a consulting firm specializing in strategic regulatory

consulting.

Next to Susie is Dr. Antonello Pileggi, who is a Program Officer and the Associate Branch Chief of the Obstetrics and Pediatric Pharmacology and Therapeutics branch at the NICHD. And he has a lot of research expertise.

And then next to Dr. Pileggi is Ron Bartek, who is the Co-founder and President of the Friedreich's Ataxia Research Alliance. He has been the president and director of about 15 different organizations that are focused on rare diseases, improving treatments, stronger FDA. He's been recognized as the -- as a hero, changing lives of rare disease patients by the FDA Office of Orphan Product Development.

And his professional life prior to this was spent in defense foreign policy and intelligence for the federal government.

And then at the very end, we have Betsy Pilon, who is the Director and Founder of Hope for HIE. I need to -- here we go. She built Hope for HIE

to support families in their journey and to advocate for trials and research in neonatal HIE brain injury.

She has partnered with a number of organizations, including Critical Path and INC. She has helped to launch a registry for HIE and is currently also working on a project that will help reduce barriers to participation and research.

So this is an esteemed panel. Each of them is going to have several minutes to sort of reflect on the meeting and provide their own perspectives on the lessons learned and the future of neonatal/rare disease product development.

And then we'll have some discussion time and hopefully some audience questions as well. So, Yuliya, you can take it away.

DR. YASINSKAYA: All right. Well, good late afternoon, everyone. It was a wonderful meeting so far, and we continue on, hopefully this is one of many, sort of, to spear up this ongoing conversation of where the product development for rare diseases and also the enrolled patient population is moving

towards.

And, hopefully, with this informative and very insightful discussion and contribution, you know, across all the stakeholders, you know, from patient and caregivers, who share their experiences, you know, living through NICU time, but also through industry partners, academicians, clinicians, clinical trialists, as well as our regulatory partners and, you know, the non-profit organizations as well; that we can all move together again to create a very rich platform for the product development and addressing unmet medical needs for safe and effective products in this neonatal space.

I mean, as I was listening to the discussions, presentations over the last two days, I'm reflecting on them from the standpoint of the pediatric infectious disease clinician, but also my regulatory experience in the anti-infective space and also now in the Division of Rare Disease and Medical Genetics, you know, developing treatments for rare genetic conditions and inborn errors of metabolism.

And what, you know, the phrase and the important point that Ryan McAdams had brought up today during his presentation resonated with me while he was talking about, you know, N-of-1, N-of-Many, in the context of AI and developing, you know, sources that each of the patients are contributing to this big, very rich picture of, you know, patient experiences, but also, you know, creating all these additional data points for us then to build model and explore further the natural history and then progression of the diseases in that neonatal space.

I am thinking about N-of-1 and N-of-Many to the sense of, you know, how can we learn from each other as multiple stakeholders from different aspects of product development in rare and neonatal development. Meaning that we stand on the shoulders of people before us, you know, those, you know, who come up with the creative ideas in developing, designing the clinical trials.

You know, what would be the appropriate scientific evidence to support an approval of safe and

effective products in this space. But also, you know, coming up with creative ideas, you know, how can leverage the data that is available to us across, you know, the disease continuum, both in clinical practice, in, you know, in scientific research, basic research, and, you know, throughout clinical product development.

We learned from the, yeah, the drug repurposing programs. We learn from the creative approaches, you know, leveraging nonclinical model data. We learn from the clinical trial experiences with the innovative trial design every time.

You know, while the -- there's no one size fits all approach, here in this development, in this particular space, but we can learn every time. It's an iterative process. You know, we can learn, you know, from the sponsor presenting to us data and their proposal of how they want to approach a particular disease and product development in that disease.

We can understand, you know, that,

again, you know, that maybe we had been there already. We can leverage some of those lessons learned before us and take it in -- into perspective.

So, you know, Marshall Summar, you know, brought up very important points and, you know, we certainly take marching orders there, but we have been there already. We do, you know, use real-world evidence, real-world data in rare disease product development, you know, it's kind of our bread and butter.

As you can see from most recent approvals in DRDMG, we have external control data that, you know, we leverage natural history of the diseases very well. We understand the pathogenesis of the diseases well; and, therefore, we have confidence that the effect that had been demonstrated in a single-arm open-label trial is actually robust and is related to the product rather than to all other intervention that patient might have experienced during the clinical trial.

We are also are pretty versed in

repurposing of the products that are available on the market as well. And, again, you know, some of that is reflected in our most recent approvals. For example, the chenodiol for cerebrotendinous xanthomatosis.

And while, again, I heard loud and clear that, you know, there's a lot of concern in using placebo control in clinical trials in neonates and in also, you know, from patient, patient communities, and sponsors in rare diseases, we certainly were able to design a study that was, you know, for the product, that was actually standard of care for several decades in that space.

And we're able to decide the placebo-controlled randomized withdrawal trial, crossover trial, to be able to show that the product has an effect on a biomarker; that we also worked with the sponsor to develop really strong evidence that is reliably able to predict clinical benefit.

So we -- the -- those trials was able to show the effect on that biomarker and were able to approve the product based on the very rigorous

clinical trial design that was involving placebo.

And, again, you know, it's not one size fits all. Not always randomized placebo-control trial is appropriate for the conditions in this space. And, again, we -- we're able to leverage, you know, very strong natural history data to allow alternative ways to evaluate product effect in the -- this patient population.

I can also, you know, pitch in and further support the discussion that had been happening during the panel before us. That there is a lot of incentive programs available and expedited programs available within FDA and within CDER specifically, that we are able to leverage and provide very intensive guidance to the sponsors and academic researchers who are interested in developing new therapies for these conditions with significant unmet medical need.

DR. BAER: Thank you.

DR. PODURI: Thanks, Gerri. And thanks, Yuliya. So I'm Ann Poduri, and I'm at Boston

Children's Hospital. I was for almost a year at the NIH. I do want to thank all of you who are the federal workers who are persisting in your jobs with fewer colleagues around you. It's not easy, and it's heroes work, so thank you.

But I have the privilege of sitting back in an academic setting and Gerri had asked me to reflect from that perspective as a physician scientist.

And I wanted to reflect a little bit on some of the cross-cutting themes from yesterday and today. And give you one example of a project where we've tried to really shift the thinking from a reactive medicine mode -- let's see what's wrong with the baby. Let's react, and then maybe eventually a week or a month or a year or a decade later, find out what the diagnosis is -- to really trying to figure out a diagnosis early so we can get to the right medication, whether it's a precise medication or a generalized medication early.

And I think the biggest lesson learned,

though, just to cut to the chase, is that I think we all in academic medicine need to interact with you all earlier because there isn't really a point at which we couldn't have benefited from a discussion.

And we're having a lot of discussions now, and we have this group of kids and maybe they'd benefit from this sort of therapy. What are the outcomes going to be if we design a trial? And we probably should have had that conversation when we were designing our first study.

So that -- that's my punchline, lessons learned, is we really need to engage better and before we start our research.

But I'll just reflect a little bit on some of what I heard that I think is really relevant to, you know, real life as a physician, but also as we're designing studies and conducting them in the academic setting.

We all want to bring a scientific approach to medicine, and I think we all really believe that it's critical to generate generalizable

knowledge; and we do have this tension on a regular basis of a patient in front of us or a family in front of us and having to choose between doing something which may have some risks and doing nothing.

And I, you know, the mantra we hear in medical school and then as we start medicine is to do no harm. And so there's this tension between wanting to do something that could be moving the needle for an individual tot/child and an individual family that might actually move us beyond the status quo, which may not be great, but also this sort of do no harm.

And I think we have to shift the conversation to where this meeting started, which is there are potential risks; there are potential benefits.

I mean there's a standard of care -- and to a little bit challenge ourselves to think, "Well, the standard of care is not necessarily great."

And that's where we are with a lot of neonatal disorders. And that's where we are with a lot of rare disorders, which is the standard of care

is sort of held up as this, you know, this thing that's okay, but in many cases it's not.

It's not okay that we don't have diagnoses for a lot of our babies and children with neurological disorders, and it's really not okay that their outcomes continue to not be great.

And it's really not okay for the epilepsy world that there's a high risk of sudden death in many of the disorders that we see for some of the developmental and epileptic encephalopathies where there's up to a one-third mortality by age 3 and some of the single gene disorders, you know, 1 in 5 by age 20.

So those, the standard of care isn't really great and I think it's in that context that we can think more aggressively in some ways. I'm a pretty conservative clinician but aggressively about how to move forward.

So, what does that require in addition to a cultural shift for physicians? It requires really partnering with patients and families as we've

talked about in terms of what's meaningful to pursue, what risks are tolerable. And I think we need our ethics community to weigh in there as neutral parties, who can actually help us with, you know, are we all on the right track? Let's not get carried away with enthusiasm, but also let's not prevent people from engaging in research.

So, the example I wanted to share with you is one where I feel like we've done this from an academic center perspective and it's a very sort of hub-centric approach. We're starting with a few academic centers. We hope to learn generalizable knowledge, and then we'll also try to make sure that there's a change in the standard of care. And that is one approach.

But I, you know, argue that it's not a particularly broad approach in terms of reaching people. But we did start with a few pediatric hospitals in Boston; London; Toronto; and Melbourne, Australia. We started with English speaking countries where we thought let's put our IRBs together. Let's

put our process together.

And every child who comes to our neonatal ICU, our ICU, our ED, or even our clinic with epilepsy that's unexplained, we're going to try to figure out what they have with rapid sequencing. And the hospitals were going to help us with research sequencing and we could then figure out how to get clinical results return.

And we sort of said, look, this was okay 15 years ago to find the generalizable knowledge and spend the year or two publishing it and then maybe get someone to adopt it. But, you know, we, as physicians, and we, as direct providers to patients, and the patients and families would like that information next week, not next year and not next decade.

So, we had a lot of discussions and brought our IRB in, and they've really shifted from a decade ago of, do we really want to burden people with this information to honoring the requests of the families who've advised us, saying, "Of course we want

the information. Why would we go through your study where you're collecting information if you weren't going to give it to us?"

We -- to get this across these four different sites and countries, the first hundred children we enrolled -- nobody didn't want to enroll. So that was helpful. Our NICU locally required quite a lot of process to be able to make sure that the families weren't being bombarded with multiple studies and not bombarded with multiple genomic studies.

So, we sort of tried to make it as little of a burden as possible. And what we found across all four sites was that on average 43 percent of the kids, so 43 out of our first 100 at all the sites and that's persistent, have an answer within a week.

And does that always lead to a change in treatment? It doesn't always. Sometimes it leads to a very definitive prognosis. This is a condition where we know the prognosis. We can make course of care changes once in a blue moon. We're very happy

that it leads to a happy prognosis where we've seen this before. Actually, you don't need lifelong medication in every single reported case we've seen, but this does well. It's scary now, but it's going to be okay.

And then a lot of diagnoses where, hey, we don't really understand what this gene does. There's not even anybody we know who's researching it. Let's work with you. Let's partner. And some of those families have actually started to form foundations and so on. We're finding this, not surprisingly, but consistently across these health settings.

And what we have found was a lot of bumps in the road. And so in terms of lessons learned, we really didn't think physicians were going to be overly encumbered. We were asking them to refer patients.

Our residents, who are the youngest among us, actually now will write in their plan of care -- well, type in their plan of care -- you know,

we're going to get an MRI. We're going to do this and that. If there's no cause we're going to activate the Gene-STEPS protocol, which is the name of the study. So that for them it's actually kind of become their MO. This is what we do; this is how we offer what we can offer right away.

We did have some discussions and a little bit of concern from people of my generation, which was that, "Wow, you're giving people this answer, and if it's not an answer that's actually portending a good prognosis. You're not letting the family, you know, process the acuity of what's going on and these seizures and the intubation, all these sort of things. And you're just hitting them with too much too fast."

And, yeah, we are. And we had to ask families and we're going to -- we're actually formally having a research arm where our genetic counselors are doing post-study, second study, which is a survey of what we could have done better and also what worked and what didn't work.

But not one of them has said -- a lot of them have said, "Yeah. It was hard and this is what you could have done better and maybe someone who had seen this disorder before could have talked to us or something like that."

Not one said, "We wish you didn't tell us." But I think we're still learning about how to do this delivery in a more sensitive way that can meet everybody where they are. Withholding information is not only something that, you know, no longer acceptable, but it's also available.

Parents can look at the charts, and it's available to them. And so we're trying to find a way to work with this evolving system to give the information. So we do that at our four rather privileged, well-resourced hospitals.

And the idea is this is affecting these small hundreds of kids, but there are thousands of kids out there. Epilepsy is a disorder that affects 1 in 26 people. Large proportion of them started in their early year, first year of life.

So, what about everybody else? And for every rare disorder where there's only 10 and there's only 15 and there's only 20 and there's only 50 or 100 kids, we know there are scores more out there whom we haven't reached because we really only have these resources in a few places.

So, how do we shift the model, other than writing evidence reviews and writing testing guidelines and trying to implement them and using pediatric echo mechanisms and so on to teach our colleagues?

I've learned a lot from our neonatology colleagues who are equally concerned that we're not distributing this knowledge and who are trying to work with community networks. So, what I heard from a lot of the discussions from the neonatologists is that people are wanting to change and that culture shift has to happen, but we can also make it happen.

And I think the way we should all make it happen is to really partner, sort of -- some of the grant mechanisms out there could explicitly require

enrollment from rural populations, community populations. I was briefly, through the UDN at the NIH, working on some of the supplementary applications we had, where people were explicitly enrolling in rural populations where, never mind genetic sequencing, there wasn't even a geneticist.

And so how do you get somebody out there to provide a study that could do that? I think we have an opportunity. We have enough knowledge now to do that, and then to take that and have every single group of a hundred kids become the future of the natural history studies.

And so where I think we really can work together and look forward is that you all have blueprints. You all know what outcomes you've heard from families and physicians are important. You know what measures have been validated and not validated. There's really no reason we should be making up our own set of outcomes for -- and set of measurements for every natural history study we do.

I think at some point people have to

give up their sort of wanting to be branding this as the such and such disorders, such and such centers, natural history study. But to say here's a blueprint; here are the outcomes we could look at. And I think that is our way to accelerate, but it really is going to require partnership earlier.

And I do -- I have a lot of notes I'm taking back to my folks at home.

DR. BAER: Thank you, Ann.

DR. MCCUNE: Hard to follow both of you guys. So, Gerri mentioned the ancient office. I have to tell you that it actually was OCTAP, which was the Office of Counter Terrorism and Pediatrics, which was the original pediatrics group in CDER.

I -- yeah, I had originally thought that the only people that could put that together was congress maybe, but not true. Diane Murphy was a pediatric ID doc who felt that we were not adequately prepared for pandemics, whether adult or pediatric. And she was correct, but -- and historically, you'll find that a lot of the counter-terrorism folks at --

at least in CDER were pediatricians.

So, and back when I started, I was the only neonatologist in CDER, and I literally was here for, I think it was my second week, they loaned me out to CDRH to do a review of the Cool-Cap device, which was the original hypothermia review, which was tough.

And, you know, surfactant was tough as well. It wasn't easy to get even the small wins that we've had. So I -- I'm really excited about the fact that An, as the Acting Director of OPT, is a neonatologist; and my friend, Ralph Bax, from the EMA is a neonatologist. The neonatologists are taking over the world. Right, Skip?

So, and I want to, you know, thank you for inviting me here today.

I want to take a step back because -- and I'm going to be a little -- I'm not going to be maybe as positive as everyone else is because we're failing, just so you know, in the neonatal space.

DR. PODURI: Glad you thought I was positive.

DR. MCCUNE: Well, yeah, no, no. You were very -- I mean, because of all the collaborative work, you know, that you've put together and the time frame and to be able to give these parents instead of sending them on an -- on a diagnostic odyssey that we know just is terribly disruptive to families.

They may not want to hear what you have to say, but you're doing it in a time frame that at least alleviates some of that angst for them. So I think that's hopeful.

But we're failing in neonatology, just a personal opinion. And part of that is -- when I first put together the Venn diagram of the adult diseases and the neonatal diseases and that there really wasn't much overlap. I think we've got a new -- it seems awfully loud -- I think we've got a new Venn diagram in the neonatal space.

And what that is, is there's -- there are common issues of neonatology, and then there are the genetic diseases that we see manifesting in the neonatal time frame and they don't really overlap.

And the management is a little bit different, and the approach to the studies is a little bit different.

And so I want to talk kind of separately about both of them, and I'll -- and maybe I'll start with the rare genetic diseases because it's really interesting, as we've heard a couple of times over the last day and a half, that many times the more severe forms of these genetic diseases present in the neonatal space, and then the milder forms tend to be either a juvenile and then potentially adults. So they tend to follow a bit of a pattern.

And interestingly enough, the inclusion criteria, or the exclusion criteria, generally are the severe disease. Nobody wants to kind of address those. But I think that's a mistake because I think that's where we can see the most impact with respect to treating these diseases.

And so I think that actually we ought to be doing -- and Ron can talk a little bit more about what that right population is -- but I think instead of excluding the severe forms of a lot of

these genetic diseases, we ought to be studying them. And I think SMA is a really good example of, you know, how we can impact the disease.

You've heard a couple of times, it was talked about today. Michelle brought it up in particular, but just to give you a little history of this.

In 1891, Werdnig was the first that described this. So we used to call this in my ancient days, Werdnig-Hoffmann disease. And he described it initially in 1891; and really up until 1995, when they first discovered SMN1 and 2, we all called it Werdnig-Hoffmann Disease.

And for those that are neonatologists, these were the hardest babies in the NICU to take care of because -- and you always knew when you had a Werdnig-Hoffmann or a -- an SMA baby in the NICU because all the nurses would be clustered around the baby's bedside, and they would all be saying, "Hi, good morning."

The shift would come; everybody would

say hi because these babies just had the most -- they had so much interaction and absolutely no muscle tone and they couldn't breathe. They couldn't get off the ventilator, and there wasn't anything we could do for them. And it was just heart wrenching. So when we finally, you know, in 1995, had the gene for it, it took about 20 years.

And that was when the first approval for nusinersen that was talked about, antisense oligo, 2019 for Zolgensma, for the AAV gene therapy, which is IV and -- oh, sorry. I forgot to say that the antisense oligo is intrathecal. And then 2020 for risdiplam, which is oral.

What followed from that was, if you've got therapy for the -- for this devastating disease, that's a neonatal disease, you need to be able to identify it in the neonatal time frame. And so neonatal screening, newborn screening, then that was -- that drove newborn screening.

And then in February of last year, that was the impetus for actually prenatal therapy with

risdiplam.

So, we've got the roadmap, at least from some of these severe, you know, gene therapy products. And -- but what do we know about these? You know, is this an opportunity then where Becky this morning talked about opportunities to use externally controlled trials, where we know the disease course, it's very well understood, and the treatment effect is expected to be really large.

And that's where we're seeing -- well, that's what we're seeing a lot in the genetic space. But, again, what is that right population?

And so then I want to come back to the common diseases of prematurity, and really kind of understanding why we have those diseases because I think we're missing that, and I think we need to take that into consideration.

So, the reason why we have issues in preterm birth is because it's an unexpected exposure to the external, the extra-uterine environment during the normal ontogeny of organs. Okay? So you're

interrupting that process.

And then the second is that you're essentially putting them into a hostile environment that's hyperoxic. So everybody thinks what we're breathing right now in room air normal for all of us. For a baby, for a fetus, that's a hyperoxic environment. They're used to being very hypoxic in utero. And that's the environment that they -- that they're -- that they essentially thrive in.

So, we're failing that community. We're failing those patients because we're not thinking about the etiology of their diseases. So we're treating them with adult lung disease therapies, but that's not relevant to the fact that the preterm lung is still at the canalicular stage. It doesn't even -- they -- an alveoli, alveolus, isn't anywhere to be found.

And the ontogeny then is very different whether you're a 24-weeker, a 28-weeker or a 32-weeker. And so we don't think about it. We used to think -- so it was funny. We used to say, "Oh,

neonates. All neonates." Then we got a little bit better, and we went full term and preterm.

But that's not enough. That's not granular enough for us. And I think that that's where we're failing in terms of the heterogeneity of the population, and we're looking for a needle in a very large haystack. And that's why we're not seeing successful trials -- personal opinion.

So, can we think about own control studies, you know, things that we talked about today, different innovative designs in terms of trying to figure out how to decrease the heterogeneity of the population.

We talked about placebo controls, and certainly within, you know, the -- a certain context, especially as was talked about with crossover -- Yuliya, you talked about crossover designs -- and then a lot of studies where there are open-label extensions, and those are appropriate ways to kind of discuss placebo controls.

The problem in the neonatal space is

that we're talking about acute problems. And so it's not a chronic problem that you can do a crossover. It's not a problem where you can wait and do an open-label extension. And so it makes it a little bit more difficult.

We also have some interesting ethical considerations. You know, we talked about SME. And the reason why I talked about intrathecal administration is that when we have placebo-controlled trials for those, we have to think about sham and how far do you go with sham.

And then for the placebo patients, if you're doing follow-up and you're doing biopsies or you're doing procedures that involve sedation in someone who may be not so stable from a respiratory perspective and you can't get them off the ventilator after you've done sedation. You know, those are risks.

And I was going to ask a question yesterday, you know, in the ethics panel of, you know, how do we deal with those kinds of risks in a placebo

group from an ethical perspective? And then blinding can be very challenging to implement in a population where you're in the NICU.

We need to really develop surrogate markers. We need to look for what are clinically meaningful endpoints that aren't so distant from the therapy. If we give something to a baby on the first day of life to help in that transition, we're appropriately dealing with the fact that their, the ontogeny of whatever organ system we're looking at, we give it to them for the first day, the first week, and then we look at how they're doing two years later.

It -- the problem is all the comorbidities and life that happens over those two years, trying to pinpoint that to an intervention in the first day of life. Unless it is something so profound that you're taking them from moderate to severe BPD or ROP or IVH and you're essentially making them normal, then it makes it very hard to be able to look at those very distant endpoints.

And the -- we desperately need imaging

measures or other biomarkers that then predict neurodevelopmental outcome because we're limited by when we can actually evaluate these kids.

And it's not just for the trials, but it's also for the therapy and for the parents to know what -- what's going on with their kids. So the earlier we're able to provide that treatment -- or the diagnosis as you were talking about, the better we are at being able to provide them treatment or essentially to do better trials.

So how can we use external control data? And Kanwaljit, you know, talked a lot about the International Neonatal Consortium database and this is it. We have not a mountain of data. We have a tsunami of data.

The patients in the NICU, this is a -- this is a group of patients where they're in a -- they're in the NICU for three months. Okay? They're a captive audience for us. We are -- we have data down to the minute on these patients.

And so when you have that kind of data

and that much data, it's a tsunami of data. We don't know how to use it. We don't know how to curate it. We don't know how to harmonize it, and we don't know how to analyze it. And that's part of the problem right now, is that in some ways we have too much data.

So, we all have to get together and use AI and use all the tools that we have to be able to utilize these data to then be able to use those as external controls.

Part of the problem, and we've -- we talk about historical control data -- the problem is with the standard of care changing every day, and in every unit, potentially treating kids a little bit differently, that makes it more difficult to identify a good natural history control.

However, we ought to be able to utilize the data we have to know where there are differences and then be able to plan that into trials.

Study design considerations. We absolutely need to include parents and patient advocacy groups in the discussion. But what I didn't

hear about so much was we also need to include the NICU nurses because we talk about having these trials. We want to capture all the data that we possibly can, but the reality of -- this is a tremendous burden on the NICU staff who are already burdened.

And so -- and then subsequently when patients go home, the burden on parents, on patients, the blood drawing, the testing. These are all things that need to be taken into consideration.

And, you know, what was discussed yesterday about the early consent and parents even not remembering that they consent for trials. The reality of it is they may not realize what's involved in a study that may be a long-term study, not just in the NICU but in the follow-up piece.

And so what may happen is they're not expecting this, and the dropout rate for your study goes up. And it may be certain patients that are going to drop out, those that are more severely affected. So that then biases the results of your trial.

All right, so I'm going to -- I'm going to just say this is what we need. We absolutely desperately need therapies for neonatal patients, both for common and diseases, as well as the genetic diseases, that commonly occur in neonates.

We really need to improve trial designs that are innovative and specific to the indications being studied. We need surrogate endpoints as well as clinically meaningful endpoints that are temporarily related to the therapy.

We need to collaborate with parents and patient advocacy groups about meaningful endpoints and the burden of trials. And then we need to share the tsunami of data that we have in a captive population with that minute-by-minute data so that we can be able to use that as a natural history comparator.

DR. BAER: Thank you.

DR. MCCUNE: Sorry.

DR. PILEGGI: Well, I pass. No, no. Definitely, you know, very authoritative and very concrete reality check. Thanks. Thanks to all.

I want to put a little bit of a hope from the NIH perspective. I don't represent -- I'm at the NIH, the Eunice Kennedy Shriver NICHD, but here I'm sharing my thoughts, so I don't represent the thoughts of the -- so I might go a little bit wild.

So definitely I see the hope in terms of the technology that -- and that is becoming available. Today we heard from Dr. McAdams a nice overview of how AI digital health can really change the way we manage and collect data. Definitely we have a lot of data, but the data that we are collecting is becoming more sophisticated and hopefully more mineable, if I may use the term.

And that could help defining better endpoints, defining the impact of interventions, and hopefully learn on where, when, and how to intervene to change the outcomes. And that is, you know, the hope that we try -- and I definitely see that there is a movement in the -- in different disciplines.

Definitely, this meeting has been a very reassuring that people is thinking in more -- in

challenging the status quo and keeping moving in the right direction. There is, I think, an heightened attention to the pediatric space, even through the current administration, the MAHA Report.

We -- we're hoping that that is a good vehicle to be leveraged to pay attention to the neglected populations like the neonatal especially and the rare diseases. But definitely the pediatric space by and large.

A comment, and I want to tie it to Dr. McCune overview. We deal with premature babies. We need to think a step backwards why we have premature babies; that we need to also pay attention to maternity health and what happens before. Because that -- it's a continuum and we cannot just deal with the problem.

And we need to also understand that the -- that problem has origins, and we need to go to the source in order to start changing the outcome even much earlier. And learning and intervening, it go hand by -- hand in hand. So that is something that I

want to just put in the -- into perspective.

We have heard from Dr. Benjamin and Dr. Greenberg the work that the PTN is doing. I'm familiar with that because it's managed by the Branch I'm involved in. And I think that we learn a lot from those pragmatic platform trials, the -- what we call opportunistic studies.

The fact that you are able to just sample patients who have been receiving the standard of care, even if it is off-label -- sorry, off -- yeah. Off-label. It opens the door to opportunities to learn not only safety and efficacy that you can distill out from a chart, but rather getting also the dosing. And that can help understanding where we are going out of the range and trying to optimize and hopefully leading to label changes.

And not only the changes in practice, but both are important. If you cannot change the label, but you have enough evidence on what is a safe range and what type of outcomes you can obtain from a study that is opportunistic, I think it's still --

there is still value there. And that is -- goes hand in hand with the real-world data that you can collect.

And I tie this to the -- what we heard also from Dr. Singh and Dr. Romero from the C-Path and the INC work. That is definitely, you know, the -- very promising, and there is other stuff brewing at the INC that we hope to see soon in the mainstream.

I know that Dr. Massaro mentioned that this is not a medical device meeting, but I want to just put a little plug in there. I think that we heard also through the two days that there is value in technology, and I believe that the point-of-care technologies are getting to a point that can be applicable to very small babies and they can be remarkably useful.

I'm thinking not only in capturing parameters that can help understanding clinical outcomes, but also point-of-care technologies that can help measuring a very small aliquot of blood that can give you the PK data that you needed to make inferences on, are we in the safe range or learning

where, what is a safe range in the very small baby.

So I see that area becoming more and more relevant moving forward than -- and maybe making more accessible across the nation, even in low resource settings. A tool set otherwise wouldn't be available where you need specialized technologies to need to run those machines. Now, you are making it, you know, almost anybody with a device can, with a telephone can tell, you know, Dr. Spock, just to understand where we're getting to.

So, I believe that that is a foreseeable future, something that maybe we can -- we will change the way we -- we'd administer medical care in the future.

And what else? And there are some -- as NIH, we can pave the way. We don't do policies, but we can pave the way. We can help generating the data. We can help supporting the trials, but they are finite resources and we need to recognize that.

An attempt to streamline and improve utilization resources is underway. We, at the NICHD,

we are working on a concept of a unified pediatric research consortium that wants to better coordinate and utilize the resources to several of the networks that we support are pursuing. That might heighten the ability of doing or gathering more data that will be relevant, including in the neonatal and rare disease space.

It is -- we have heard from my colleague, Dr. Gus Santos Schmidt, the role of NRN, the National -- the Neonatal Research Network and the Maternal Fetal, the MFMU, has been also very, you know, interact -- interactive because, you know, it -- everything starts very early. That's what I was alluding to earlier about the, you know, pregnancy, risk pregnancies, moving forward.

And a lot of those babies are the ones who will have chronic diseases. So not only genetic diseases are going to be affecting the lifespan and the quality of life of those individuals and their families, but also the fact that they have been exposed to severe conditions may affect their quality

of life and in many districts.

And that having tools and studies that can -- like opportunistic studies that can -- could provide the knowledge, I think, could help us in the future. We are supporting a number of studies that are really changing the way we are thinking; and they're not mainstream yet, but we are hoping that there will be a change. More drugs in the armamentarium that currently are -- has been stagnant unfortunately.

And without going out of the boundaries, I'll stop here because I'm starting to mumble. So, it's dangerous when I start to --

MR. BARTEK: So I first want to echo Ann's wonderful comments about all of you. I always get emotional when I talk about you guys because -- thank you for all you do, for all of us. You are heroes to our community.

Many of us in our -- in the rare disease community are working hard with U.S. Congress to get you the resources you need to continue to do

all you do for us. So thank you.

Despite your losses about which we grieve every day, you continue to do your work and you continue to do it on time. I don't know how you do it, but thank you.

Now, I'll try to clear my throat and say, secondly, I want to say what a terrific workshop this has been. I've learned so much. I learned so much this morning, for example, that by lunch I'd thrown away my notes of what I was going to say, and I decided to focus on what I've learned in the last two days.

And the first thing I learned -- and I want to thank Susie McCune for suggesting to me months ago that I participate in this workshop. Because what I learned this morning that was so important to me, and what I'm about to say, was I learned why I'm here.

Because I have to say, I was struggling a little bit about the title of this workshop. You know, Neonates and Rare Diseases. Okay? So, I know a lot of neonates have rare diseases, but our rare

disease is not manifest until much later. So, where's the connective tissue between my rare disease and neonatal research?

And what I learned partly from Ryan McAdam's presentation was there is connective tissue. And even though -- well, before I go on with that, I'll want to give you a little, a bit of a backdrop about our disease so you put into context what I'm about to say.

So, our rare disease is Friedreich ataxia. We learned our first lessons about FA, as I will call it now, when our son at age 11, Keith, was diagnosed with FA. That was a year after -- the year after -- two years after the gene was identified. So -- actually, no, it was one year after that. So he was among the first to be genetically confirmed with this disease.

We learned, too, that night in front of our old gateway computer that our son was going to get very sick very fast. He was going to lose a great deal of his vision, hearing, speech. He was likely to

developed diabetes.

He was going to lose strength and coordination in all four extremities. So he'd likely be in a wheelchair by his mid-teens, and most condemningly, he would develop a serious cardiomyopathy that would result in congestive heart failure, which is the biggest, the most condemning symptom. It leads to death in early adulthood. All that happened to our son.

But when we first found out about it, we said, "Okay. We see that there -- there's no treatment, no interest in the pharmaceutical industry, no organization devoted entirely to supporting research into this rare condition. And so not much hope.

And we decided we needed to do what we could to change those metrics from zeros to what we call in baseball, crooked numbers. And so that's why we established FARA in 1998.

We learned, too, that those symptoms that would develop are usually clinically manifest

between the ages of 5 and 15. And -- but we also learned that that's not when the symptoms begin. We learned quickly that the damage begins in the womb, and it's relentlessly progressive thereafter.

So, we knew our son, by the time he was 11 and diagnosed, a great deal of the damage had already been done. So, we learned then that we must begin to treat these -- well, first we had to develop a treatment, and once we would get that treatment, we would have to begin to treat kids younger and younger.

And -- but in order to get that treatment, that would be most, as Marshall likes to say, at the point of maximal impact. We would have to get those same kids engaged in the clinical trials, and in many cases, before they are clinically manifest or we wouldn't be able -- some of our scientists are saying we'll have to intervene in the womb if we want to be profoundly beneficial. So that set a new direction for us.

But we knew that we had to start intervening at the best time for these kids, at a time

when we could begin to prevent symptoms rather than work so hard to try to treat those symptoms later.

One of the things I learned this morning, and I have so much respect for all of you neonatologists who are trying to help these babies in the NICU. I mean, thank you. Our patients don't show up in the NICU.

But then I started thinking this morning about how as you are working with these babies in the NICU, we're working from the other end of the spectrum. We're working with adults and adolescents and increasingly with children. We're trying to close that gap between the NICU and our patients for whom the damage began in the womb. So we will continue, you know, to conduct -- we've never done a NICU clinical trial.

We've never done a neonatal clinical trial, but we're working on clinical trials that are, you know, are the only -- well, I got to tell you about that first treatment.

The label, unfortunately, says for

16-year-olds and older. And that's because it, despite our best efforts, we could not convince the little biotech to include children in that registration study. I asked for age 10, to go down. We had good data down to 8 or 10 in our natural history database.

They said the FDA would never buy that. I think I said to them, maybe we know a little bit more about what the FDA will buy than you do. I -- then I told them about the Rare Pediatric Disease Priority Review Voucher program that you talked about earlier. That helped talk them down from 18 to 16. That's why the label says 16 and older.

But so now we've got -- that -- the tragedy of that is that we knew when that -- you know, approval was given. It was great. We celebrated. I opened a large bottle of champagne that night and we toasted ourselves. But we didn't want that to ever happen to us again. We didn't want it to ever happen to anybody again, that they would -- their children would have to wait years.

The pediatric study for that product, which was approved three years ago, didn't start until last month. That will be going for another three years. So those poor families that have kids that won't see that therapy for another, you know, three years, all that damage will have been done and probably to a large extent irreversible unless we develop more profoundly beneficial treatments.

So, what can we do to close that gap faster? Well, it's going to need a revolutionary change, isn't it? It's going to need revolutionary advance in newborn screening. Ryan and his colleague talked this morning about how AI is used in the NICU to identify within minutes, you know, what disease that NICU baby has.

Also, I think Michelle mentioned biomarkers and other people have mentioned whole genome sequencing. We need to revolutionize newborn screening so that whole genome sequencing can help us identify kids at birth.

And that while we're closing that gap,

getting down to age 2 -- for example, in the therapeutic that we're working on right now -- in fact, that pediatric study goes down to age 2 in this approved treatment. So then we can extrapolate from age 2 down to newborns and you talk about administering a treatment at the point of maximum benefit or maximum impact. That would be it.

So and -- so one last point. If we're going to develop clinical trials in which we engage younger and younger kids, we're going to have to bridge that gap with kids that are presymptomatic. And, boy, you talk about endpoint requirements for presymptomatic kids. We can't use our modified Friedreich ataxia rating scale, which is a neurological function test. So, we'll have to have biomarkers.

And somebody mentioned -- maybe it was you, Susie -- mentioned imaging aspects, and we've got a global imaging program going on for the spinal column. So, we could revolutionize clinical trials for children if we're able to use surrogate biomarkers

that tell us when the damage is done, where the damage is done so we can target those sites at the right time at the best time for them.

And we'll need help from all of you. And, again, thank you very much for all that you do.

MS. PILON: I am so thrilled to be here and hopefully this -- I can do this justice and not be so popcorned around my notes, but there's so much that I am just buzzing to be here for the HIE community.

And I want to really open, again, thanking the conveners of this and the investment that continues to go into these programs.

HIE, neonatal hypoxic ischemic encephalopathy is not a new diagnosis. It's as old as time, and, actually, you know, you may or may not know the root of the NICHD and Rosemary Kennedy and her legacy, where the story that is shared about her was being born during a pandemic; and the doctor being very busy with other patients telling her mother to try to not give birth until he could get there. And they believed that she suffered a hypoxic event

because of that and lived with the devastating consequences of that.

So, it's pretty full circle to be here today and to be able to speak among people that are continuing that legacy for a diagnosis that today in 2026 -- and we're grateful for it -- has one intervention that is somewhat effective.

I would say my son is proof that it is, and is a living proof at almost age 14, being born in 2012, which was, if you're familiar with the HIE community, in the process of cooling. That was literally the month before Seetha Shankaran's long-term outcome paper came out in May 2012.

Based in the Detroit area, I was down the street in another NICU that was a part of the NRN trials, and this was -- after it had concluded, but my son absolutely benefited from the care and the knowledge of that team.

And as we began our journey with HIE -- and my background is in marketing and communications in healthcare in a nonclinical setting -- some of the

gaps that appeared very quickly were a lack of educational information for families, a lack of support and connection, and then really diving deep into what is this life going to look like and how can we help him improve and meet his individual potential and then getting connected to a wide community of impact.

And so HIE, I feel, as I've really dove in over the past almost 14 years, kind of suffers from this identity crisis. And it's really mirrored, I think, across advocacy, regulatory, clinical sponsors.

HIE begins in the neonatal period, and there's -- it's a very heterogeneous diagnosis. So there's a lot of people that, you know, like to talk about the weeds, and I've been living in the weeds for almost 14 years.

But we also have a lot of, you know, a lot of things that we can look at improving and looking at just the, you know, the cross-cutting between neonatology and rare. And rare is so ironic to me to, even though, like, we meet the definition of

FDA, if you know about HIE, it is anything but rare outside of -- in particular high-income countries.

The Lancet neurology report that came out a couple of years ago lists neonatal encephalopathy, which HIE is the top cause of, has a second leading cause of infant mortality and lifelong morbidity in the world. So it is anything but rare.

But as we hear, and as you might hear on the neonatology side, there is a significant focus on prematurity and very, very rarely until meetings like this -- which is, again, thrilling -- that HIE is even mentioned as a top priority.

And so I think what we're doing now is -- this surge that has started -- and I want to thank our genetic advocacy colleagues. Truly, for the past, you know, decade, we have benefited as an advocacy organization and advocacy swell to learn -- and from rare.

Because the unlocking of genetic codes and the wonderful work that's been done has really kind of let us take advantage of that when, you know,

a lot of times after our kids are out of the NICU, they're seen as there's not much you can do other than early intervention and you're just managing symptoms.

And I've sat in large conference spaces where, you know, something like infantile spasms or another subsequent diagnosis that is very common in HIE, they'll say 80 percent is structural and 20 percent is genetic for this type of epilepsy. We're going to focus on the 20 percent because these kids are really hard and the damage is done.

Which is, obviously, very upsetting as a parent to hear that your, sometimes your community is left out. And -- but there's so much, I think, that we have been able to, again, harness as we look forward.

And so one of the things that I think we really benefit from with the genetic view in neonatology is that the Agency has asked sponsors to engage with advocacy early and often. And I think that's been one of the most amazing experiences, thus far, in my advocacy journey, is having a behind the

scenes view, talking to so many people that are interested and might have something that they're working on the -- in the preclinical space and how they can move things forward.

And so, you know, there's a lot of talk and takeaways from this that I wanted to share a little bit of. You know, we talk about definitions a lot and HIE really, you know, continues to evolve with getting better definitions. We now have a mild cooling study that has a very definitive, you know, set of parameters that they're doing and that will, I think, eventually influence care.

And when Susie talked about, you know, the people that are excluded at the table, sometimes the nurses, you know, the CRCs, that's another untapped resource. These are the people that are spending time, a lot of times with families, and they need to be included with equity as well.

And, again, for HIE, only the moderate and severe kids were the babies originally enrolled. We have this whole cohort that was excluded, and what

we find now that our families have been connecting since 2010, so we have 16 years of anecdotal data, is these mild kids are not quite so mild.

And what's really hard in these clinical trials, obviously, is you can't wait 8, 10, 12 years, right? I mean we'll never get through it.

So, I'm really, really intrigued and encouraged to hear everyone's talk about operationalizing the novel study designs and really looking at things like external controls that our community and many others in neonatology could definitely benefit from.

And so, you know, when we talk about how we can all work together, you know, and registry comes up and data comes up, and there is a lot of data, obviously, more than any before, but we all also understand that there's a lot of limitations.

And one of the things that I think advocacy involvement has really done well on the rare side that we've started to bring over into HIE and other neonatal indications is looking at registry,

looking at that long term.

We were talking about this at lunch, and how, you know, the neonatology is so often the acute care, but that there is a disconnect in many places with the longitudinal neurodevelopmental care and how those children move and move forward in life.

And how we can work together to develop common data elements that we can harmonize, you know, global data and data within the U.S. and be willing to give that data to be harmonized as well. So that way we have these small cohorts can learn even more about.

It really also resonated yesterday the protecting from research angle, especially in neonatology. These are very fragile babies, and our babies are very sick and often the biggest babies in the NICU because they tend to be full term.

And, you know, one of the things that we have found being on the back end, behind the scenes view, of a lot of the studies now because we've engaged early and often, is seeing some of the things that come up, the trends and the sites that are

nervous to approach families because they are going through so much.

However, you know, as a parent, I would be devastated to know that I was not given a chance to enroll my baby in something that may have helped. And this is where I think and where we're trying to build -- and I hope this can be a helpful framework for others in the neonatal space -- is this collaborative, longitudinal partnership with industry and with academia to -- we're all around the table to help families and to give these babies their best shot at life.

And families need that support and they're not consenting themselves. You have to take care of the parents, right? So, you know, one of the things that we do is we have built out our support services really to be as a stop gap for families as they leave the NICU or in the NICU because it's very isolating often to have a full-term baby in the NICU so sick.

And, you know, and so what we've been

able to do is partner with our industry colleagues and our academic colleagues to infuse that support longitudinally in the studies.

And what we're finding is that, you know, these families are better supported, oftentimes they will not report something of concern of being able to participate in the study or not. They might just drop out and not talk to the studies, to their study sites.

But they will talk to us. They'll talk to our social worker, our child life specialist, our peer support mentors, and then we can coach them and help them and make sure that they have the resources, you know, to move forward and feel confident.

You know, and even today we're -- I was sitting in the session earlier and my team was texting about a new baby that was enrolled in the study and they had been reached out to, because the mom is currently separated from her baby, stayed away, and they connected into support today.

So it, I mean, live in action. It's

really amazing to see all of these things come together. And I really encourage, you know, the advocacy models on that rare to translate to neonatology.

And I encourage our, my other neonatal advocacy groups to really dig deep and learn more about the drug development side of things and where you can help and where that specificity is so important to bring people together to move things forward.

So, a couple of the takeaways that I just want to leave you with that I -- that are always interesting to me in conversation is the "aha" moment when neonatologists in particular find out that HIE is considered rare on the FDA designation. I cannot tell you how many times people have said, "Are you sure? Like, is that" -- you know.

So, I would encourage neonatologists that are really interested in things like HIE, you know, like, really learn more about how to get active in understanding the Agency's processes and the

benefits of some of the rare disease frameworks that we can bring into neonatology. That's the whole purpose of this event, I believe, one of the big takeaways.

And I think on the dovetail of that is getting the word out to more academic researchers about things like clinically validated biomarkers and what it takes to have a regulatory ready biomarker and what we need to do to get that so we're all in it together and can move these things forward so it doesn't take ten more years.

And, really, we all become advocates of the work here together. So when we go back to our spaces, we need to be evangelists of this collaborative approach and of making sure people want to be excited and learn more about the entire process of drug development for these most fragile populations.

And so, you know, I, again, want to thank everyone for your immense work and dialogue and inclusion of this very important topic and look

forward to how we move forward.

DR. BAER: Thank you, all. I guess I shouldn't be surprised that this panel had so many incredible insights and experiences to share.

You know, from what I heard along the line, I think we're in a sort of a mixed bag. We have failed in a lot of ways. I agree with Suzie. The -- there are non-incentives, and I can't -- it's heartbreaking to see development programs that are promising be dropped because of a lack of incentives or, you know, funding that has dried up.

And so we still have a gap, for sure, in our -- particularly in the common, but still technically rare neonatal diseases.

And at the same time we have disruptive technologies that are sort of, you know, emerging like AI, digital health technologies, and a lot of sort of modeling that may be able to help facilitate developing therapies and being able to monitor and understand how they're impacting babies.

My takeaway here is that, as always,

families and patients are the showstopper here. All of, you know, anytime I go to a workshop with patient and family advocates, there's such a rich experience and thoughtfulness about these processes and a wealth of knowledge.

And so for the one, two, three, four, first five here -- wait, one, two, three, four of you, if you have an example of family or patient input that impacted a program that you were working on to move the needle forward, because I want to know how we can make sure that the family voices --

You know, we have our patient-focused drug development programs here, but does anyone in our first four here have a comment about a positive experience with involving families and their expertise?

DR. YASINSKAYA: If I can take the first one -- the first -- in rare diseases where I am currently, our division is so intimately involved in all things, you know, patient-focused drug development.

We attend numerous externally, you know, focused -- patient-focused drug development sessions. And then afterwards, we meet with organizers to further reflect what we heard.

You know, for many of those, we are invited to give opening remarks, but we are there, our reviewers are there, to listen and really absorb, you know, what matters to patients? What matters to the caregivers? What things do caregivers and patients would like to see being addressed in the product development for their conditions? What are currently their unmet medical need?

We'll also see that those sessions being organized around also, what are the barriers for the patients and families participating in the clinical trials as well? And how could those be addressed in, you know, by the industry sponsors in developing those protocols?

You know, that intimate involvement, you know, of the patients, their caregivers in the disease space, you know, and across different advocacy

groups for that matter is so critical.

So, when we are providing advice to the sponsors on their individual development program, we are asking them, so you are proposing all these endpoints, did you speak to patients and the families in that disease space?

Because whatever you're proposing doesn't seem to align what we had heard in, you know, from this community. So please go back to the drawing board. So do you understand, you know, whatever you're proposing, it's well beyond any patient or family capacity to be addressed in the clinical trial.

And we don't think, you know, what you're proposing, it makes any sense from the sense of, you know, I don't think that that is clinic -- going to be considered clinically meaningful.

So please go back and bring us back the information that you actually spoke to the families and patient advocacy groups and the protocol that you develop actually reflects, you know, the disease in question.

We also are very, you know, happy to engage with the sponsors further and further in their drug development to address, you know, those concerns, as Ron had brought up, incredible heartbreaking story where you know that intervention early enough will save so many lives.

And also will be able to show that robust effect of the drug in the patient population if you intervene before of the point of no return, you know, where the condition had progressed so far that you are unlikely to show the effect.

So it's -- it is very critical to identify in the continuum of the disease, what is the patient population that is most likely to benefit, enrich the patient population for the analysis purposes, not necessarily not enroll patient on the disease continuum, but really, you know, focus on the patient population where you are most likely to see that benefit.

So, you know, for sure and we are encouraging the patient communities and the caregiver

communities to also bring us, you know -- and request patient listening sessions as well to -- for us to hear what else is on their mind. What do they think works and, no, doesn't work in the product development currency for their disease?

And if there's no product development, what do they think, you know, still are the path forward in creating that fertile background when that, you know, potential therapy will come, you know, will be identified, you know, that they will be able to reach to employ the data that they had already collected and the knowledge that they had gained about the natural history of the disease in order to develop the programmatic, the most efficient path forward, in the product development in the space.

DR. BAER: Thank you. Just, Panel, we have nine minutes so brief.

DR. YASINSKAYA: Sorry.

DR. BAER: No, no, no. It's okay.

DR. PODURI: You asked if we had one example and I don't have one example because it's

everything that we do that -- actually, it's all of them.

So, I will draw on one community, which is a single gene community I've worked with, which is the KCNQ2 Cure Alliance.

This started as a couple of groups. They've coalesced. And the person who's been so influential to me starting that is one of the moms who started it and has really been involved from the beginning.

And, you know, her child is much older now, and this group of families comes and says, you know, we started this hoping for something for our children. Our children might be out of the window, and we're here for the next generation of children.

And I think that is what we hear from many different disorders. And these are disorders we've known about for two decades, where the molecular knowledge has been known about for longer than two decades. We're -- but we're finally coming together in the last decade and we have trials.

And I think that that is because, you know, we have had pilot grants for postdocs and for students to get people into the field, and you cannot do this with the current workforce. We need to build the workforce.

So, I think one of the messages is really people should not engage because people should engage because you tell them to, but people should really engage because it's the only way to really understand what's important to families. What are they willing to take in terms of risk tolerance? What are they willing to take risk for, for what type of outcome?

And, you know, my friend Al George at Northwestern says we shouldn't be asking families to have bake sales to support our research. And while I agree with that and there's a lot of responsibility to do that, those bake sale opportunities bring us together and let us partner together and learn what's really important.

And sometimes we have the hard job of

saying, you know what, we're not going to be able to do a four-year study, but let's use the other outcomes and biomarkers we might have to get to that first step, and then we will follow in the intervening years after that.

I think there's a lot to be learned from the families who've been doing this for a really long time. You know, as Ron said, who's own children are not going to benefit from what comes but who are so committed to doing that. I mean, if they can do that and spend a little bit of their free time and some of their weekends and some of their nights really trying to move it forward, we should do that, too. Thank you.

DR. MCCUNE: I would just add to Yuliya not just considering what's in the protocol, but how to implement the protocol. So a lot -- lots of times we hear, "Oh, we're going to put everything into the day. It's going to be ten hours, but you'll be done in one day." Not going to work.

So, we're going to start the day by

drawing blood, and then we're going to do the functional test -- because they're going to want to do the six-minute walk test after they've just had blood drawn -- and then we're going to do everything else during the day, and at the end of the day we're going to do their cognitive testing.

So, you know, thinking about how to optimize the outcomes for the research and how to do it in a way that's not burdensome to patients, families, and sites.

MS. PILON: Can I just add a comment about that? And that's something that I touched on, I think, maybe a little bit, but you know, we learned so much during COVID of what can be adapted.

You know, one of the groups that I love working with is the Neonatal Seizure Registry, and it's a longitudinal group with many different main and ancillary studies and you know, the very large involvement by the CRCs in that collaborative.

And we learned so much and problem solved during COVID of what we could do via

telehealth; right? I mean, like, that's -- it's so huge. What is the burden that we can take down from families that is, you know, a clicky button survey on their phone or, you know, making things accessible, making sure that they're translated and also making sure that, again, that we're -- they're -- we're very aware of the cognitive load for children, for families, and optimizing what that looks like and being really resourceful with the tools that we now have.

DR. BAER: Thank you. Anything from the audience? Ron, did you have something else?

MR. BARTEK: I did. Thank you. I can't let this moment pass without referring to, you know, I mentioned how devastating it was to get our first label, and it was 16 years old and older and we all vowed that never happens to us again or anybody else again.

About that time I got a call from my dear friend, Amy Comstock Rick, with whom I think she and I agreed, we've been working together for about

157 years in that ballpark, roughly. Right. And she agreed that this was an issue of grave concern to all kinds of disease groups, rare and common.

So, we set about to organize and execute a pediatric inclusion roundtable, which we conducted on -- in July of 2024. And it, the opening fireside chat panels, consisted of the three medical product center directors from the FDA and two center and institute directors from the NIH, NINDS, and NCATS.

They all made it clear. I'll quote the CDER director as saying, "We have already pivoted. We have already pivoted from trying to protect children from clinical trials to trying to protect them with well-designed clinical trials that give them safe effective treatments at the best time for them." Her staff went on to say that we want to start preventing symptoms rather than treating them later.

The CDER Director also said, "Speaking to all of you and to all of us, we've got your backs. Nobody gets thrown under the bus." And so by lunchtime of that round-table discussion, Amy and I

talked, said this is exceeding our greatest expectations. We're hearing all the marvelous things we wanted to hear.

We've got to start an alliance that socializes this powerful message from this wonderful FDA. And there were industry partners in the room and advocates in the room, not just FA, not just rare disease or common diseases.

And we have that alliance going on now, and we're looking to execute the second round table, and I'll be in contact because we are socializing. We know the problem isn't here.

The problem is in industry partners and other advocacy organizations, not an understanding that the imperative, the moral and scientific imperative, here and elsewhere, is to get these children engaged in clinical research at the best time for them at the point of maximum impact.

Oh, this was well before Amy Comstock Rick came to bless us here in the Rare Disease Hub.

DR. BAER: And I think that's a perfect

ending. So thank you all so much for all of your fantastic insights and continue the good work.

DR. MASSARO: Thank you all and thank you to this wonderful panel and a really great reflection. And I think a great take-home message is, I think Gerri used the word, here comes the caboose.

I'm pleased to welcome Lynne Yao, who's the Director of the Division of Pediatric and Maternal Health in CDER, and she's going to reflect some more and give us some closing remarks.

DR. YAO: Thank you, An. Thanks to everybody, all of you who persevered and stayed with us to the end of the meeting. My brain is, like, full. I don't know about you guys.

But I do have some slides that I wanted to share. I think they have them.

It's always tough to try and kind of synthesize everything we've heard, and so I did create some slides to try and help me to remember the things that I wanted to extract and then to present to you as the group.

It's also a hard act to follow, not just the panel that we had just now and their, I think, very important points and summary. But, honestly, the whole meeting and all of the incredible insights, I would say, that each of our presenters and panelists have brought to the discussion over the last few days.

Perfect. Thank you. So I can advance with this, right? Okay, terrific. Yeah, yeah. Okay.

So the first thing I wanted to do was -- hmm. That's -- oh, there we go. Okay, I got it. Thanks.

So, I just wanted to recap from the beginning of yesterday's meeting at, like -- we started at what? -- one o'clock? It feels like it's been days. I don't know, but so just to remind folks of what we -- where we started just 36 hours ago or less than that.

But, you know, I do want to say, and, of course, this is maybe bragging a little bit, but I feel like FDA has made great strides in increasing the

availability of pediatric specific labeling and drugs and biological products. Yeah, thank you. For all of the -- of us at FDA.

I mean, you know, it wasn't that long ago when we were celebrating 500 labeling changes and that was like 2015 or 2016, and now we're over almost 1500. So, the pace is accelerating and that's really due in large part to the efforts of all of you in this room and online.

Of course, I think why we're here, and we've heard it throughout the last day and a half, is that the labeling for drugs for use in neonates lag significantly.

And both, as we heard in the last session, drugs used in neonates for conditions that have a broader age range, right? Genetic diseases that start in the newborn period but can go even into the geriatric population. And then drugs used specifically to treat conditions related to prematurity as Susie brings up.

And I couldn't help but use the quote

that I just heard. "We are failing in neonatology. We are failing in diseases of the premature." And so I think that, I think, sets up, you know, our current state. If it's in one sentence, that's it.

So, I do believe that the goal of this meeting was to understand what the challenges are in this space and to discuss potential solutions that leverage what we know from rare disease frameworks. So I hope that sort of encapsulates why we were here the last day and a half.

Now, I do want to put my disclosure and disclaimer -- oops. But more importantly it's -- the disclaimer, it's that third bullet, which is, these are my final thoughts. And they're not even necessarily final thoughts, they're just final at, you know, 3:30 today. And any omissions that I have made in the robust discussions we have should be regarded as my omission and not a reflection of everybody's important contributions to this meeting.

So, what's similar about neonates and other diseases, rare diseases? I think we heard this

again quite often in the discussions. They are small numbers; we don't necessarily understand the natural history well. It's a high unmet need. Most of these conditions are serious and life-threatening.

I also heard that, you know, we have standard of care treatments because you know what? We have to treat them. We can't wait and do nothing. So the problem is that, number one, these standard of care treatments may not be approved and, number two, may not even be that great.

So, it's not even that standard of care is available, it's that we got to do better than what's out there if the drugs aren't approved. Okay? And if they're not, if they can't be -- if they could be improved upon.

I think there also is a lack of consensus. We've heard about experience with endpoints, the timing of assessments, the affected -- effect sizes. These are all situations that plague, again, successful rare disease drug development.

Now, the ethical considerations, I kind

of took some quotes that I heard throughout yesterday's. And I think that when we talk about ethics, I think what I heard was we got to talk about understanding, truly understanding, the risks of a drug, the risks of enrollment in a clinical trial. And that risk is not necessarily measurable, as I heard Skip say.

And it -- it's very oftentimes based on a moral judgment. And if it is based on a moral judgment, then we have to have parents and patients and providers involved in the discussion about the ethics. So I think that's another thing that I feel like is important. It's not simply a statistical or clinical design issue that's ethical or not, or that's Subpart D or not. I think really to understand the ethics, we have to understand the true risks.

And then I heard -- and I think this is an important marching order for us from Dr. Summar -- that failing to approve a drug that actually works is tragic, right? That's the worst thing that can happen. And we worry a lot about approving a drug

that doesn't work, and I think that's a fair concern. But if we have a drug that works that we fail to approve, that's really the tragedy.

So what about other challenges besides those that I heard are part of kind of rare disease development overall?

Well, there's also this issue of navigating uncertainty. And I think this is something that also struck me very -- it was very impactful yesterday, the discussions; that, you know, we talk about uncertainty in terms of statistical uncertainty or, you know, worries about the operational uncertainties, but uncertainty is an everyday lived experience for families who have rare diseases.

And that not doing nothing is itself a risk. So I do want to emphasize -- at least that really impacted upon me the conversations that I heard, the speakers that were in our first panel -- that -- and also that families are not reckless.

I mean sometimes I feel like we sit in our offices or we're in the clinics and we kind of

know what's best, and when families don't agree with us, well that would be reckless. I don't think that that's true at all. I think families just want the best for their kids, and they are not reckless.

And I think it's important then if we understand that they're not being reckless, that we actually communicate to them with transparency. And then need to understand that even if we have limited data, that may be data that's critically important and that we can use in a non-reckless fashion and for non-reckless families.

And then, finally, I think again this point that I think is really important for me, that we can't -- we need to avoid conflating uncertainty with recklessness, right? So we are always going to have uncertainty. That just doesn't mean we're necessarily reckless; and that we have to navigate that uncertainty responsibly.

The other thing that I heard that, you know, this degree of uncertainty and the amount of uncertainty, we need -- we should consider in terms of

tolerating, has everything to do with this benefit risk.

And to avoid -- I'll -- I'm going to quote Skip from now on this one, worshiping at the altar of p equals 0.05. So, I think that that's another thing that's important is that this whole notion of p equals 0.05 is just that we want to have a 5 percent chance of, you know, failing to reject the null hypothesis that we approve a drug that doesn't work.

Well, whoever said the 5 percent was the appropriate level of uncertainty we should have if the disease is very serious and very life-threatening. So I think the idea that how much uncertainty we can tolerate really has to do with risk benefit, not necessarily this statistical p-value.

Another challenge, and this is one that I have experienced in my role here at FDA, not just in neonatology and not just in rare diseases, but in conducting clinical trials in children because it comes often after adult approval. And that is when

there is this perceived or true loss of equipoise.

How do you get investigators, practitioners, and families to agree to enroll in a clinical trial, especially if there's a potential randomization to a different treatment or no treatment or just standard of care treatment if there is really strongly held belief or data that support that the investigational drug or the unapproved drug in that particular pediatric population is not approved? So, I think that that's a real question that we have.

And what that all speaks to me is that we got to be better and more efficient and faster so that we haven't lost that equipoise. Taking nine years or ten years to approve a drug after adult approval is only feeding this whole problem.

And the other point that I want to make that I think can't be under emphasized, and if we haven't heard it -- I think we heard it throughout the last couple days -- and that is that systematic exclusion of certain populations is really a problem for our country.

And I think that if we, at the very least, if we systematically exclude certain populations, it certainly decreases the generalizability and the interpretability of the results. But really it becomes more an issue of access to and equity in clinical care. So I think that that's another challenge that I heard we have to address as part of our creating solutions.

That's a lot of challenges. I get it. And before I talk about the potential solutions that I think I heard throughout the last couple of days, I did want to talk a little bit about what makes, you know, diseases of the premature infant as a rare population different from the other diseases that we've talked about as rare diseases.

And I don't -- I'm not doing this intentionally to split. I'm, in general, not a person who likes to split. I prefer to lump. And I do think that we can each help each other by potentially lumping, but there are some differences that I wanted to discuss and at least point out.

And this has to do with the diseases of the premature infant rather than, you know, single gene or gene -- genetic disorders that affect children all the way down to birth.

So, we heard also that, you know, this is an ICU setting. We aren't talking about community care of the 25-week preemie who weighs 350 grams. This is a -- this -- these are patients who are enrolled in the intensive care unit. And so there is an -- there's an urgency and sometimes an emergency to implement treatments is what I've heard.

And how do we then simplify the enrollment process? How do we think about strategic or innovative ways to provide informed consent and implement trials when there's a need for urgent and emergent care?

And by the way, there are models that are available, emergency room treatment, adult intensive care treatment, that can be leveraged to consider that. And I heard some ideas about, you know, pre-delivery informed consent of the mother

before the baby's even born. I heard that that's challenging and requires a lot of effort. But, again, the ideas that we're thinking about how we can navigate this problem.

Another difference I think is that, and maybe it's not a big difference, but, you know, in premature infants and what we heard in the neonatology units is that by necessity -- right? -- we have had to choose off-label treatments as the norm. And how do we change that situation? How do we change the culture in neonatal ICUs such that an off-label use becomes either undesirable or wholly unacceptable?

Also, in addition to neonatal conditions being rare or prematurity -- conditions of prematurity being rare, they're also in complex situations. We heard day-to-day-, minute-to-minute changes in development, as well as the fact that it's these infants are also critically ill.

And then also, again, maybe we have a little bonus here that if we were going to measure an improvement in a critically ill neonate, that maybe

that measurement wouldn't require years and years of follow up as opposed to maybe a long chronic genetic disorder. Or maybe not. Because if we're talking about Betsy's experience, if we're talking about HIE, we might be able to show some improvements immediately in a patient with HIE.

But is that going to ultimately translate to improve cognitive development when the child's 3 years old, 5 years old, whatever? So maybe or maybe not. It to me is really a question still.

And then regulatory differences. So what I heard is that, you know, it's hard in disease of the premature infant to require studies because we don't necessarily have the correlate [ph] in adults that, sort of also you've heard, precludes or minimizes or decreases the ability to extrapolate information, efficacy, safety from older populations.

But I also heard that, you know, maybe the incentive structures that we have don't work as well for neonates. And so maybe we do need to think carefully about how to bring improved or better or

realistic or interesting and useful incentives to drug developers.

So, onto the solutions. And these are not necessarily solutions that I think are easy or even feasible right now, but I -- they're just my thoughts on what I heard are potential solutions.

And I heard this from Kanwaljit. I heard it from Ron; that we need to really think about if we want to get people interested, we want venture capitalists and drug developers and industry to be interested in this space, we need to probably de-risk it and we need to create interest.

And I think the way we do that, as Ron mentioned, is to start the revolution. So here's to starting the revolution.

And I also heard, I think what Klaus said, which is we can sit in the room and, like, you know, wring our hands and say -- or maybe not even wring our hands -- and say, "We are going to do this. We're, you know, I'm going to carry the flag," but we're in the echo chamber here, so we need to probably

get out of the echo chamber and in -- and into the places where we think those decisions are being made about Go/No-Go for developing a product.

And so I just put a few areas where I think, potentially, I heard we could de-risk the development in premature diseases and how these are -- areas are different than, for example, a successful rare disease development program.

So, innovative clinical trials, you know, we -- I heard a lot about innovative clinical trials. I don't really want to spend a lot of time on that, but which innovative clinical trial designs work for neonatology as opposed to a rare disease that is genetically -- we know it's genetic basis, we know what the natural history is, or even if we don't, we have a good idea that the pathophysiology by adding this enzyme back or removing this toxic element should and is in the causal pathway.

That's not the same for diseases of the premature infant. There -- it's a muddier space. And so the idea of an -- sorry, a baseline-control trial,

while I think it's very attractive, I think we have to think about, is that going to give us interpretable data in a population of patients with BPD?

Now, I'm not here to say yes or no, but I think we need to think about it. Okay? And it's not necessarily the same innovative clinical trial designs for -- you know, a rare disease that affects neonates may be different than the innovative clinical trial designs we use to assess diseases of prematurity.

Same thing for the endpoints. I also heard a lot about standardization of data collection. I'm going to talk about that in another slide. But anytime we can standardize data collection, that -- those data become more useful and more interpretable. That is that we can rely on it potentially for an external control. That would be terrific. At the very least, it helps support the safety of a drug. So we don't necessarily need to have a huge safety database.

And I think the efforts that we've

heard in standardization of data collection, particularly NIH and INC I think are very relevant and hopefully can be expanded.

I am fascinated by the discussions and the presentation today on AI tools and simulation tools on digital health technologies. And, you know, I'm a Luddite by nature and even worse, I'm an old Luddite, so I'm going to need younger folks who are more engaged and interested in moving kind of this idea of AI forward. I think that that holds incredible promise just in the little teeny tiny bit that I understand.

I think that another potential solution I heard, an avenue is that there is, I think, something that we can all try to do wherever we are is to educate whoever is in our sphere of influence.

Now, that may be, if you are in the NICUs as clinicians changing the culture of the NICU and understanding that there's a way to enroll patients in clinical trials and that the standard of an off-label use is not the standard we should

necessarily accept.

We can educate. I can educate my colleagues in the Review Divisions about how these innovative trial designs can be used in neonatology. We don't necessarily need to rely on a randomized placebo-controlled trial with a power to -- of 85 percent to and a p-value of 0.05. So I think everywhere we are, maybe we could take the opportunity to educate.

I did want to also mention, and we heard a lot of information that I hope folks who are interested in diving into this space, that they take advantage of all the expedited programs that we offer at FDA as well as globally at EMA.

I just wanted to make one little modification and that is -- and thank you, Najat, for bringing this to my attention -- that the START Program that had been discussed in the earlier panel is actually no longer accepting applications, but they are working through the applications that have been accepted. So just one little clarification on that.

And then this is something that is, we've been, you know, trying to help industry, academia, anybody who will listen to us at FDA, understand and that we really encourage early interactions. But here's the part that I think we can work on, and that is helpful interactions.

So sometimes we are willing to engage early, but then there's this reluctance to give any real advice because it's too early, right? So if we're going to say honestly that we want you to come in early, then we have to be prepared to give you helpful advice, not to say, "Yes, we want you to come early, but actually it's too early to talk about anything." So, I do think that we have to do our job in understanding where we can be helpful.

We may not be able to tell you yet, go with that endpoint. That's fine. But we may be able to tell you this is what we think is necessary before we agree on that endpoint or before. So, it's not just that the endpoint is not acceptable, but here are some ways that we can help you get to the information

necessary to agree to that endpoint.

What else? Well, this is probably one of the best new words. I'm going to submit this as the best new word of the year, a "momatologists." So we need to engage -- we heard this again throughout -- parents and caregivers early and often. We need to hire momatologists. We also need to seek input from NICU staff. I heard that loud and clear. And also to engage the nursing staff.

And by the way, this doesn't mean that we tell -- we engage our patient and provider and caregiver experts, you know, before we launch or at the end of Phase 2, or maybe before the clinical trial starts. Again, what I've understood and what I've experienced and what I've heard is that engagement with patients, parents, and caregivers early should be included in all phases of drug development and should be included as part of meetings with regulators and investors.

And I snuck in the word investors. I didn't hear investors. That was me adding it. But I

think it's important because I think part of who's maybe missing from the discussions today are the investors.

And I think they're the ones who need to hear from parents who say, this is really important to us because a KOL, you know, who's a professor of thus and such, maybe doesn't have the same impact as a parent and all the parents that are still here in the audience and telling their stories about their experience.

And then the other thing that I want to also point out -- this was not included in the discussions. So, this is Lynne Yao adding it, and that is that I have heard from other workshops that we have convened -- and I think Alison was actually part of that workshop on diversity and inclusion.

And one of the things that was made very clear to me is that the benefits of having parent and patient and caregiver engagement throughout the cycle, particularly early, is that it can actually increase the uptake and the use of that drug once it's

approved. What do I mean by that?

What we heard was kids who come and agree to participate in a trial, they -- if you've done a good job at enrolling and finding them -- they come from all different places, all different socioeconomic classes, all different geographies.

And what happens is that once they've enrolled, if you've done a good job in explaining, they go back to their communities and someone says, "Oh, I don't believe in that drug. That's just some government coverup."

That child, that family can say, "Wait a minute. Hold on. I enrolled in that clinical trial. I was a part of that clinical -- I was a part. They asked for my input. That is a drug that I feel like is safe for me, my family to use, and you should consider it, too."

So, these are the added benefits of including patients, parents, and caregivers as part of the drug development process. It has really positive consequences all the way through.

What else about -- what else? And so here's another place where I heard really strongly that we're not necessarily doing a good job. And I don't mean, you know, we at FDA. I mean we at FDA, we and IRBs, we in clinical practice, we as clinical investigators; that we're not really good at explaining what we should be doing and what we're planning to do.

And maybe not even understanding to the extent that the IRBs or the informed consent documents that they don't understand what the real intent is. So I think what I heard was that maybe an improvement would be to include parents or at least patients or some form in the IRB composition.

I think this whole notion of coercion that I heard was really impactful to me as well. What are we really trying to tell parents when we ask them to enroll in -- their kids in clinical trials? And I think what we all hope, what we all think, what we all believe, is that we are hoping that this drug will work. That this drug will be the cure, but is that

really what we're actually doing by this clinical trial?

And I think maybe what we need to do is be clear about what the clinical trial is actually going to end up helping us to understand. So an option when an option doesn't exist is what I heard. Or even just, this is going to be information that we can help the community at large.

Those are really important, I think, important ways to explain and to help patients and families understand what the clinical trial is intended to do, rather than it's going to cure your kid or, you know, you won't have to worry about anything if you just enroll in this clinical trial.

And then another thing that I'm going to take back because I think this is a really, another really great point, is that palliative care experts are really good explainers; and maybe we should be thinking them as another group of people to engage in the consent process or in the drug development process just in terms of how they communicate.

And I have firsthand experience of, you know, in my own personal life about the use of palliative care specialists, and I could not agree more with that idea.

And then, of course, this idea of engaging in early communications with regulators. I've already mentioned that. And I think, though, maybe the one idea I have here is that -- and it's been kind of percolating in my brain for a while -- is that we hear -- we heard Ralph Bax from EMA and talk about all the ways you can engage with EMA. And we heard from a lot of people at FDA about how you can engage with FDA. And we heard about how at the Cluster, regulators can talk to each other.

But I think one piece that may be missing, or maybe can be approved upon, is why can't we have everybody in the same room at the same time or at least on the same call at the same time. Couldn't we have industry and FDA and EMA and the patient, you know, for any particular product, at the table at the same time?

And I think that that kind of pathway for creating a joint meeting or a single meeting would be one that certainly I think at FDA we'd be interested in trying to move forward. Oh, and I -- as I mentioned, that's Lynee Yao's opinion, not the official position of FDA.

So, and then clinical trial operations. One of the things that -- thank you to Melanie Bhatnagar, who actually pointed out to me -- I, you know, when I was thinking about these ICFs and these 50 pagers, I'm like, that's too much. Nobody reads them and nobody understands them. So what about improved and plain reading of ICF?

And it turns out there is actually the Common Rule was revised and FDA has issued guidance about how to include key information, you know, in a bulleted kind of two-page summary at the beginning of an informed consents. And that is now a part of the Revised Common Rule. So HHS has to follow that. So, I just brought that in to let you know that actually this is a really important development.

FDA follows the Common Rule. We don't actually have past regulations that aligned with the Common Rule, but we do follow it and we do have it as part of guidance.

Almost done. So hang in there. What about harmonization? So I heard this, too, and I thought this was really important, that it's not just about harmonizing data or harmonizing regulatory advice. It's really how do we implement protocols in a way -- how do we develop protocols and implement protocols in a harmonized way such that there isn't this dilemma at the bedside that do I follow the protocol or do I break the protocol because I need to do this treatment?

So there needs to be some way, I think, to harmonize methods and pathways to incorporate protocol implementation and protocol amendments that support and minimize this moral distress.

Standardization of common and core data elements across networks. I think you've heard a lot about that.

And then the creation of federated data networks. So what I mean, is, you got a great INC database. You've got a great NRN database. You got a great pediatrics database. And do they talk? Are they federated? Is there a way that we can have them talk? Because I think that's another way that we can increase the power of each of these already important databases.

And maybe the way to do that -- and, again, this is Lyne Yao talking, not anybody else. But as I'm thinking about it, is there a way to create incentives? I mean real incentives for people to share their data, not just data networks, but we heard in the platform trial, why won't industry sponsors conduct a platform trial? It's because the key opinion leaders and the pediatric champions within industry are all for it.

And then you hear about PI. You hear about the attorneys saying we can't collaborate like that. So how do we create the incentive for data sharing?

Okay. Well, I think this is my second-to-last slide. So, what's next? These are the ideas that I've put together that maybe are ways that we could move this conversation forward.

So, again, one thing that was very clear to me is that we sit on top of mountains and mountains of data. So, what can we do to maximize the utility of that mountain that we sit on? I think that what I heard was we need to figure out standardized disease definitions, particularly in the diseases of the premature.

How can we use these data to fill in gaps in knowledge, not just gaps in knowledge that again would not require a trial, but gaps in knowledge about an endpoint selection or the length of a trial or the use of a surrogate. All of these I think ideas can be interrogated with these large data sets.

I mentioned that can we create a federated database based on all of these proprietary or regional databases? And then can we consider incentives for data sharing?

My other point about repurposing of drugs, you know, I heard that repurposing of drugs is kind of a low hanging fruit. That's what I heard. It's low hanging fruit. It's a good idea. We should do it.

One of the caveats that I want to bring forward to you, and this is I've seen it in unfortunately nefarious ways; and that is that there's a drug that's, you know, old as dirt. Nobody's using it, or only one person makes it anymore. And then a company has the great idea of repurposing it to use in the NICUs. And then they do it and they get the data they need; and they jack up the price a hundred thousand times.

So that's not really doing anybody any good either if you create a drug that was formerly available off-label but now is unavailable on-label because it's not affordable. So, we do have to be a little cautious in understanding the potential pitfalls of repurposing.

So, grow and integrate collaborations

that already exist. And, you know, I put them all here because they're all collaborations that we should all be doing and rather than the echo chamber that Klaus describes, maybe it's just a beautiful chorus instead. Because we all know each other's parts and we're all working together.

Embracing emerging technologies and innovative trial designs. Whole genome sequencing, I think, is really going to be the next big thing that we do to identify patients with rare diseases earlier on and it's already being done.

And then how can we utilize these emerging technologies? How do we align clinical development programs, whatever we way we can through meetings with FDA and EMA jointly or with meetings across advocacy groups, whatever it takes.

And then, of course, educating the entire ecosystem. And I added in there, too, all the usual suspects. But I've also included I think importantly payers and venture capitalists because I think they need to be part of the conversation if

we're going to generate interest.

I want to thank everybody over the last day and a half, the presenters, the panelists, especially our parent and family advocates. Thank you to OPT to help organize ADEPT 10, and, of course, all of you in the room and online. Hope you had a great meeting. Thank you very much.

DR. MASSARO: Thank you all. We are at the end of our meeting and thank you, Lynne, for that wonderful summary. There was a lot to digest I think, which is why we're a little over time. So I won't belabor this anymore.

But just to give a final word of thanks and we hope -- and many folks have asked. We will be posting recordings and meeting summaries on our website, on the meeting website. So hopefully this conversation will continue. And, as well, a reminder about the events for Rare Disease Day towards the end of the month again to continue the conversation. So thank you.

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(Whereupon, at 4:05 p.m., the proceeding was concluded.)

CERTIFICATE

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

KYLE G. JAMOLIN

Notary Public in and for the

District of Columbia

CERTIFICATE OF TRANSCRIBER

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

BENITA LE MAHIEU