Advancing the Development of Pediatric Therapeutics (ADEPT) 10: Addressing Challenges in Neonatal Product Development – Leveraging Rare Disease Frameworks

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Reported by: Richard Livengood

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A P P E A R A N C E S

List of Attendees:

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Melissa Lestini, MD, OPT, OCMO, OC, FDA

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Lindsey Wahlstrom, MPH, CPH, Rona's FUN LAB

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P R O C E E D I N G S

DR. MASSARO: Okay. I'd like to welcome everyone to this year's Advancing the Development of Pediatric Therapeutics meeting. My name is An Massaro, and I am the Acting Director of the Office of Pediatric Therapeutics here in – the Office of the Commissioner of the FDA.

I'm thrilled to see everyone here in person and online and want to thank everyone for bearing with us over the past few months. I know there have been times of uncertainty, including rescheduling this meeting. So we're just really thrilled that we could finally get together today.

I also want to thank our planning committee that included FDA staff from across the centers, including CDER, CBER, the Office of the Commissioner, and our sponsor for this meeting, MCERSI.

For those of you joining us for the first time, the ADEPT workshop series was started in 2014 as a forum for public discussion on ways to

advance development of medicines in children and jointly hosted by FDA's Office of Pediatric Therapeutics and CDER's Division of Pediatric and Maternal Health.

ADEPT meetings have created opportunities for public forums for stakeholders to meet and discuss challenging scientific issues related to pediatric product development and pediatric regulatory science.

This year, I'm excited to open our 10th ADEPT meeting focusing on two areas of continued challenge in pediatric medical product development -- oops, sorry -- rare pediatric disease and neonatology.

As we'll hear about over the next day and a half, the challenges in both of these spaces are many. And these challenges are hallmarked by rapid growth and development in our youngest, most vulnerable patients.

This dynamic system poses unique drug development challenges as ontogeny not only affects identifying appropriate therapeutic targets but also

approaches to assessment of safety and understanding and measuring potential drug effects.

Meanwhile, the potential impact of effective disease-modifying therapies for neonates is great, not just for the individual child and family, but for public health as a whole, given the lifetime socioeconomic costs of diseases that have onset in the neonatal period.

So, over the next day and a half, we hope to bring together stakeholders for both the rare disease and neonatology communities so we can share experiences, lessons learned, and ideas about how we can move forward in these two challenging product development areas. This will, as we say, take a village.

We hope to foster discussion between patients, families, academics, regulators, and industry sponsors, as we understand that making progress in advancing therapeutics in neonatology and rare diseases will take a combination of legislation, regulatory solutions, including expedited programs and

pathways, financial incentives, and most of all, multi-stakeholder collaboration.

Before we get started, I want to frame our discussion today regarding what we will and will not be discussing.

Our goal is to describe the current landscape of medical product development for neonates and rare diseases, discuss gaps in priorities, as well as identifying potential strategies and future directions. For the purposes of this meeting, we will not discuss medical devices.

While we may touch on some aspects of pediatric medical device development, where relevant to our discussion, we'll primarily be focusing on drugs and biologics for the purposes of our meeting over the next few days. We also won't discuss fetal therapies or new approach methodologies.

Again, while relevant to many of the disease areas we'll be discussing, these topics have been and will continue to be discussed in other forums and arguably warrant their own individual and

dedicated discussions.

So, we will consider, as I said, the -- the issues on the right and of course hope to foster continued dialogue on -- on many topics that are touching these areas.

So, in fact, we consider our meeting today as a lead-in to coming events associated with Rare Disease Day later this month.

So, some topics we touch on in this meeting, as well as additional topics, will be further discussed at both FDA and NIH events that are coming at the end of this month, and I wanted to make sure I share this information with you all.

Additionally, FDA's Rare Disease Innovation Hub will be hosting the RISE workshops series. And the next meeting, which is focused on data sharing, will be held in March.

So, I've included all of these in the slides that are available to you for links for registration, as I think many of the -- many of the folks coming to our meeting and have the -- those

interests will be interested in these forms as well.

So, what are we going to be discussing specifically? I'll provide a -- a brief overview of our agenda and our plan for our map for the next day and a half. Today, after these opening remarks, we're going to spend the rest of the day focused on our ethical considerations.

We'll have two brief introductory setting the stage talks, both from the neonatology perspective and the genetics rare disease perspective, and then dive into our ethics panel discussions, as you see on the slide.

And then tomorrow morning, we'll start with a series of short talks on different innovative strategies that we can deploy in neonatal and rare disease clinical trials.

We'll have a panel discussion on leveraging networks, consortia, public-private partnerships, and other tools to optimize operational feasibility for rare disease and neonatal trials, including global harmonization, which is very

important for these small populations.

Then, after our lunch break, we'll have a regulatory panel that will focus on describing the regulatory landscape, both here as well as in Europe, with some representation from the EMA, and talk about expedited programs, pathways, and other initiatives that may be leveraged in these spaces. Then we'll have some closing remarks.

So, without further ado, I want to turn over to Mallika Mundkur, our chief -- Deputy Chief Medical Officer, to provide some introductory remarks.

DR. MUNDKUR: Hi, everybody. Nice to see everyone today. I want to start by thanking An, and Melanie -- I think I saw her somewhere around here -- there, Melanie, and -- Prabha back there too. Great.

I just want to say that An and Melanie have been wonderful leaders and stepped up in supporting OPT and carrying forward some of this great work that's so important for the agency.

They've been -- you know, just -- I

can't -- I can't say thank you enough and just say what a tremendous job you guys have done. So I'll start with that.

And I'll also say that it's -- it's a treat for me to be able to attend a conference like this, sort of, you know, led by our agency and, you know, seeing the diversity of topics. I -- I'm really looking forward to learning.

As you guys know, the -- the rare disease, kind of, topic is a great priority for -- for the current administration. You know, I think there's a lot of energy going into this.

A -- a few areas that I'll mention that I -- it looks like they're -- they're already on the agenda, which, you know, is -- is not a surprise, is, you know, thinking about the use of AI, for example, in accelerating identification -- appropriate -- or effective therapies for -- for rare diseases.

I'm actually very excited about this as an emerging theme that we'll start seeing more in -- in the coming -- coming year or two.

Plausible mechanism pathway. So a lot of interest in trying to remove barriers to approving new therapies for rare disease populations, and -- and looking forward to seeing those frameworks kind of implemented again in the coming months.

I am also excited to just share that the agency continues to support research for rare diseases and, you know, has awarded several grants to various groups that are -- are conducting research in this space.

Research is -- you know, obviously, this is not something we take for granted anymore, kind of getting money in this space. So very happy that our FDA and -- and our office in particular has continued to award grants to support research in rare diseases.

The -- you know, the "Make our children healthy again" sort of agenda definitely focuses primarily on addressing the root causes of childhood diseases. This extends not just to rare disease, but also to chronic diseases.

And I think we're going to see some really interesting sort of knowledge advancements given the -- the intensity of focus on these -- on these areas that I don't think we've seen before.

It's -- it's -- a sort of an opportunity and for -- in -- in pediatric health and in rare diseases. So it's -- it is really exciting.

I think that given -- given the constructs that we're -- we're still kind of working with in terms of the regulatory environment, identifying effective products are going -- this is going to continue to be challenging.

But I think that with some of the things that I've mentioned, the new frameworks, real-world evidence -- again, this is another area that we're very interested in developing as an agency. I think we are going to see a lot -- a lot more of drug development that's happening in this space.

So I -- I am not going to go on longer than this. I think there's a fantastic agenda and just really grateful to have all of you guys here

today, so thank you.

DR. MASSARO: Thank you.

And now we'll dive right into our -- our first session, which is setting the scene for our discussion for the rest of the meeting. We're going to have a -- a pair of talks.

First, I'd like to introduce Melissa Lestini. She's a neonatologist in our Office of Pediatric Therapeutics, a wonderful person, and -- and expert in -- in what she does.

And she's going to share with us her perspectives on neonates and rare diseases and why early diagnosis and approved treatments are really imperative.

DR. LESTINI: Thanks so much, An, for that very kind introduction.

And it's so great to see so many of you here in person, and I'm so excited also by the number of folks who are tuning in virtually. It's just great to see the interest in this topic.

Before we begin, though, I'd like you

to know that the comments I'm sharing are personal and do not necessarily reflect the views of the FDA. Please note that all specific product development questions should be discussed with the relevant review center and division.

I have no financial conflicts of interest to disclose. And the off-label or unapproved use of medical products may be discussed, as it's common practice in pediatrics and especially in neonatology, which we'll touch upon soon.

And just another note, when I talk about drugs or drug development in general, this applies equally to biologics.

Prior to joining the FDA, -- oops, let me -- there we go. Prior to joining the FDA, I spent almost 15 years practicing clinical neonatology and cared for many infants such as the one pictured on the left.

I didn't think of the conditions I was treating as rare. Rare to me, meant all of those board-worthy diseases that you might see once or twice

in a career.

When I joined the FDA, my first role was in the Center for Biologics, reviewing submissions for cell and gene therapy products for just such rare pediatric diseases, often referred to as zebras.

I soon realized that from a clinical design and regulatory perspective, I'd been caring for loads of baby zebras for years without even realizing it.

Per statutory definition and for regulatory purposes, a rare disease is defined as a disease or condition which affects fewer than 200,000 persons in the United States.

When we think of rare diseases in newborns, we often think of inborn errors of metabolism or other rare congenital disorders that present in the neonatal period.

However, many conditions unique to neonates, including both full-term and pre-term neonates, fall well below this threshold, as shown on this graph.

Infants born pre-term, particularly those born at 34 weeks or less, are more likely to experience morbidities, the occurrence of which is inversely related to birth weight and gestational age, such that conditions like bronchopulmonary dysplasia and necrotizing enterocolitis occur more frequently in the approximately 50,000 very low birth weight infants born in the U.S. each year compared to their larger, more mature counterparts.

Over the next 20 minutes, I'll talk about the current state of products approved for use in neonates, as well as touch upon some of the challenges to neonatal and rare disease drug development.

I'll then dive into the impacts of early diagnosis as well as the long-term impacts of some conditions unique to neonates.

For background, in the U.S., pediatric drug development is largely driven by pediatric-specific drug legislation. This includes the 2002 Best Pharmaceuticals for Children's Act, or

BPCA, and the 2003 Pediatric Research Equity Act, or PREA.

Together, these laws have led to a significant increase in the number of pediatric studies conducted and a subsequent increase in the number of pediatric labeling changes for drugs and biologics over the last -- over the past several decades.

In September 2022, FDA announced the historic milestone of achieving over 1,000 medicines that include evidence-based pediatric information and product labeling.

This milestone represented the collaborative efforts of the FDA, federal partners, industry, researchers, patients, families, advocacy groups, and many other stakeholders who played an important role in informing the current approach to developing medicines for children.

While it's clear that progress has been made in pediatric drug development and labeling changes, it's also clear that progress in the neonatal

population has lagged behind.

In the NICU, we continue to practice in a setting where the majority of medicines we prescribe to neonates are done so off-label, meaning that they haven't undergone sufficient investigation to establish safety and effectiveness in neonates.

Despite what I'd shown you on the prior slide, it's important to note that of the now over 1300 pediatric labeling changes, less than 15 percent of those have included studies in neonates or indications for neonates.

We have a scientific and legislative mandate to address this gap, not only by conducting clinical studies in neonates for medications that are approved in adults and older pediatric patients, but also by developing new treatments for conditions that are specific to the neonate.

So why is it that neonatal product development has lagged behind? The reasons are many. As shown at the outset of this talk, neonatal diseases are rare, creating challenges with study design and

treatment, as well as recruitment.

In addition, neonates are rapidly growing humans with those born premature, experiencing critical periods of development in the outside world or ex-utero instead of in their cozy, in-utero environment.

During the neonatal period, there's rapid development of organs and tissues with continued growth in maturation through infancy and into early childhood for some organ systems.

Developmental maturation at the cellular and biochemical level also represents a challenge, as many enzymes, receptors, transporters, neurotransmitters, and other signaling molecules are expressed differently with age.

Additionally, physiologic changes associated with the transition from the in-utero to ex-utero environment after birth must also be considered, as changes in circulation, oxygen tension, and function of organ systems such as the lungs and GI tract are triggered after separation from placental

support.

Finally, due to many of these factors that characterize the immaturity of the neonate, they are vulnerable to comorbidities and disease conditions across organ systems, making safety and efficacy assessments of a drug product particularly challenging to discern.

These neonatal specific challenges are added to by challenges inherent to drug development and rare pediatric disease -- diseases in general, some of which include a lack of definitive outcome measures and assessment tools, the need for additional safeguards for children as a vulnerable population, the logistical hurdles to completing trials, especially with the need for longer term follow up to establish safety and efficacy, and importantly garnering interest from sponsors and investors.

These are just a few challenges encountered in rare disease drug development. I'll refer you to the publication by Carla Epps and colleagues noted on this slide, which

provides a much more comprehensive review.

But before I move on, I wanted to reemphasize that all of the rare disease drug development challenges I've just mentioned apply equally to product development in neonates.

There are several existing tools and incentives that can be leveraged to promote therapeutic development in neonates through BPCA and PREA.

Under PREA, sponsors are required to conduct studies in pediatrics for new drug moieties if there is clinical and pathophysiologic overlap between the neonatal and adult disease condition.

Extrapolation is one of the tools used to facilitate product development in pediatrics when the course of disease and the effect of the drug are the same for pediatric patients and adults.

However, extrapolation to neonates is often challenging due to the rapid physiologic changes and organ maturation I've just mentioned. BPCA helps to foster product development for disease conditions

specific to the neonate without an adult correlate.

BPCA is a voluntary incentive program, which allows a six-month extension of existing marketing and patent exclusivity for conducting voluntary studies requested by the FDA.

Off-patent drugs can also be studied through this program and have led to several labeling changes, enhancing the safe use of off-patent drugs in neonates.

In addition to PREA and BPCA, which have been in effect for nearly 25 years, there are a few other pieces of legislation which have helped to progress the drug development specifically in rare disease, namely the Orphan Drug Act and the Rare Pediatric Disease Priority Review Voucher program.

This two-pronged approach, leveraging the progress in adult diseases for parallel development in neonates and utilizing all available tools, resources, and incentives for neonatal-specific conditions, is essential to overcome the many challenges that neonatal and rare disease drug

development face.

It's important to note that orphan conditions that occur in both adults and pediatric patients are currently exempt from PREA requirements.

Thus, rare diseases that affect both adult and neonatal populations may not see the benefit of legislative mandates like PREA unless this Orphan exemption is changed in the future.

As shown by the bar graph on the left, the Orphan Drug Act has increasingly helped to expand the number of drugs approved for rare diseases over the last 40 years.

It's important to note, however, that there have been no novel drugs approved for neonatal-specific conditions since the approval of surfactant products in the 1990s.

Over the first ten years of the RPD Priority Review Voucher program, 569 designations were granted in 17 different therapeutic areas.

Across therapeutic areas, receiving RPD designation, there were 33 neonatology products

designated, representing 6 percent of total rare pediatric disease designations, notably neonatal seizures, bronchopulmonary dysplasia, necrotizing enterocolitis, and retinopathy of prematurity were each associated with four RPD designations.

Both programs will be discussed in more detail during the regulatory panel discussion in session four tomorrow afternoon.

Now that you have a lay of the land with respect to the current state of neonatal product development, let's talk about the importance of early detection and diagnosis of neonatal conditions.

Early diagnosis and timely treatment can prevent severe disease complications such as those seen in metabolic and immunologic conditions, including brain damage, intellectual disability, organ failure, and death.

When effective treatments are administered early in the disease course, they can improve quality of life and lead to reduction in healthcare costs.

Importantly, early diagnosis can also empower families by providing them with important disease-specific information, providing access to appropriate ancillary services and consultants, and connections to support networks, as well as reducing diagnostic uncertainty and helping them plan for their child's future.

Newborn screening has been an incredibly effective way to detect rare disorders in the first weeks of life for which there are known interventions.

Newborn screening programs are available in all 50 states, with each state determining which conditions will be screened for. Although states are not required to screen for all recommended conditions, there are many states that screen for even more.

Currently, California leads the pack here and has the most comprehensive program, screening for more -- over 80 conditions.

The number of infants identified by

newborn screening has been steadily increasing, and now over 7,000 infants with possible rare disease are detected by the newborn screening test in the U.S. each year.

However, as the rare disease community knows, the numbers are far less important than the impact that these interventions can have on patients and families, some of which are highlighted in the CDC link at the bottom of this slide, which spotlights newborn screen stories and which early disease detection changed the course of the disease, including in many cases saving patients' lives.

While I spent some time to show that neonatal conditions should be considered generally rare, that's not to say they aren't important. Actually, having effective medical products to treat neonatal conditions could have significant impacts on public health.

Perhaps the best way to demonstrate this is to consider the way the Global Burden of Disease Study evaluates relative impact of disease

condition on overall health.

Disability adjusted life years, or DALYs, are an absolute measure of health loss. They count how many years of healthy life are lost due to death and non-fatal illness or impairment.

As seen here from one of the seminal publications of the 2010 Global Burden of Disease Study, there is obviously a balance between years of life lost, or YLL, denoted by the green bars, versus years lived with disability, or YLD, denoted by the orange bars.

For each age group, this balance is a little bit different. For example, for newborns, nearly all disability adjusted life years for this age group are attributed -- attributable to years of life lost, as obviously early mortality does not allow for years live with disability.

But this metric accounts for quantifying burden of disease beyond survival, so that as patients survive the neonatal period, they may have many years ahead living with disability as a

consequence of their condition present at birth.

The most recent global burden of disease update contains a comparison between disease burden in 2010 and 2020 and shows the number one causes of disease burden in the world can be attributed to neonatal disorders.

In 2021, this was surpassed only by the global COVID-19 pandemic and essentially tied with ischemic heart disease.

While neonatal conditions are rare and absolute numbers, that is, there are far fewer neonates affected by disease than adults with ischemic heart disease, the magnitude of loss of years of healthy life is great when considering the impact that reducing burden from conditions affecting neonates can have.

Longer-term social, emotional, and behavioral outcomes, as well as the disease impact to family, are aspects of disease burden that are difficult to measure in studies like the Global Burden of Disease disability-adjusted life years metric.

Two recent studies give a glimpse into these outcomes, which impact daily function.

One publication reports the longer-term behavioral, emotional, and neurocognitive outcomes observed in children diagnosed with hypoxic ischemic encephalopathy at birth and reports increased anxious and depressive symptoms at three to six years of age, as well as cognitive impairment, learning disabilities, and behavioral issues at school age.

The other study I'll mention examined child health outcomes associated with severe bronchopulmonary dysplasia and their impact on the family.

The thickness of the line connecting the health outcome to family impact total score represents the strength of the correlation, with autism diagnosis being the most impactful, followed by use of a feeding tube.

These are just two examples of conditions for which targeted product development has the potential to impact important outcomes. But there

are many others, some with outcome data, but many without.

While the clinical impact of these diseases to the individual child and patient are the most important outcome, the economic impact of conditions specific to the neonate cannot be overlooked from a public health perspective.

This graph shows the incremental cost increase with additional morbidities encountered in preterm infants.

The study was a retrospective analysis of infants born at 24 to 30 weeks of gestation, evaluating the cost attributed to five neonatal conditions associated with prematurity, namely bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis, retinopathy of prematurity, and nosocomial infections.

The total additional median cost of Morbidities, ranges from approximately $170,000 if one morbidity is experienced to almost half a million dollars if all five were experienced.

Of note, severe bronchopulmonary dysplasia, surgical necrotizing enterocolitis, and severe retinopathy of prematurity are the costliest morbidities and contributed the most to incremental cost, especially for the higher cost patients.

It's important to note that these additional costs account for in-hospital economic impact only and do not account for costs experienced over the child's lifetime.

While similar lifetime cost estimates for specific neonatal conditions associated with prematurity are not readily apparent in the neonatal literature, there have been a few publications over the past 20 years which have estimated the lifetime cost of prematurity in general, including a report from the National Academies in 2005, followed by a more recent report published in Seminars in Perinatology reporting 2016 cost data.

This study suggests that the total incremental lifetime cost associated with preterm births a decade ago was estimated to be over $25

billion.

With those infants born extremely premature, that is, less than 28 weeks gestation, experiencing incremental cost of nearly $350,000 per patient, of which 82 percent was spent on medical care.

Clearly, the treatment of neonatal-specific conditions can have a tremendous impact for the individual child, their family, and on public health.

Given the paucity of drugs approved for use in this space and the relative lack of novel drug development compared to drug development for adult conditions, there's an urgent need to help these therapeutic orphans.

As neonatologists, investigators, industry sponsors, investors, and regulators think about clinical development programs in the neonatal population, I urge all interested parties to recognize the link between neonatal conditions and rare diseases, both the challenges and opportunities to

leverage the tools, programs, and resources, some of which are listed on this slide, that may be directed to rare diseases in general and applicable to conditions in neonates meeting requisite criteria.

Before I finish up, I wanted to take a moment to talk about the neonatology program within the FDA. With the passing of the Food -- or the FDA Safety and Innovation Act in 2012, Congress mandated that the FDA maintain expertise in neonatology.

Our program lives in the Office of Pediatric Therapeutics within the Office of the Commissioner, which allows for awareness and coordination of agency-wide initiatives.

We provide consultative support to all FDA centers and neonatal and perinatal medicine product development, which includes drug, biologic, and device development, as well as foods.

We also collaborate -- collaborate externally with interested parties to improve and accelerate product development for neonates.

As mentioned, within the FDA, review

divisions can request a neonatology consult for products intended for neonatal use. Likewise, when sponsors submit materials to the FDA for review or feedback, they can also request that the neonatology program be involved.

While I have the opportunity, I also wanted to mention a few FDA resources specific to the neonate, including the neonatal clinical pharmacology guidance and the long-term neurodevelopmental safety guidance, which can be found at the associated links on this slide.

In summary, I'd like to reemphasize the rarity of common neonatal conditions as well as the critical unmet need for product development for conditions unique to neonates and for rare diseases with the knowledge that detecting, diagnosing and treating conditions in the neonatal period can greatly impact public health and that rare disease product development resources can be used to help in the advancement of therapies for conditions unique to neonates.

And because I'm a pediatrician and a neonatologist, no talk is complete without a cute baby picture to end with and further reinforce the importance of therapeutic product development and helping the most vulnerable in our population lead happy, healthy, and productive lives.

DR. MASSARO: Thank you. What a phenomenal way to open our meeting.

So we're going to keep moving on and -- and it's my pleasure to introduce Marshall Summar. Dr. Summar has pretty much worn every hat, I think, in this field. A geneticist, an investigator, a clinical trialist, an innovator, a teacher -- taught many of us in this room, I think, including myself.

So we're really fortunate to have him set the stage from the rare disease perspective. Thank you.

DR. SUMMAR: Really appreciate the chance to be here today. This is a great topic to be tackling. Let's see -- I have no conflicts to report. I'm just going to talk about theory.

Nice thing is I can kind of say things that are on my mind. Some of these come from conversations with Janet Woodcock over the years.

We're still working on some stuff together. I'll actually show you some data from a paper we're about to put out, on some things like that. So I think it'll be fun.

Don't read this, but basically what this says is I'm old. And over a 40-year academic career, you do get to wear a lot of hats. I was privileged to be NORD's Board Chair for a while. I ran the Rare Disease Institute at Children's.

But I kept track, and from 1977, when I was a high school student, until currently, I've been part either as peon or PI of over 200 clinical trials. So I've made every mistake you can possibly make or seen them being made.

And kind of what I want to talk about today is sort of that knowledge you pick up along the way, and what you see and what you learn. So, one

thing to remember is that rare diseases are rare, and we lose track of that sometimes.

But when you actually start looking at prevalence data -- Orphanet has done a great job with this -- you actually find that about 80 to 90 percent of the diseases have fewer than 150 or even 50 patients in that.

And, you know, so, you'll see a lot of folks go back to the same diseases again and again, because they're the only ones with numbers where you can use some of the classic clinical trial designs.

But as we discover more and more new diseases, some of them are in the numbers where it's single digit for how many patients there are. But very few of them have large numbers that we're used to in the historical clinical trial design world.

So why do clinical trials fail? There's been about three good studies on this. One of them we did internally and two out there published. And you'd think, "Oh, it's the science. The science just wasn't going to work."

But particularly in rare disease, about 60 percent to 55 percent of the time, it's actually recruitment and retention, which actually comes back to study design because we're using studies that were requiring large numbers of patients that just may not simply exist or very hard to get to.

So, it's -- that's kind of one of those interesting things. And if anyone wants some of these slides, I'm happy to make them available. Let's see, where did we go? Oh, sorry. There we go.

So, one of the things that's different about rare disease is we've been trying to, from a research standpoint, fit a square peg in a round hole for many, many years.

Obviously, by definition, they're rare. And, you know, this ideal model for treatment responses, where you want to have all the patients look the same so that your placebo and your control group are very uniform in all things, it doesn't exist in rare disease.

Genetic heterogeneity plays a huge

role. Urea cycle, which was one of my fields of study for many, many years -- my youngest patient presented at four to six hours of age, my oldest patient presented at 75 years of age, both with genetic defects in the same gene.

So, you get this huge variation, and the patients behave different clinically. Dr. Debra Regier, who now runs the program in Charlotte, and I think would also confirm that even with PKU, a disease that we've known about for a very long time, every single patient behaves differently.

And so, trying to fit that genetic heterogeneity into a clinical trial design becomes very, very challenging.

Also, natural history -- we're getting better. The NORD programs, like the IAMRARE, the NIH's Rare Disease Clinical Research Network, and other efforts, are starting to add clinical data and clinical background data. But we're still kind of swimming in a sea of we don't necessarily know what we don't know.

I mean, for great examples, you want to look at FARA, Friedreich's Ataxia, Cystic Fibrosis Foundation, who have built those registries.

But they're difficult to do, and they take a long time to build up a -- sort of a critical mass of data where you can start to use them. But those are still some of our most useful tools.

Finding patients. Diagnosis is difficult. You know, there's the whole thing of the diagnostic odyssey in rare disease, where it can take years to get a diagnosis.

As genetic sequencing is becoming more readily available, that's improving. Newborn screening obviously helps as well too. But many patients can go quite some time before they're ever discovered or ever found.

And then, effect size and frequency. When you're trying to design any type of clinical study, you know you're supposed to know where you're going to end up before you take the journey. In rare disease, we don't have that luxury.

We don't know what's the effect size going to be for even the outcome measure we're going to look for. What's the effect size going to be for a drug we're going to use? And I think this is true, not only in rare disease, it's true in neonatology.

And by the way, a lot of my research was working in neonatology back at Vanderbilt University back in the days.

I had the great privilege of training with Dr. Mildred Stahlman when I was pediatric president, working with Dr. Judy Aschner and working on bronchopulmonary dysplasia, persistent pulmonary hypertension -- same rules apply there as well too. So, there's kind of a nice carryover there.

Okay. So, one of our bigger risks in rare disease clinical research for clinical trials is actually not so much the false positive, which is what everyone fears, but it's actually, the false negative.

The way we design trials -- we have very small numbers to work with. The models we're

using of the double-blind placebo control trial actually create a really large Type II or false positive -- I'm sorry, false negative -- a risk for that.

And I apologize for the cartoons. I use -- I like visual aids there. But it's like you go up to the fridge and you're looking around, "Where's the butter?" Well, it's right in front of you, but you can't see it because you're not looking in the right place.

So randomized, double-blind placebo controlled trials really can increase that Type II error rate, even though it's something we've all become used to, we're all comfortable with, it feels safe, it controls for placebo effects and things like that.

So this is something that Janet Woodcock and I will be submitting next week for publication, but I went ahead and -- and we're going to trot it out today.

So, we took power calculations, and we

did them across three trial models, one of which is your classic randomized double-blind placebo control.

The other is for what we call a natural History-matched pair, where there's a decent correlation between the patients and the natural history study and the patients in your study.

And the other one is patient is own control, where you actually use the patient's historic data or their data and a lead in into the trial to do that.

And while the different models have different areas where they tend to work better, which you see pretty quickly, is the number of patients you need for different models can vary quite a bit.

In the, you know -- an effect size of 0.5 in the double blind, you need about 150 patients. To do that same effect size in the natural history, you need about 60, 70, somewhere in there -- need about ten.

Now I wouldn't use ten. I'd always want to use more than ten because you get edge effects

and things like that statistically. But it's interesting how fast it drops off.

And a lot of that is you're controlling for that heterogeneity, you're controlling for that patient's difference from all the other patients by making them their own control. So, it requires a different thought around study design.

Now, the thing that will immediately run through all of your mindsets, "but what about placebo effect?" So, placebo effect is where you have to be careful, first off, what your outcome markers.

There's a ton of studies out there. There are so many meta-analyses on this. It's really interesting. You can actually start to classify your outcome markers by the effect size.

So, for instance, a binary, like survival, that has really no placebo effect. If you look at biochemical markers, which is -- I'm a biochemical geneticist. We love those things.

It's really hard for me to think hard and influence my phenylalanine level or my -- well, my

ammonia level, I probably could, but my phenylalanine level's a little harder. So, the effect size there is minimum.

And then if you start getting into blinded physician scoring, that's still pretty good. Unblinded physician scoring, not quite as good. Patient scoring -- and interestingly not the worst one are parents scored outcome measures. So can -- those can have a 0.3 to 0.5 effect size.

But if you know that going in, you can actually accommodate that. You can use concomitant measures, you know, that are more objective to match those and things like that.

So, it's not that it is an insurmountable problem. You just have to think it through on the front end on how you're doing your study design.

So, as you can see, if you've got 80 percent of your diseases having less than 50 patients, even to get a robust effect size like 0.5, your double blind placebo control trial isn't going to get very close to doing that.

So, you actually do have to look at these other models, and you have to accommodate for some of their design problems.

So why does own control outperform? Well, heterogeneity, we've already talked about that. I won't beat that drum anymore. Between-group comparisons can lose sensitivity. Inter-patient variance often exceeds the treatment size.

One of the things I actually, people are finding in very small groups, placebo effect in one or two patients in a blinded double-blind placebo control can actually have an outsize effect on that placebo control group, whereas you might not -- you just see it in that individual patient instead. So, there's a whole bunch of things like that to think about.

Within-patient comparisons can actually be more informative. You can look at different markers. Let's say you're doing a combined pediatric adult study. You want to do some MRIs?

Well, you can't do that in the little kids unless you're going to take the risk of

anesthesia. But you may have a better marker for the younger patients, something like that. So, you can use combined outcomes. There are a lot of things like this.

And people have gotten very good at being creative in clinical trial design around this. And I think in neonates, it's the same thing. You really have to look at what you have available.

Think about the differences between centers and neonatology with treatment. You want to kind of limit a lot of that variation by trying to go across multiple centers again and again and again.

So, in heterogeneous rare disease, and I would say neonatology, the most reliable comparison is often the patient against themselves, not against another patient.

So, I, -- I picked up a good phrase recently. While we pursue regulatory safety or predictability, we actually may be giving on -- up on success for the trial.

So, because we are taking a model that

people know and it's a path everyone's tried, on the back end, we may be actually missing drugs that work that our patients actually need.

And we can't afford that. Because most rare disease trials get one shot. So, you want to really go in with your best design.

Natural history studies. I have to beat this drum because I love these things. It's a way to do a couple of things. One, you learn what the disease actually does.

A lot of those imponderables, like what's the effect size of your outcome, how important is it in that patient population, but it also pulls the community together before a rare disease trial begins.

People who participate in natural history studies are often the ones that will want to participate in a clinical trial.

And if you design your natural history study, you can actually, almost build control data for those patients that can then cross over into a

clinical trial. Thus, giving you almost a patient-controlled study from that standpoint.

But trajectory in these diseases is, again, highly variable. You've got to start to understand that. You got to get the safety context.

One of the things I love doing is I've been working with Ron Bartek with a program that he and Amy Rick started around pediatric inclusion and why that's so important in research, but it's also better science because kids behave differently than adults.

Safety in kids is not the same as safety in adults. And let's face it -- oh, sorry about that.

You said it beautifully, Melissa. If you're going to change the course of a journey, where's the best place to start? At the beginning.

You know, if you're leaving from a boat from New York going to England and you wait until you're five miles, you know, off the Spanish coast to make your course correction, that's really hard to do.

But if you do it when you're leaving New York, it's a lot easier to do. And I think the same is true in pediatrics here.

All right. Surrogate markers. That's the other thing we have to use a lot in these studies. Because a -- a big majority of the studies coming through now are neurodevelopmental or at least that's an aspect. So, one thing we try to -- neurodevelopment can take, you know, 10 to 20 years to manifest.

That's been one of the problems we've had with doing studies around things like PKU and stuff is it takes so long for the phenotype to evolve, it's really hard to build that into a trial.

So having surrogate markers like phenylalanine, or in my field, ammonia, or things like that become very helpful. I sort of call them the stunt doubles of the clinical trials world.

So, we use them to fill in for the star of the show, which is going to be brain preservation, something like that. So, while we may not like them, I think we kind of have -- we're kind of stuck with

them.

But you have to build your design so that long-term on the back end, you really do validate those things against what you're actually trying to achieve.

And, you know, I know places like Virginia Tech and others now are working on actually building programs around validating clinical outcome markers.

And I think that's going to be a field that we haven't paid as much attention to as we should. We usually wait until we're ready to do a trial, and then we say, "Oh, let's -- we got to get these markers validated." Well, that's why we're still doing six-minute walk tests.

Just anecdotally, since I'm actually a little ahead of schedule, in our clinical trials clinic at Children's, we had one nurse who I would call -- was a bit of a cheerleader, and the other nurse who was a bit of a grump, and there was a statistically significant difference between their

six-minute walk test outcomes when we were doing those.

And so, you have to remember that that's a possibility when you're doing these things. But I think there should be a new generation of things that we can use, new markers, new imaging techniques, things like that.

So pediatric inclusion, since Ron is in the audience and Amy and others, I have to do this. Also, I'm a strong believer in this. And like I said, I think a lot of us have talked about this before. Seventy percent of rare diseases are pediatric in nature.

Interestingly enough, if you look at drug use in hospitals, what is it, something like 70-plus percent of kids are exposed to drugs for which there's really no pediatric dosing data for them.

You know -- guys are doing a great job on catching up, but there's still a lot of ground to be made there. And the other thing is, a kid is not an adult. A preemie sure as heck isn't an adult.

Different metabolism, different biochemistry, the whole nine yards.

So, when we think we're protecting children from research, we should be protecting children with research. So, we should actually be looking at, "Okay, early on, what is, you know, the effect on this patient?"

And we come back to that point of -- point of maximal impact, like that journey to England. Where do you want to study a disease that has brain development issues? You want to study it before the brain is fully developed.

If you're going to make a difference, you don't want to wait until the patient's an adult, the journey is kind of run, and there's very little room to move therapeutically.

So, you're not going to really learn much, and you're going to end up discarding good drugs that you might otherwise have used. And there's a strong scientific justification for this.

There's also some equity issues and

things like that. But if you can make a good, strong science case, I really think it's something we need to keep looking at.

And there's a lot of examples where drugs deemed safe in adults, were not safe in kids. And vice versa, drugs that were not effective in adults-- actually, if you can get the pediatric study done, actually can make a difference.

All right. So, I just talked about point of maximal impact. Are you going to blow on the straw house? Are you going to blow down the snow -- the stone house? You're going to go for the straw house every single time.

Off-label use, we talked about that. Oh, good. I can skip some of these and save y'all some time.

All right. So, you've also look -- if you look at trials where they've combined adult and pediatrics, the success rate goes up.

And it doesn't go up a little bit. It goes up a lot. Because you're actually looking at

more of your relevant populations. Now you get broader effect size distributions and everything else.

And then let's talk about rare diseases and ethical sustainability. So interestingly enough, if you look at where should you do clinical trials -- I see a lot of trials done in different parts of the world and you want to try to do those trials where that drug's going to be available after it's gone.

I've seen some sad situations where folks have started a trial with enzyme replacement therapy, trial finished, was successful, and then that enzyme was no longer available for that patient because that country had no way to afford that.

Gene therapy trials, actually, kind of go around that. Small molecule -- oral drugs can still be affordable in those countries, but a lot of our biologics are not. So when you're designing clinical trials, you kind of need to give some thought as to where you're doing them.

And if you pick up one end of the stick, you've got to pick up the other end of the

stick as well, too, and make sure that those patients have -- I think Brazil just passed a law where if a drug's approved, it has to be provided for the patients in the study for four or five years afterwards.

So, you're starting to see some of these countries now putting things in place to prevent that. What does all of this kind of sum up?

Using patients' own control does not lower the rigor of your study. It's a different design model. It has -- it has its inherent issues like anything else does.

But what I would say is you may be giving up some placebo margin, things like that, against trying to do a study design for which simply the patients don't exist.

If you need 150 patients roughly for an 80 percent chance of success for a 0.5 effect size in a double-blind placebo, and you don't have 150 patients, you're kind of condemning those studies to failure before you've even started.

And, if you have one, where maybe I just need 10 to 20 patients for a patient's own control, yes, there may be some issues around some of the outcome markers.

You want to make sure that's built in. You want to make sure you're accounting for it. You want to try to make sure you got some objective markers in there because those are gold when you can find them. But own control does not necessarily equal lower rigor.

Early pediatric inclusion doesn't necessarily equal higher risk. We're all terrified of hurting kids. But if we don't ever learn to treat them, then they're going to get hurt.

The other thing that happens is if a drug gets approved in adult, particularly in rare disease, what's the first thing that happens? Off-label use.

So that drug's actually, probably not even been tested well in a pediatric population, but if it's a desperate disease, people will go ahead and

use that.

And I've seen that happen a couple of times in my career. And then it's almost impossible to go back and test the drug in kids because everybody's already on it because those families aren't going to wait until that's been done.

The worst error in rare disease is missing a real signal. I know from a regulatory standpoint, you're always looking at I don't want to send a drug through that didn't actually work. And I get that, I understand why. It also means you're the first one that put the spotlight on and drive a bus over.

However, in rare disease, we're so much more likely to miss a signal that was there because we either didn't use a design that fit the disease or fit the biology, things like that.

So rare disease drug design, I think, is a really critical issue. And I think good design flexibility improves safety, but also the science as well too.

Take-home message. Rare disease trials often fail because designs amplify noise, heterogeneity, not because therapies fail sometimes. Patient is own control and adaptive models can preserve signal in small populations.

And you want to do some long-term follow-up too. You can't just do a one-and-done. In pediatrics -- in -- the patients should be included early, not for equity but for actually scientific truth.

And on that, I have to end with a good joke slide. Thank you.

DR. MASSARO: Thank you.

We have a few minutes so -- before our break, so if there are questions for Marshall or Melissa -- sorry -- folks online can't hear. So just we have a few minutes, and then we'll take a break. But if there are questions from folks, there are some microphones here.

I'll just start with one that was in the Q and A box for you guys -- was about -- and I

think you spoke on this a little bit, Marshall, with the equity and the -- and the access to medications, especially in low middle income countries.

So both in the rare disease space and in neonatology, kind of what you touched on with -- with trials and then the accessibility of both the trials and the medicines for -- in these areas.

DR. SUMMAR: Yeah. There's a problem in the -- so one of the folks I get to work with -- this guy named Andrew Lowe -- come on over.

Andrew Lowe, who's an economist up at MIT, who's looked a lot at the pricing around rare disease drugs in that whole economy and market, and what we have is what's called the denominator problem.

If it costs a certain amount to get a drug through the process -- and last estimate was about 60 percent of what it would take for a mainstream drug -- but then you're dividing that by a very small number, that leaves a carrying cost for those drugs that's quite high.

And so even in a lot of countries where

access is an issue -- you know, and they can maybe be in the trial, but it may not be accessible later. And then if you look at biologics and the cost of manufacturing there, that's another huge issue from that standpoint.

So, it's not that nobody wants to treat those patients. Everybody that I've met out there in the market wants as big a market as they can get, but it's more kind of, can you, actually, go into those markets where they're affordable?

And interestingly, the pie is shrinking there. So, it used to be you had pretty good access, but a lot of sponsors now are looking at the U.S., Germany, Japan, and sometimes Australia as the primary countries -- they can go to. And that's smaller than it used to be.

Melissa?

DR. LESTINI: I don't know that I have anything to add that's so specific of sorts in that regard.

But I would just say that -- that, in

general, we're always thinking about the ethics of enrolling children in clinical trials at the FDA and certainly any -- any products and files that we're involved with in our office. We oftentimes have dual ethics consults as well, particularly when issues like this arise.

I didn't talk about the other aspects of our Office of Pediatric Therapeutics, but there is an Ethics Program that is a little nascent right now, but we will be back up and running soon, hopefully, where we offer that -- that expertise to help in just such kind of ethical dilemmas when they -- when they come to the agency.

DR. SUMMAR: I -- I do want to say something, y'all have one of the toughest jobs out there. So, on the outside, it's easier for us to push faster, faster, faster, include, include, include. And that's great, but if something goes wrong, you're the first one that it falls on.

So, one of the things I like to keep in mind is that it is a tough job for you guys because

you do have to worry about that -- that disastrous occurrence, which you know is going to happen at some point.

DR. MASSARO: There's another question from the audience for Dr. Summar.

You made a good case for baseline control study designs. Can you comment on what type of endpoints are most suitable for such a design, how well should natural history be characterized, and comment on the length of a run-in?

DR. SUMMAR: Yeah. Particularly when you're doing patient is own control, you can actually rank order the outcome measures you want to use.

If you've got a binary -- like I said, survival or not survival of time to event, those are good. Next comes biochemical markers, things that you can't physiologically change.

Next comes what I would say are the -- some of softer physiologic markers, you know, blood pressure, temperature, things like that. Then you get into your reported outcomes.

A blinded physician or blinded score is probably the best one. The impact on effect size is about 0.02, 0.03. Then it goes to unblinded score.

And then you get into what I would call measure outcomes, where someone's doing a survey -- a neuropsychological pain scale -- pain scales are probably one of the highest placebo effect size from those. So, those are the ones that you really have to account for.

But if you've got a hard biochemical marker, that's your best bet. Stable isotope studies are really wonderful in some of those things, if you're available for what you're working on.

But realize that a lot of the trials coming through that -- are for neurocognitive diseases, and those things just don't exist.

DR. LESTINI: I'll just say my two cents from a neonatology perspective. First of all, I am -- my personal opinion is I love the idea of a patient is their own control design.

I feel like cognitively I'm having a

difficult time, like at this moment, thinking of a neonatal condition which would easily fit into that model.

And I think that there's a lot of room for development of biomarkers, which we talk about a lot in the neonatology space, and certain disease conditions that could certainly help that type of trial design to be really feasible and meaningful and impactful in the future.

DR. SUMMAR: Yeah. One of the reasons I got involved in persistent pulmonary hypertension in the newborn is we were developing biomarkers to try to study that. And we actually found some really good ones.

I mean, thing to remember, biochemistry in the newborn is stressed at a level it's never stressed later in life. There's a reason why kids lose 10 percent of their body weight in the neonatal period. They are running full out.

So, in some ways, it's almost, if you really look for it, you can find biomarkers that you

might not be able to find otherwise. You know, in bronchopulmonary dysplasia, some of the markers of oxidative injury, things like that, can be better.

But you kind of make -- you've got to make a -- you got to start early to do that.

DR. MASSARO: We'll just do one more -- one more question for the audience about rare diseases and common mechanisms. Does this provide an opportunity to develop clinical trials that might focus on bundled rare diseases?

So I don't -- we'll talk a little bit tomorrow about platform trials and things like that, but if you want to comment on that?

DR. SUMMAR: You want to go first this time?

DR. LESTINI: I feel like this is more in your wheelhouse. I'm trying to figure -- I mean, I guess from a broader neonatology perspective, there's -- you know, you think of all of the kind of major morbidities that we talk about that I feel like I've mentioned multiple times in my talk that go along

with being -- being born premature, like bronchopulmonary dysplasia, necrotizing enterocolitis, interventricular hemorrhage, a retinopathy of prematurity.

What I will say in clinical practice -- and this is more anecdotally, I don't know that there are hard and fast numbers about this. Like the saying is kind of, if you've got good lungs, you've got a bad gut. If you've got a bad gut, you've got good lungs.

Like, oftentimes those diseases don't track together. So, I'd have to think a little bit harder about what a bundled approach would look like, but --

DR. SUMMAR: In rare disease, it's -- it's we're going to have to. Because as we're detecting smaller and smaller groups, you know, whether it's N of one or N of two, N of three, those -- the patients -- even for a patient whose own control trial, really don't exist to meet the classic standards for an approval.

So, we're going to have to do platforms,

we're going to have to bundles, baskets, take your pick, and whatever you choose to call them.

But it's almost going to become a little more like transplant science, where each patient's got to come in with their own set of problems and issues, and then you're trying to match them up with a therapy. That's one example I've heard from that.

But yeah, I think -- I think we're -- it's going to require a whole new pathway that will -- you can't take the current existing drug approval pathways and really bend them into this without twisting them so far out of recognition that they don't really mean anything anymore.

You're almost going to have to have specific pathways for these very ultra-small groups, which is going to be probably the majority of rare diseases, the way things are going.

DR. MASSARO: Thank you both so much. This is a wonderful way to open our meeting.

We are going to take a -- we're going

to take a 15 minute break, approximately, and we're going to start back up at 2:45.

(Off the record.)

DR. MASSARO: -- get started, so if folks can make their way to their seats? We're going to head into session two, which was going to be focused on our ethical considerations and discussion.

Unfortunately, Dalia Feltman, who is our -- she's a neonatologist and ethicist in the Office of the Chief Medical Officer. She was going to be here with us and -- and be our -- our -- introduce this session and -- and moderate our panel.

Unfortunately, due to illness, she wasn't able to travel. But she is well enough, thank goodness, to be with us virtually.

But we are going to start off with her -- her brief overview and introductory remarks, and then we will bring our panelists up. So we can go ahead and -- and start her talk.

DR. FELTMAN: Thank you for joining us for our second session of the day, Ethical

Considerations in Neonatal and Rare Disease Clinical Trials. My name is Dalia Feltman, and I'm a physician ethicist at the FDA and a neonatologist by training.

First, I'd like to take a few minutes to introduce how we think about ethical considerations when we're evaluating studies for pediatrics.

And given this conference topic, I'll try to highlight challenges in neonatal and rare disease. Then I'll introduce our panelists, and we'll get into our discussions.

As you know, the FDA regulations that safeguard children live at 21 CFR 50 Subpart D. After going over some basic foundations of human research protections, we'll dive into those Subpart D additional safeguards for children.

Children are considered a vulnerable population when it comes to research participation because they cannot provide informed consent for themselves.

Historically, the pendulum of how we navigate this vulnerability has swung from the

unfortunate reality of unethical inclusion of children in trials to the inappropriate exclusion of children.

The latter has resulted in fewer therapeutics, drugs, biologics, and devices labeled specifically for children.

Over the last few decades, legislation has been placed to incentivize and require the consideration of pediatric studies for more therapeutics, with the goals of both protecting children in pediatric research and advancing their health through research.

So, when we're considering whether a pediatric study is ethically appropriate, we first consider whether the study is scientifically necessary.

We look at the value of the question for children's health. We look at whether the study is designed to be a successful study, meaning it will yield clinically interpretable results. And we wonder if the enrollment of children is necessary.

If -- if it's not, if adults are able

to consent, they should enroll before children. And if we can use extrapolation from other indications or therapeutics or populations, that's also preferable.

Once it's determined that the study is of value and requires direct study in children, we look at the research activities involved to understand under which regulation the study might be approvable.

So here are the Subpart D additional safeguards for children in clinical investigations. These safeguards from 50.51 to 50.54 provide the regulations under which we can approve the enrollment of children in studies.

With limited regulatory exceptions, parents' consent for their children's enrollment in pediatric studies according to 50.55, and children that are seven years old and above usually are also supposed to give ascent to, actually, affirm that they want to be in the study.

So, honing in on the regulations under which we approve pediatric studies, usually 50.51, which requires no more risk than minimal, is not how

FDA therapeutic studies are approved, because most will involve more than minimal risk.

So, 50.52 and 50.53 are actually the regulations under which we evaluate most studies and their components.

And the way we can look at this is First, whether the research intervention, usually -- especially the investigative product, but also the other components of the research that will happen, we look at those to ask whether there is a prospect of direct benefit.

If yes, then the study and the research intervention needs to fulfill the other criteria of 50.52.

That is that the risk is justified by the anticipated benefit and that the relation of the anticipated benefit to the risk is at least as favorable as those that are presented by available alternative options and treatments.

Now, if the study intervention or study participation does not give a prospect of direct

benefit to the child, then the regulation 50.53 limits the risk that can be presented to that of no more than a minor increase over minimal risk.

There -- that's the famous criterion of 50.53. But, the other parts have to be fulfilled as well.

So, the intervention or procedure has to be reasonable -- reasonably commensurate with those inherent in the child's actual or expected medical, dental, psychological, or educational and other situations.

It also has to be likely to yield generalizable knowledge about the subject's disorder or condition that's of vital importance to understanding or ameliorating the subject's disorder or condition.

So, studies presenting the prospect of direct benefit need to have favorable benefit risk balances. We have to evaluate existing evidence to understand what those benefits and risks are.

And sometimes, as we'll hear from our

panelists in the first panel discussion, the evidence can be quite limited, making risk-benefit calculations rather challenging.

We may have clinical data from using the drug in other populations or other indications or using a similar drug for the same indication, and we might be able to extrapolate some of that data or at least inform our benefit-risk evaluation, but sometimes we only have nonclinical studies, such as animal or in vitro data.

In neonatal and rare disease, the therapeutic window may be limited by age, lessening the benefits with advancing age. So, trying to enroll children earlier to get the best prospect of direct benefit also then makes us think about what risks are occurring in that -- in those early developmental phases.

I'd like to clarify that the prospect of direct benefit comes directly from the intervention and directly benefits the patient.

So, for example, if the cutie in this

picture is in a study and is receiving the cookie as an investigational product, it has to benefit her.

The smile on Grandma's face who baked the cookie would not suffice at the -- as the prospect of direct benefit, nor would testing out the taste of the cookie to benefit children in the future that might eat the same type of cookie -- would -- those-- that wouldn't fulfill the prospect of direct benefit either.

And again, if there -- the research intervention does not present the prospect of direct benefit, then the risk presented must be no more than a minor increase over minimal risk.

And what helps me to understand that phrase is that the risk poses no significant threat to the child's overall health or well-being.

Using the component analysis, we look at each intervention being performed for only research, and depending on whether it presents the prospect of direct benefit or not, we evaluate it under 50.52 or 50.53 criteria.

The majority of therapeutic studies are designed with an intervention and a comparator arm. To ethically randomize a patient to either arm requires the presence of clinical equipoise. This is the genuine uncertainty about which arm is most beneficial among medical experts.

If we knew that one arm was highly superior, then -- or clearly superior, it would not be ethical to enroll a child in the other arm.

Provided there's clinical equipoise, control arm types are designed to yield the most clinically interpretable results while limiting control arm risks to that minor increase over minimal risk required by 50.53.

Control arms pose difficulties when there's -- when the numbers of eligible children are rare or difficult to recruit. We'll discuss control arms more in depth in our second panel, Study Design Considerations.

Thank you all for your attention, and I wish I could be there in person with you today. But

I'm very grateful to collaborate with you as we come from different roles with the same goal, to protect kids in research and promote research advances for these patients.

And now, let's get started with our first panel discussion.

DR. MASSARO: So, just as we get our panelists up here and assembled -- I think Dalia is joining us live from Chicago.

So hi, Dalia --

DR. FELTMAN: If you-- I don't know if you can see me. Hello.

DR. MASSARO: We can see you. So thanks --

DR. FELTMAN: I'd bring you deep-dish pizza, but I didn't want to bring these germs, so, thank you for having me virtually.

DR. MASSARO: So, as we get everyone settled here, we'll turn it to you to introduce the panelists.

And then I think -- so you have

directed questions, and then if the panelists who want to flag her attention, then you have a little stick it note there. You can put it on your name tag so she can see it from the cameras.

And then a special thanks to Dr. Nelson, who's going to be our boots on the ground, helping to co-moderate and -- and call things to Dalia's attention so that we can tag team this effort.

So we'll turn it over to you, Dalia.

DR. FELTMAN: And thank you, An.

And thanks again, Skip, for -- for pitching in and helping be my boots on the ground.

I actually can see you all pretty well, so I'm hoping that I will figure out who I'm introducing in the right way. So it looks like everyone's settled. So let me start by introducing our panelists.

And we do have two panels that will be happening today. And in the first panel, two of our parents will be participating, and then -- then in the second panel, they'll be switching out with two new

parent panelists coming on.

So first, I'll just introduce the people that are on the -- on panel one. Let me start with -- I'm going to start from my -- the -- the left to the right.

And so we're starting with Ashley O'Neil. She is a family nurse practitioner, writer, and speaker, whose advocacy is shaped by both clinical and lived experience.

A NICU preemie mother, widow, and bereaved parent, she brings a deeply personal perspective to maternal and neonatal education, practical resources, and compassionate care, authoring books like it's a NICU World -- It's a NICU World, Your Guide During Your Baby's NICU Stay, and hosting the, “Ask a NICU Mama” podcast, which amplifies the voices and needs of NICU families.

Thank you, Ashley.

Next, we have Matthew Rysavy. He is an Associate Professor of Pediatrics at McGovern Medical School and practicing neonatologist, and Director of

Neonatal Research at UT Health Houston. He oversees the conduct of clinical trials at one of the ten largest NICUs in the country.

Dr. Rysavy's research focuses on outcomes and management for extremely pre-term infants. This led him to -- to found and co-chair the International Tiny Baby Collaborative, and he leads the humidity in incubators for tiny infants trial.

And this is the largest trial ever conducted that is focused on the management of infants that are less than 25 weeks gestation.

Next to him is Dr. Elliott Weiss, who is an Associate Professor in the Division of Neonatology at the University of Washington, and he is faculty at the Truman Katz Center for Pediatric Bioethics in Seattle Children's Hospital.

One of Dr. Weiss's areas of scholarship is recruitment in pediatric clinical research, and that includes improving recruitment processes, improving parental engagement and research, and decreasing disparities in clinical trial

participation.

Another of his interests is clinical decision making, including models of shared decision making, decision making in times of uncertainty, communication during those times, and considering the chronically critically ill children.

Next, we have Allyson Berent. She is a Veterinary Internal Medicine specialist and Interventional Radiologist who shifted her career focus to rare disease drug development after her daughter was diagnosed with Angelman syndrome in 2014.

As the science -- sorry, Chief Science Officer of the Foundation for Angelman Syndrome Therapeutics, or FAST, she co-founded Gene Therapy Biotherapeutics to develop the first antisense oligonucleotide therapy for Angelman syndrome, which was subsequently acquired by Ultragenyx Pharmaceuticals in 2022.

She currently co-directs the Angelman Syndrome Biomarker and Outcome Measure Consortium and leverages her expertise in animal clinical trials to

advance therapeutics for human rare diseases.

Next, we have Alison Bateman-House, who is an Associate Professor in the section of Medical Ethics at New York University's Grossman School of Medicine. Dr. Bateman-House co-chairs two academic multi-stakeholder working groups.

The first is the Working Group on Compassionate Use and Preapproval Access, or CUPA. This study is patient access to investigational medical products and related ethical issues.

And the other, the one I've interacted with her in, is the Pediatric Gene Therapy and Medical Ethics, or PGTME, Working Group, which advances research, policy, and education on ethical issues in pediatric genetic interventions.

She also serves as Principal Investigator of the NYU Janssen Pharmaceutical Compassionate Use Advisory Committee, which won the Reagan-Udall Foundation for FDA's 2019 innovation award.

And last, but who we spoke a little bit

about first, is Dr. Robert Skip Nelson. He is the Executive Director of Pediatric Drug Development in the Child Health Innovation Leadership Department at Johnson and Johnson.

We know him better, though, from 2006 to 2017, when Dr. Nelson was the Deputy Director and Senior Pediatric Ethicist in the Office of Pediatric Therapeutics at the FDA.

Okay. So, I think we can get started. If anyone wants to share a little bit more about their own stories, you know, I'd -- I'd encourage you to do so.

So, for our first panel discussion, called "Weighing Benefits and Risks When Evidence is Limited" -- this is going to be based on what we talked about or what I talked about in the regulations where we look at interventional products and we see what is the evidence that supports the benefit risk profile of those products and how do we inform the comparison of benefit risk profiles of the investigational product to other available products.

The other thing that we use evidence for to figure out the prospect of direct benefit is wanting to make sure that the dose and the duration are supported by evidence to -- to provide that prospect of direct benefit.

So our first question for this panel has to deal with uncertainty. And I'd like to ask you all, how do we navigate uncertainty when evidence is limited and benefit risks may be valued differently?

Allyson Berent, why don't we start with you?

DR. BERENT: Great. Thank you -- answer that question. Here we go. Hopefully, you can hear me now. So, uncertainty is really an interesting word, particularly for rare disease families, because we are frankly experts in it.

The day a family receives a diagnosis of a severe and debilitating rare disease like Angelman syndrome, for example, uncertainty becomes all-consuming.

We're immediately confronted with

questions about our child's future, their prognosis, their morbidity, their mortality, and how we can possibly give them the best possible life.

And although Angelman syndrome is not classified as degenerative, its impact is deeply debilitating. And as a parent, that difference can feel equally painful and uncertain.

And over time, as families acquire what I often call a virtual MD and PhD in their disease biology, some of that uncertainty, actually becomes quite certain. We learn exactly what happens if we do nothing. We know the trajectory with a 20-year prospective natural history study.

We know that our children will never live an independent life and that every aspect of their lives will require lifelong adult support. In severe and debilitating disorders with no approved therapies, the baseline risk of doing nothing is actually the most certain thing that we know.

Families live that certainty every single day. As a result, we think about benefit and

risk deeply, thoughtfully, and with education. We recognize that action carries uncertain risk, but inaction carries certain risk.

And for many families, that distinction matters enormously. Not all families are willing to take that certain risk, and that must be respected.

But from my daily conversations with caregivers across scientific, clinical, and deeply personal contexts, I can say that many, if not most, are willing to consider participation in development programs if there is a meaningful possibility of altering their child's trajectory.

Importantly, families are not reckless. They want to understand the data that does exist, however limited it might be. They want transparency. And at what stage are they willing to engage in drug development will vary from family to family.

This is why clarity around both certainty and uncertainty, of both risk and benefit, is essential. We cannot discuss one without the other.

Clinical trials are, by definition, experiments designed to resolve uncertainty. They are the only path to generate the evidence that all stakeholders ultimately want.

And I live this reality every day with my daughter Quincy, who lives with Angelman syndrome. It is a severe and devastating neurologic disorder. It is a single-gene disorder that is not degenerative.

And while it's not degenerative and her beauty radiates every room she walks in, it is profoundly debilitating.

And time matters. Younger brains likely have greater capacity for change. The more we intervene earlier, the better chance we have of success. And improvement in her development trajectory to gain any level of independence is actually what we all strive for.

In the absence of a single approved therapy, the certainty of doing nothing is very clear. While the uncertainty of potential benefit becomes

less frightening and actually hopeful, the perspective is different to fully appreciate unless you live it while also understanding the science, the risks, and the clinical realities from multiple vantage points.

So, I do, I wear many hats, and I recognize that different stakeholders will view uncertainty quite differently. Wearing the family and advocacy hat, lived experience drives what outcomes truly matter.

Advocacy organizations work hard to educate families about the science, the experience in their diseases, and both the known and theoretical risks and potential benefits that novel technologies can have.

Until there is human data, both risk and benefit remain theoretical, and families do understand that. We conduct judgment scale studies to define what minimal meaningful change looks like for families. These studies help set meaningful bars for development, but they are not promises.

We share animal data where disease

phenotypes closely mirror the human condition, recognizing the limitations of extrapolation and applying scientific rigor in early development of all programs. Sharing all we know, that is the best that we can do in these early-stage programs.

This makes truly informed consent critical. Families must understand uncertainty honestly. Yet too often informed consent documents are heavily weighted toward potential risk and nearly devoid of any discussion about potential benefit.

That imbalance does not reflect how families actually make decisions, nor does it foster trust.

If I wear my industry hat, uncertainty is inherent, especially in first-in-class therapies for rare diseases. The responsibility to characterize uncertainty rigorously, reduce it where possible, and communicate it transparently is critical.

This requires early and frequent engagement with the agency and with families to align on endpoints, trial design, risk mitigation

strategies, while acknowledging that patients may value potential benefit differently than traditional paradigms might assume.

But they may experience risk differently than traditional paradigms may assume, as well. So, transparency and data sharing are essential. Managing uncertainty and early development is unavoidable, but it is not unmanageable.

So, in Angelman syndrome, we have a strong biological rationale supported by robust animal data, and translational work has informed dosing and safety. Study designs can and should include thoughtful staggering, safety monitoring, and predefined stopping rules.

This is how uncertainty is responsibly managed while evidence is generated in a pediatric population. Equally important is the selection of endpoints that matter. Our foundation, FAST, has invested more than $5 million in a biomarker and outcome measure consortium.

We have worked to create an equal

playing field for all sponsors, enabling rigorous, efficient trials focused on outcomes that are meaningful to families. Families are uniquely positioned to contextualize benefit relative to risk.

Thorough focus groups and externally led patient-focused drug development meetings have had learned -- we've learned that willingness to participate in drug development, especially in gene and cell therapy trials, is very strong.

And that challenges, which may seem modest to unaffected observers, can be life-altering to families living with Angelman syndrome. Listening to those perspectives is not optional, but it's obviously essential.

So ultimately, when evidence is limited, the challenge is not eliminating uncertainty. It is navigating it responsibly.

And the FDA has long recognized that in serious and debilitating rare diseases, like Angelman syndrome, patients may value potential benefit differently than traditional risk frameworks might

assume.

Uncertainty should never be confused with recklessness. It calls for partnership between regulators, developers, clinicians, and families to generate evidence thoughtfully, protect patients, and enable informed decision making that includes both potential risk and possible benefits.

In pediatric, rare and debilitating diseases, especially for first-in-human studies, balancing scientific rigor with regulatory is critical. Doing nothing is also a decision and one with known and meaningful consequences, and there is no uncertainty there.

Any questions --

DR. FELTMAN: Thank you, Allyson.

Sorry about the echo.

So Allyson, you -- you talked a lot about the -- trying to figure out how to stop the echo. I don't think I will.

So Allyson, you talked a lot about first-in-human trials.

And -- and what do you -- I'd like to ask the panel, what about when there is an alternative therapy?

I know, Ashley, you had talked a little bit about that previously in our discussions. Did you want to comment on that?

MS. O'NEIL: Yes, I do. So, when we are considering the risk and the benefits with the new interventions versus the ones that are already available, we have to take a good look at what those available drugs are and the quality of life that those kids have while they're on their medications.

Is their quality of life the best that it could be, regardless of the medical conditions that they have? What are the unintentional effects of those medications? What are the side effects of those medications? Because we know that these drugs were not really designed with the neonates in mind.

I'm a mother of a former 25-weeker, who spent six months in the NICU with bilateral IVH grades three and four, hydrocephalus, a few PVLs, like all of

these things.

And at the beginning of the NICU stay, neonatologist after neonatologist sat us down and said, "These are -- these are the outcomes that we expect of your child. This is what -- he's most likely won't be able to breathe on his own, eat on his own, maybe blind, deaf" -- like all of these things.

And so, I'm sitting in the NICU, I'm holding my baby, and I'm thinking about the road ahead. What would this look like? And so, we already know what the statistics show. Right?

So, if someone sat me down and said, "Hey mom, this is what the standard treatment shows. These are statistics. Let's try a new medication. Let's try a new therapy. We don't have all of the evidence of it, but this is what we do know."

And so, when you're a parent in this situation, you're getting thrown either in the NICU or your kid's suddenly getting diagnosed with a medical condition. You're already thrown out into the wild.

And so, when you have a chance -- all we

want as a parent is to have -- oh, is that better?

UNIDENTIFIED SPEAKER: Yes.

MS. O'NEIL: Oh, sorry.

So as a parent, all we really want is hope, even if it's guarded. Because we already know that our kid was diagnosed with this condition. We know what the statistics show. That just threw me off. I'm sorry. That's okay.

UNIDENTIFIED SPEAKER: -- you're good.

MS. O'NEIL: We already know what the statistics show. We already know what the life projection of our child is.

So, if someone came up to me and say, "Hey, Mom, this is a treatment that we want to try. We don't have all the data, but this is what we hope to accomplish."

And you compare it in a side-by-side chart and easily digestible information, a lot of times the parents would take you seriously and go home and ponder and think, "Okay. What's -- how can this affect my quality of life? What does this mean?"

My son is six now, and he has, you know, BPD. And there isn't a year that we don't spend at least two weeks -- or two visits in the PICU, multiple ED visits. And then on top of that, he has epilepsy. And how many times are we in the ED or getting admitted for epilepsy?

And he's currently on three different medications for seizure control. One causes sedation, and one causes unintentional weight gain. And you already have a kid with left-sided CP.

And so now he's overweight, and he's in and out of the NICU -- or the PICU, because he can't breathe, how is that on his overall quality of life?

Once we get to a point where he's able to ambulate with the walker, we're in the hospital for a week, and so that sets us back.

So, if there was a medication in hindsight that we could have used and tried, would it have been better? Who knows? But we already know what the statistics show long term of a neonate that's born at 25 weeks, 650 grams. We already kind of know

what that shows.

So, what is the -- in my opinion, like what is the harm of trying something new as long as the parents are truly informed and they know what the risks are.

DR. FELTMAN: Thank you, Ashley.

And -- and for what it's worth, I heard you the whole time, so you sounded great.

How about Dr. Nelson? Skip, would you like to talk about your idea about sliding scale of evidence, as a regulator in your -- in your past life? How do you look at that?

DR. NELSON: Sure.

And – and, it's a very nice position to do so following those two sets of comments, because I'd like to link the sort of clinical view to the research regulations.

And if you go back, one of the things I did when I was at FDA is I went over to Georgetown to the Kennedy Institute, and I read through all of the minutes of the National Commission.

And if you also look at the report, which was published in the Federal Register in January 1978, the framework that they used to create the regulations that we have -- and it's literally -- the regulations are word-for-word out of their report, was this idea of the kinds of decisions that responsible parents make. All right?

So, they started with that framework. So that's why you get this daily life minimal risk kind of language. Parents make decisions every day that hopefully involve minimal risk, may not, but hopefully.

And then this category of 50.52, they said parents make clinical decisions every week around -- every day around the health of their children. And so, they wrote that category to try and reflect in their mind the sorts of considerations that go into that clinical decision-making.

So, that's where you get this idea that the risk is justified by the benefit, and then that risk-benefit balance must be comparable to the

available alternatives.

And so, if you think about it, imagine yourself -- I -- I trained in neonatology, worked there briefly, but then most of my career was in the pediatric ICU.

Imagine yourself at that bedside having a conversation, whether you're there as a parent or you're there as a clinician, and you're faced with a critical decision around a -- a child who's seriously ill. What are the data that you feel you need to intervene?

That's going to depend upon the severity of the illness, what you expect might happen if you don't treat it, what are the options that you might have otherwise that may or may not have good data with it, and – and, how willing are you to tolerate the uncertainty that you have around that whole picture?

So, all of the considerations that have been talked about, in my mind, come into deciding whether or not an intervention should go forward under

the Federal Regulations Subpart D 50.52, really are framed clinically.

And that's not a single threshold. It's not as if there's -- you've got to hit this bar, everybody has to hit this bar. That's not going to happen. And that's going to vary.

No alternative serious disease, hopefully a great animal model, maybe not, but as good as you can get, the FDA is put in a position of having to make a decision to allow that to proceed under those conditions.

Now, a -- a couple other comments around uncertainty. Lynne [ph] will know this. One of my favorite sentences in ICH E11A, in the context of extrapolation, is that the tolerable degree of uncertainty is a clinical judgment.

Any statisticians in the room? I apologize deeply. It is not a statistical judgment. It's a clinical judgment. Okay? It's in there. It's in extrapolation. But I would argue that's true in all of these circumstances.

In other words, we don't have to worship at the altar of – p0.05. It may be something else is appropriate. Now, we can then debate what that else is. I'm not saying there's a magic number out there.

But at the end of the day, these decisions are what I would call deliberative. And what I mean by that is it's a conversation.

When I was the ethicist at the FDA and I -- hopefully, this might ring true with Dalia's experience -- you're in conversation with the division, you're in conversation with people around -- you know, does this protocol fit?

And it's not as if the ethicist had the last word, and hopefully, the lawyers never had the last word. All right. Separate issue. We won't go there.

But it's a deliberative. And what's key into that deliberation? It's the patient's voice, and it's the parent's voice. It goes to the risk -- you know, the trade-offs in that risk.

And I'll end with this. I felt -- I don't know if it's changed, but I felt when I was at the FDA, that if the sponsor wanted to have an impact, bring a parent. Don't bring a key opinion leader clinician. Bring a parent.

I think the parents probably had -- or parents' groups probably had a bigger impact on FDA decision-making than whatever gaggle of key opinion leaders the sponsor could bring in -- or our clinicians.

So, I'll stop there, and -- and I appreciate the comments that y'all made. I will say people can clap after every panelist, but I guess at some point it is a panel, and you don't have to clap in between each one. But anyway --

DR. FELTMAN: We're clapping on the inside.

DR. NELSON: Yep. Anyway, so -- so, Dalia, I'm not sure where you want to go next. I mean, I'm -- hopefully -- we've precipitated comments on people's part, so – so, I don't know --

DR. FELTMAN: That's okay -- yeah -- is -- yeah, that -- that's fine.

I don't see any Post-it notes up yet, but is there anyone on the panel that would like to say more, or -- I think that we've got --

DR. BERENT: I would just love to comment, if you don't mind, Dalia, on Ashley's topic because I totally agree with you.

And I think when we think about risk and benefit at different levels for different diseases at different ages, I think it's really important you have to understand what the alternatives are.

And I think when you're talking about whether you can use an investigative therapy as a small molecule to try to prevent hypertension, it -- it's a different conversation than a single treatment gene therapy for a rare single gene disorder.

I think those are very different conversations. Those are balanced in very different risks and different urgencies. Because in a neonatal ICU, you need to make decisions probably within

minutes or hours.

As you're developing a gene therapy that could take three years. And families are really educating themselves over those three years to understand what those risks and benefits are.

So, when a -- when you come to a parent with them signing consent to enroll in a gene therapy clinical trial, they are so well educated on what that means and how that could or could not impact that child versus a child in the NICU with premature challenges in which they need to make a decision on A or B in the next 60 minutes.

I think those are very different challenges. So, it's not only having multiple alternatives, it's having also urgency. And we all have urgency. But that's a different type of urgency, I think, and I think we have to think about them differently.

DR. FELTMAN: Thanks, Allyson. I think something you highlight makes me think about different characteristics of risks.

So, they might be -- it might be a risk that is really annoying and happens all the time for a patient, versus it's very rare, but it can be extremely severe.

The reversibility of things -- so, you know, gene therapy, maybe it's one and done, maybe they have to, you know, re-dose somewhere along the line, versus, you know, in a -- Dr. Summar had mentioned, you know, you could have a study where a person is their own control.

That would work if you have a medication that is -- you know, has temporary effects and certainly not long-lasting effects. So, you know, those are some of the ways we think about risks when we're looking at that balance.

And it's -- sometimes it's hard because which one is worse or wins, you know, a very rare but terrible effect versus a very prevalent -- something that changes quality of life, you know, negatively.

So, thanks for bringing all -- all that up.

I think we'd -- the last speaker might be -- unless -- unless Matt causes more people to want to say -- crosstalk.

But, Dr. Rysavy, I think you were going to talk about --

DR. NELSON: Dalia, could I just make one quick comment to what Allyson said?

DR. FELTMAN: Okay.

DR. NELSON: One thing I think is important to understand about risk. We think of risk as a data-driven issue. It's not. Risks are actually incommensurable.

Because you have the probability. That's data. But then you have whatever harm you're trying to prevent. And those are -- you know, we -- we compare them all the time.

Do you want to lose your left hand or your right hand? Well, it's going to depend on whether you're left-handed or right hand or whatever you do if you're -- you know, and we may vary on that.

But the key point is, I think risk

assessment is fundamentally a moral judgment. And it's important to recognize that because that's precisely what opens it up for the importance of the patients and the parents' view about the trade-offs on that risk.

So, it's fundamentally a moral judgment. It's not just data-driven judgment.

DR. FELTMAN: Yeah, it's both the probability and -- and the actual degree of harm, I think. I would agree.

And, Dr. Rysavy, were you going to talk about some of the off-label use of -- of drugs and repurposing drugs -- evidence -- yeah --

DR. RYSAVY: Yeah, thanks, Dr. Feltman. And -- and this is -- this is great context.

So I -- I'm a neonatologist, and I'll speak from that perspective. I also am a clinical trialist, and -- and I also am the parent of a baby who died in the NICU many years ago.

And so I -- I want to thank the folks who coordinated this panel for making sure that that

voice was heard. I think that that's really, really important.

But I -- I think an interesting thing about neonatology is that the majority of the treatments that we give are off-label.

And this creates some really important considerations when we talk about risk and when we talk about research and comparing it to usual care, to what's happening outside of the context of research.

Just as a little background, as a little history, that sounds really bad, everything's off-label. But I think it helps to put it in context.

Neonatology is 50 years old. It was started as a subspecialty in 1975. So we just celebrated that 50th year anniversary.

And it started with people who said, "Hey, here's a new population of little babies often in prematurity, where I'm going to use the tools that exist, that I have access to, to try to provide treatment."

Well, these were tools for bigger

patients. That's all that was around. We heard a little bit about Dr. Stahlman before. Dr. Stahlman, famously at Vanderbilt, setting up the unit there, put babies in an iron lung. That's what she had.

Very early neonatologists used the adult ventilator. Now we have pediatric and neonatal ventilators, thank goodness. And those are devices. But you can see how this works with drugs too.

The baby's got an infection, oh, I better grab an antimicrobial. Baby is in pain, I better grab an analgesic. Well, we use what we've got.

And if it's on the hospital formulary -- because it has been labeled for something, it's -- it's available to us as a product, but we've never studied it in neonates, that's what we do.

We also heard a really nice talk from Dr. Berent here about we know what happens when you do nothing. That's certainty. And so in these

decisions, you have to understand that neonatologists make the decision to do something.

So, if we do nothing, we know what's going to happen. The question is what's the right something. So that's what -- that's why we have so many things off-label. And thank goodness, over 50 years, some things have been labeled now.

But the context of normal neonatal care is that the majority of what we're doing is still off-label. If you can look at research out there, you might see, for example, a statistic of like 90 percent of babies in a neonatal intensive care unit getting some off-label medication. Still a huge issue.

It's relevant to this conversation about risk and benefit for two reasons. One, in terms of benefit, we have a lot of low-hanging fruit here. There's a ton that we can do with stuff that's already in our toolkit, and finding out whether or not it's safe and effective is really important.

I should also mention, you know, we know that babies are different. Our first talk was

really important.

I really appreciated that it was distinguished. That this isn't just pediatric research, but neonatal research, and we have a lot of history of using even pediatric drugs in neonatology because that was the tool available.

And finding some harm -- chloramphenicol -- we call it gray baby syndrome, not gray child syndrome, because the liver metabolism is different in babies.

Think of sulfa antibiotics. Still widely available, great drug, on label, can be used to treat as an antimicrobial for older children, don't give it to a baby.

That was an available tool -- toolboxes -- neonatologists grabbed it. We didn't study it. We were wrong. We caused a lot of kernicterus, a lot of brain injury because babies are different. So, huge opportunity to develop safe and effective medications.

But the other thing I wanted to talk

about is how this really skews perception of risk on the ground as the doctor and as the trialist, enrolling patients in trials, talking to families.

So, to illustrate this, I'll give an example of an ongoing trial I'm participating in right now. This is a study of a drug called milrinone.

This is a drug in the hospital formulary. It's on-label for some indications. It's not labeled for neonates. It's been widely used in neonates to support cardiac contractility.

We have a neonatal-specific condition. That condition is postcardiac ligation syndrome. So something only babies see after the patent ductus arteriosus part of fetal circulation gets clamped.

Makes sense. It's rational. Lots of guidance out there. You look in literature, a lot of places have been using it for ten years -- have written about this. You see it in some sort of, you know, recommendations or guidelines that this is a rational treatment for doctors to use.

We have a study on an IND. We are

actively conducting a trial of milrinone versus placebo.

You meet with a family who's in a situation -- we might get 20 such babies in our NICU every year. You talk to them, "Hey, we're doing this study. We have this drug. Here's my ten-page consent document, and you can read about all the risks and benefits.

"You should be aware that we think that it might help with cardiac contractility. It might help with these other things. This is why it's a rational treatment. We don't know if it's safe and effective. We'd like to talk to you about whether you'd like to be in the study."

So, imagine that we go through all of the elements of an informed consent, and then the family says to you, "Well, what happens if I'm not in this study? What's the alternative?"

Oh, well, your baby might actually get it anyway. It really -- it just depends on which doctors on. Some of the doctors like it. Some of the

doctors don't. So, if you're not in this study, your baby could get it.

I mean, we probably for sure wouldn't have given you the ten-page consent form, and we may or may not have actually talked to you about whether or not it was experimental.

For sure, there would've been no safety monitoring, and we would've also collected none of the data to keep, to make sure that we could improve care for the future.

We don't actually say that by the way. But that's the dilemma. And that's, I think, part of the issue that you have this distortion effect when the vast majority of what we do is off-label.

And so, trying to study that is a little bit difficult in neonatology. Huge opportunity. It just makes that discussion much harder.

I think -- you know, you could -- you could say that there are some incentive questions here about industry, about parents, about doctors, about

researchers. We can -- we can leave that to broader discussion and how we can best study those things.

But I just wanted to highlight when we talk about risk and benefit, recognizing the differences in risk between what is a formal experiment, which is participating in research, and what you might call an informal, unassessed experiment, which is the thing we call usual care.

Informal because we didn't actually make it a formal experiment. Unassessed because we're not really doing any of the safety monitoring or keeping any of the data, but we think it's the best that we can do because we know we better do something.

I think that's really important in how we think about it at the bedside, but also how our families think about it. If the drug were to cause harm, but nobody was there to study it, does that child still suffer?

And so those are some of the things maybe the group can talk to us about. And I'd love to hear the parent perspective on -- on thinking through

that, the risks of research versus the comparator.

Thank you.

DR. BERENT: I'm happy to comment, but I wanted to give Ashley an opportunity.

Do you want to comment? Okay.

I -- I feel that I live that same life of off-label. I'm a veterinarian, so I live the life of everything is off-label, but it is in your toolbox, and making those decisions is very challenging at times.

Again, I -- I do go back to, you know, my lived experience, which is in a very rare debilitating disease in which we're trying to develop gene and cell therapies to improve trajectory of life and independence in life is -- is similar but different.

One is we have no alternatives. There is nothing. We know what happens if we do nothing. Two is that we don't have anything off-label to try. And -- and three is that, you know, the -- the incentives are different between different

stakeholders.

But if the north star is the improvement of life of a child, then everyone's incentives should really be the same.

Because industry benefits from the improvement of the life -- that -- that child's life. The agency benefits from the improvement in that child's life in making good decisions, and, of course, the child benefits.

And so, if we always think about what's in the best interest of this child and let the parent really think about what we know about risk and what we know about potential benefit -- which, starting in first-in-human, never been there before -- we have animal data. That's all we have.

There's a brave soul that's going to make that choice to be in that trial. And then the second patient's going to have more data to go off of, and the third is going to have more. And the bravery of those first few patients is enormous.

But we have to give them the

opportunity if there's a possible option, and they have the choice to say yes or no. And I think it's -- just has to be grounded in evidence, the best we can give them.

And it may be your personal evidence of your own personal experience as a doctor, and how you treat your patients and what you feel like in your hands, the outcome is, which is anecdotal and not strong data.

But you are the treating physician at that moment, and the parent is going to trust you, I bet, because you have a great bedside manner, you've been in their shoes, and they are going to say, at least if they say what they say to me, "What would you do if this was your child?"

And you're going to make a choice of what you would do if it was your child. Whether you want to make that choice or not, you're going to make a -- have to make a recommendation. And that's likely what the parent's going to use because they trust you.

DR. FELTMAN: Thank you.

Ashley, did you want to also say something, or -- you don't have to. I can move on too.

MS. O'NEIL: Being the -- being the mom of a patient that's been in the NICU for six months, and he's seven now, and time after time we're offered different treatment plans.

And you go home, and you research everything, and you come up with the best possible choice that you can make when you're -- when you're consulting the providers.

And as a mom, we always weigh, is this the right decision? And no matter what we choose, there is a little bit of, I don't want to say regret or sadness, but just this nagging feeling, is -- is this the right choice? Is this the right option?

But in the end, all we really can have is, like, hope. And then you pray that the decisions that you and your team have made, is in the best choice of your child. And that comes with time and practice as we as parents come to trust our instincts and the

knowledge that we've gained.

And I -- you know, as a medical mom, I look to, like, all of my medical mom peers and say, like, "Did this work for you? Like, what are your thoughts?"

And then a lot of times they'll give us the right questions, and we go back and add our -- ask our providers, like, "Hey, did you think about this? Is this a good option?" And then it's more like a collaborative effort of what's for -- what's in the best interest of the child, so --

DR. FELTMAN: Thanks for raising that point of -- of community, kind of figuring out what evidence is even needed and what questions to even ask.

I think we'll move to the next -- we'll move to the second question of the panel, and then we'll take questions from the audience after that.

And this is about patient selection, again, within this idea of weighing risks and benefits. What are ethical considerations for the

inclusion of pediatric patients in whom risks and benefits might be different?

Alison, would you like to talk about that?

DR. BATEMAN-HOUSE: Sure.

First, I want to say I feel a little bit at a loss here because everyone knows what a pediatrician is or what have you. And then I come in and say I'm an ethicist, and people give me blank stares.

So, I am someone who am honored enough that people turn to me and say, "I don't know what to do in this situation. What is right and wrong? Can you guide me?"

And, of course, I don't have all the answers, but what I try to do is to interact with all the involved stakeholders and find out, you know, what are the relevant issues, worries, things that might be unintended consequences, et cetera, and try to use those as well as, you know, memories of past similar experiences, laws, policies, other such things to

guide people.

So that's what I do as an ethicist. And one of the questions that does come to me, both from sponsors of pharmaceutical companies, biotech companies that are doing drug development, as well as from patient advocacy groups that are interested in participating in those drug development efforts, or perhaps even, you know, sponsoring them -- themselves, are these questions about, you know, well with whom should we start our research?

You know, first-in-human, should we start with someone -- we've heard earlier, you know, younger means that there's more plasticity, someone might be able to have more of a benefit, and -- and then that hopefully transfers to demonstrable impact from the intervention.

Or should we go with someone who is older, and perhaps this is their last, you know, decent chance of having an intervention? You know, should we go with people who are ambulatory?

Because we have things like the

six--minute walk test that Marshall mentioned earlier, that even if they're not great, they're commonly used, and – and, we can, you know, rely upon those patients and this endpoint that has been used traditionally and get the -- the answer to our question about the safety and efficacy of this product.

Or should we say, "Hey, we all know that this particular test isn't ideal. Let's stop using it. Do something different."

And doing that something different might actually mean that we're potentially going to involve a different pool of patients, maybe patients who aren't ambulatory, et cetera.

So, when people come to me and ask those sorts of questions, as I said, I don't have the answers, but what I say is, "How well do you know what your patient group, or your potential, you know, purchasers of your drug for this particular population feel about this question?"

I want to disclose that part of my funding comes from Parent Project Muscular Dystrophy.

And I am so blessed in that organization in that long before I met them or they met me, they made a real concerted effort to find out what their patient community -- and that means the patients themselves as well as their caregivers -- thought about issues like how much risk is acceptable for what, you know, possible level of benefit, et cetera, et cetera.

So, when I am talking with stakeholders who ask me what should we do, I will want to know things like, does your patient group value, you know, most explicitly life, they just want to have a longevity and that's most important, or are there other things such as ambulation or ability to self-feed or self-toilet or speak that is most important to this group?

You know, how would they evaluate different possibilities? And then knowing that there is uncertainty, how likely is it that those possibilities are going to, you know, result or be involved some way, shape, or form with this trial?

So I -- I put a lot of it back on either the sponsors, to say you have an obligation to your hopeful users of this drug to go find out more about what's important to them.

And also on the patient advocacy groups, to say before you are speaking on behalf of your community, you need to really understand what your community thinks.

And that last part is difficult because, as I'm sure you all know, not everyone within a patient community has a unitary -- unitary point of view.

So, someone may say yes, you know, ambulation is worth a risk of a certain amount of, you know, potential death from a product, whereas other people may say no.

And it's not just questions about who should go into trials. It's questions like someone just posed a minute ago -- maybe Skip, I don't remember -- about dosage.

Do we start with a low dosage in the

name of safety, or do we start with a higher dosage to try to amplify the likelihood that there's going to be an effect from that intervention in that first-in-human situation?

So, I think I'll stop there and see what others have to say.

DR. FELTMAN: Thanks, Alison.

I -- and I know with patient selection, Elliott, your work has a lot to do with inclusion of equitable sample sizes and people from different groups. Did you want to talk about that?

DR. WEISS: Yeah.

I am going to share a little bit about justice and representativeness in asking the question of who ends up enrolling and then completing participation in neonatal research. Does the research population match the clinical population we want it to?

And when I think about this, I think about it in two different ways. One is temporarily and one is by issue. And for each, it's important to

think about how these things differentially impact participation based on characteristics of the patients themselves.

Said another way, if there's a snowstorm that made participation go from 20 percent to 5 percent, but it was perfectly random, that would not be a justice or a representation concern. Where these come in is where they inequally impact who's in research.

And within a group of others, we came up with this idea, and this is how I've been thinking about it, five different stages of what -- how someone ends up in research.

So, the first is clinical, who gets to the clinic in our setting, prenatal clinic, the NICU, or a follow-up clinic?

If you can't take the day off work because of risk of losing your job, if you have fear of seeking medical care due to violence or threats between leaving your house and getting to the clinic, do you have -- do you have coverage for other

dependents, whether it's elderly parents or other children, and then once you're in the clinic, step two, who approaches those families?

We have -- a lot of big children's hospitals have multiple sites. They've -- to provide clinical care in the community. That's fantastic. Often, the research enterprise only exists at one of those places.

And then the third idea is relational discussion with these families. And research shows that that part is the most important when parents are deciding whether to participate or not in research.

What is this connection between the researcher and the parent, between the researcher, the clinician, and the parent in this triad?

Next, we have the informed consent form itself. That's important. And it can be very challenging when it's very long and incomprehensible, and also is probably not where most people make the decision from their own report.

And then finally, study procedures

themselves. If you need a stable cell phone number in order to be reached for follow-up questions -- there are families that don't have that.

There's studies that will pay for parking. That's great if you have a car. And if you don't, you're spending hours going from bus to bus to get to a follow-up visit.

And then the other way to think about it is based on issue, and I'll go through this pretty quickly. But one example is language. And it's easy to think -- and a language other than English, we just need to translate an informed consent form.

But we also need an interpreter. We also need a validated tool in that language. This impacts all the way across these different stages.

There's the level of risk which we've talked about. In -- in really complicated ways, this impacts who ends up being in the study.

There's infant state. We know that the sickest infants end up not being in neonatal clinical trials. And the neonatal research network has been

able to look at this in really elegant ways using a generic database, combined -- compared to who ends up in the study.

And it shows that before they join the study, these populations were different and tend to be that the sickest ones don't participate.

And then finally, as other has mentioned, it's the parent state. The -- whether it's the birthing parent or another, they might be on meds, they might be at the delivery hospital, the neonates three hours old, already at their third hospital, and now we're trying to enroll in research.

There's stress. There's pain. The -- the delivery itself could have been a result of an acute use of drugs. And all of these impact who ends up being in our studies and who don't -- who does not.

And I think just to say that all of these issues are things that we need to think about because if we're systematically excluding certain populations, certain severities of illness, certain subpopulations, then the downstream clinical data that

we have, even from the biggest, most robust, well conducted neonatal clinical trials are not going to answer the questions we want in the patient populations that we want and need the most.

Thank you.

DR. BATEMAN-HOUSE: I totally agree with what you just said in terms of all those different points at which either a successful ask can be made or a successful decision to join or continue to participate. In so many different ways, things can fall apart at those times.

Most of my work is with gene therapies. And I just wanted to point out that when you're talking about gene therapies, you have a whole other set of issues that come first, which is who gets what genetic testing, who has a diagnosis, who is referred to what sort of specialty clinic that might even be thinking about certain things to screen for.

And we know, just as you were talking about a second ago, there's vast inequity, not only globally and who has access to what, but also within

the United States.

There was a study a couple years ago looking at, you know, who even has access to pediatric specialty care? Not to mention, you know, once you are in that facility, do you have insurance? Do they take your insurance?

Do you, you know, are you going to be asked to do step therapy in terms of first you have this one screening test that only tests for a couple things, then you screen for another thing, or will you get a, you know, sort of broad spectrum screening test at the very beginning when hopefully you can make the most difference?

So just wanted to point out that once again, none of us are going to be able to give you a one-size-fits-all answer or an algorithm that you just insert your, you know, yes, it's a severe disease, you know, yes, it's life-limiting, and it spits out an answer.

All of these are going to have variables unique unto themselves.

DR. FELTMAN: Thank you, Alison and Elliott. I think you illustrate very well that many potential pitfalls, and -- and hopefully some of the -- being aware of those pitfalls, we can ensure more ethical recruitment, even from knowing who, you know, is eligible for a study based on their diagnosis.

I'd like to, if it's okay with the panel, give you -- share with you a question from the Q and A from the virtual audience. It -- it talks about Dr. Rysavy's comments, but I think that it's -- it would be helpful to hear from -- from you all.

It says, "I think Dr. Rysavy's comments and context is very important. The concern I have is that in the NICU research, maybe especially drug development research, is not a high priority, and we are not educating parents, nurses, or the community of the importance of this research, which leads to lack of strong advocates for neonatal drug development.

"I present the contrast to pediatric cancer centers where drug development research is a

priority, parents seek centers that provide research options, and there are strong advocates for oncology drug development.

"Both NICUs and pediatric cancer patients have outcomes that need improving. Why does this discrepancy exist, and is there some ethical consideration" -- I don't -- "diving this difference?"

But I think -- I'd love to hear your -- your comments and thoughts about kind of the -- some of the infrastructure differences that occur within pediatric cancer center drug development and NICUs, if anyone wants to talk about that?

DR. RYSAVY: I can give a few words.

I think we could think of a multitude of differences. I agree that there are some really important similarities here.

Pediatric cancer, if we do absolutely nothing, we expect -- you know, we have an expected outcome. We need to do something.

High risks of life-threatening or high morbidity disease -- we're in a pediatric population

where we're talking about surrogate decision makers, often a surprise diagnosis, we're interested in long-term outcomes, not just what happens next week or in a couple months. So, there's a lot of similarities.

I think some really important differences that exist include -- for a lot of neonatal studies and maybe this will come up too in the next panel discussion, not only is it emergency research, not only is it research of a pediatric population, which we have a surrogate decision maker, but there is, I think, a third complexity that maybe is under-recognized, which is a surrogate decision maker who often herself is sick or incapacitated, who just had a c-section, who just delivered a baby, who's under general anesthesia, or recovering from it on pain medications herself.

Premature birth, as an example, often occurs in the setting of maternal illness. So mom is on other medications and dealing with this.

This actually comes up a lot in research. We run a lot of focus groups, and we talk

to families about how we can improve our processes.

And I can tell you, unfortunately, a few times, Mom, in talking to me now two years out, says, "Yeah, actually, you know, I remember coming up to the bedside and saying, 'Oh my God, my child's in this study. What on earth is going on?'

"'And then my husband putting his hand on my shoulder and saying, 'It's okay, Honey, you signed this document two days ago.' 'Oh my gosh, I have no recollection of that.' 'I was there. It's okay.'"

And I -- I think that that brings up some really big issues and informed consent. Certainly, pediatric cancer involves a lot of anxiety and other things, but it's not the same that Mom herself, that the surrogate decision maker, is incapacitated in dealing with specific medical issues.

So that's true of at least part of neonatal research. That's not everything.

But I -- I think that that sort of contextual difference, in addition to the fact that

there are really important differences and incentives, make this a little bit different.

So, some of the incentive differences -- I would point out that for neonatologists, when we're doing stuff off-label, you know, the easiest way to study it is just to do a before-and-after study.

We changed the unit protocol last year and, you know, this was a -- right -- because of this issue that everything's readily available, it's already on formulary, et cetera. And look at our outcomes got better, and then we can publish that.

And then you get a few of those in the literature, and, you know, that becomes the most dominant treatment for any neonatal condition.

A lot easier than getting an IND and paying, you know, millions of dollars to do placebo control and working with the investigational drug pharmacy and paying millions of dollars to get coordinators at all of the sites so that you can go and try to reach Mom in a very difficult condition where it's, you know, frequently a no, not because Mom

didn't like the study, but because she's like, "Oh my God, I just delivered and I'm in pain, get out of my room." You know, this -- this was a shock to me.

And so, I -- I think that those are some of the huge burdens that -- that we deal with.

I -- I will leave to somebody like Skip to maybe talk about some of the industry incentives that might be different. I think that there might also be differences in incentives for some of the nurses and doctors, and part of that's just cultural and how we think about it.

Thank you.

DR. NELSON: So Dalia, I -- I don't know if you see Alison's got her little orange -- or --

DR. FELTMAN: I sure didn't. I'm sorry.

Yes, Alison, please --

DR. BATEMAN-HOUSE: I -- I was just going to say --

DR. FELTMAN: Or is it Elliott? Okay.

DR. BATEMAN-HOUSE: I was just going to say two brief things. One, having nothing to do with neonates, but during COVID, I remember very clearly one attending who said, "We are too busy treating patients to do research."

And I think one of the -- the things in the background of what the question that was just asked is -- is, you know, indicating is that in oncology research and use of investigational medicines has really become thought part of the therapeutic modality.

It's not something that you've tried everything else, and then when there's nothing else to give, you turn to investigational medicines. So I just wanted to -- to say that there's sort of a culture difference that might be at the root of this question.

The other thing is I wouldn't -- I mean, yes, there's a divide that we're talking about right now between, you know, say the NICU and, you know, pediatric oncology.

But there's also a divide between academic medical centers and, you know, county hospitals or -- or other such more -- you know, less likely to do research centers.

And I think it goes back to what was just being said a minute ago.

If you have coordinators who are used to doing research, it's a lot easier for people to get involved in a research project, you know, start at a younger age, and -- and just sort of like learn by doing, and -- and have the sort of catalytic energy needed to be a lot lower than if you are in a place where research is not the norm, and you say, "You know, we have this important research question, let's tackle it."

You may have a crucially important research question, but you also are going to have a larger uphill climb just trying to figure out how to start that investigational process.

Elliott?

DR. WEISS: Yeah, just to add, I think

there is a confluence of very specific factors that makes it particularly challenging.

One is this exceedingly short enrollment window, which is really quite different in neonatology than in, say, pediatric oncology. These patients need to get a drug or an intervention in -- in minutes or perhaps hours.

Second is this time of exceedingly high stress for the people who are making the decision, as myself and others have discussed. And then the milieu that we're -- everything we're -- so much of what we do in neonatology is off-label already.

So many of the most important studies could be considered comparative effectiveness research, which I think makes some of these definitions that exist in FDA really challenging, no greater than minimal risk, or when what is already happening in a single NICU or in other NICUs may already surpass that threshold.

How do we think about the research testing what's already happening? And there are all

of these mechanisms, including EFIC, Exemption from Informed Consent, or so-called deferred consent, or waiver of consent, that -- which has been used internationally but very minimally in the U.S.

And all of these have some huge potential advantages in patient inclusion and representation while -- while having other challenges.

And I think the neonatal context is still figuring out how to make use of the -- use of these in a way that can make our research as robust and meaningful as possible.

DR. FELTMAN: Okay. That's great. Thank you for all of your comments.

I feel like we could talk a lot more about this, and unfortunately, we -- we need to stay on on time track. So I want to thank the whole panel.

I know there was some question of when to clap. I think this is a great time, especially to clap for -- Ashley and Allyson Berent, who will be changing spots now.

And then why don't -- we can have our

other panelists come up for our panel two, and people that have to stay can stretch their legs.

DR. NELSON: We are ready if you are, Dalia.

DR. FELTMAN: Okay. Great.

So I'll start with Jennifer Degl. If you want to wave or something?

Jennifer is a mother of four, including a micro preemie, born at 23 weeks. She's the founder of Speaking for Moms and Babies Incorporated and an author who has published three books and multiple articles in pediatric and perinatal journals.

She serves in leadership roles across several organizations, including the International Neonatal Consortium Leadership Team, Co-chair of the President of the NICU Parent Network, and Board of Directors for the NIDCAP Federation International.

With over 25 years in public education, she created and coordinates Maria's Hope, a NICU parent mentor program at Maria Ferreri Children's Hospital in New York, and is a passionate advocate and

public speaker for maternal and neonatal health issues.

Welcome, Jennifer.

And then our last panelist is Lindsey Wahlstrom, who I'd like to introduce. Lindsey has overseen patient engagement for 230 clinical research studies, many in the rare disease space.

In 2022, Lindsey's then five-year-old daughter, Rona, was diagnosed with a rare disease. Together, the two, mom and daughter, participated in four cell therapy trials in one summer, Lindsey as the donor and Rona [ph] as the recipient.

After Rona's death, Lindsey founded Rona's FUN LAB, a nonprofit organization that supports quality of life measures for critically ill kids in care and research settings.

So, thanks -- thanks for coming.

And we'll move on to our second panel, which is talking about study designs. So, we heard from Dr. Summar that many -- unfortunately, many

clinical trials fail.

And we want to talk about some ethical considerations that we think about when optimizing study designs to try to collect data consistently and data that's -- that is clinically meaningful and interpretable to make children's participation and enduring for families and children's research burdens worth the -- their trouble.

So, what I'd like to do is have you all talk about this question.

How do we balance the need for scientific rigor with accessibility when considering study group comparators, for example, placebo arms, external controls, other comparator groups, other study design considerations as well, recruitment approaches, stakeholder input, and other factors?

And Alison, maybe we could start with you -- Dr. Bateman-House?

DR. BATEMAN-HOUSE: Sure.

Someone -- again, I think it might have been Skip -- I need to remember who says what more

accurately than I am at the moment -- said earlier that what we're talking about is not a question of, you know, necessarily scientific decision making. It's moral decision-making.

And I think that that is also a question that we need to talk about in this panel, which is when we are giving unproven interventions -- and I'm going to say drugs just for the sake of simplicity.

When we're giving unproven drugs to a patient, what is our primary motive at that moment? Is our primary motive to help the child or the -- the patient in front of you? We're talking about neonates, so -- child.

As would be the case when you are engaged in medical treatment of a -- of a patient. You know, the doctor is there to advocate for that patient and do what they can to try to make things better for them.

Or is the primary motivation research defined as the -- oh, I should remember -- creation of

generalizable knowledge.

And it's not to say that these two can never happen at the same time. We hope that people who are engaged in a research study, such as a clinical trial, do gain some benefit from it. But we can't promise that.

And if we did promise that, I -- I think that would be inappropriate, unethical, a number of other words.

What we're trying to do is -- Allyson said a minute ago, we're trying to resolve uncertainty about the possible risk and benefit of this unproven agent.

And again, we hope it'll help people as they go through the process of being the ones on whom that data is being gathered, but it may not be.

In contrast, if you're talking about an access program -- an access program is just trying to provide that product, whether it's an unproven product like I'm talking about now or some other product to people who may benefit from it.

Again, there's no guarantee they're going to benefit from it, but they may. And the purpose that we're engaged in at this moment is to try to make access to that product available to those who -- for whom it would be appropriate.

Now we may collect data, just like we did in the research situation, but it's not necessarily going to be the same quality or caliber of data then if we were actually doing a research study in which we try to, you know, limit confounders, really sort of minimize the chances for effects that are due to something other than that particular intervention.

And I find that this is frequently confused. If you look at any discussion of clinical trials or investigational medicine provision, people are almost always talking about the treatment or the therapy or, you know, sort of implying that there's a benefit to be had simply by being in the clinical trial.

And we say yes, you know, there are

benefits to being in a clinical trial. You have more routine contact with clinicians. You know, there are people looking at your -- your lab work, and if it starts to – show a sign of infection, they can intervene more rapidly, et cetera.

But thinking about the actual intervention "X" that you are testing, you know, the question is, are we just trying to provide it to people because we think that's the right thing to do in a particular situation, or are we trying to collect really regulatory quality data?

And sometimes we can do the two at the same time, sometimes we can't. And I think that's appropriate, and we can talk about it. But I also think it's very important to be clear upfront about what is the motivating impulse. I'll stop there.

Actually, I won't stop there. I want to quote what Marshall said. Marshall said a minute ago that once a drug is improved, it's almost impossible to go back and test, you know, if you want to, like, enlarge the trial sample or something. And

I completely agree.

So not only is the question about are you trying to collect generalizable data, the question is, you know, you have this window in time in which there's uncertainty.

That uncertainty is going to close one way or another at some point. And what caliber evidence do you want to use in closing that window of uncertainty? Marshall is nodding at me so, yes, I -- I said what he said correctly.

Thank you.

DR. FELTMAN: Thanks, Dr. Bateman-House.

As a trialist, Dr. Rysavy, would you like to talk about how we balance scientific rigor and accessibility?

DR. RYSAVY: Yeah. Thank you, Dr. Feltman.

There are so many things we could talk about here that are unique to the neonatal space, but I -- one I'd like to just talk about because I think

interesting and I was so glad that Marshall -- that Dr. Summar brought -- brought this up earlier -- is the use of placebos.

And I want to talk about this in context of what I talked about last, which is in neonatology, the majority of what we do is off-label.

And I think a lot of families come to get that. We were talking about culture of research and different incentives and how -- you know, but maybe we're a little bit different sometimes than in oncology, but in some places there is sort of a culture of research.

And at least at the bedside, the nurse or the doctors get, okay, being in the trial means taking random care and making it randomized care.

And I think some families, when they understand that sort of description that I gave you before, maybe not in exactly those words, kind of get that like, "Okay. This is something that my baby may have otherwise gotten if I went just, you know, to a different place in town that wasn't participating in

the trial," for example.

Or "If I'd come to you six months ago before your trial started, you know, I might have received the same medication."

What I find interesting is in that context, the use of a placebo is really difficult. If the only major difference in a drug development study of a repurposed drug that doctors would otherwise are routinely using in the NICU is the process of masking, of blinding, some parents are uncomfortable with this.

This comes up in some of our focus groups. "Okay. We get it. There's no extra drug levels or pokes or prods or exams, and like we'd be really open to this trial.

"But, you know, Doctor, I just feel really uncomfortable, well, not knowing what my kid's getting, but more importantly, sometimes not knowing that my doctor knows what my baby is getting."

And so I bring this up -- I -- I feel like a little bit of a heretic talking about having controlled trials that are not placebo-controlled.

I -- I believe strongly in evidence-based medicine, and I worry -- you know, if you look at Cochrane reviews and their levels of evidence, you know this counts as a ding against the study and its robustness.

But on the flip side, it might let you get the study done. It might give you a more representative sample because you bring in families that have that fear. I think it might actually allow you to perform it.

So as -- as Marshall showed, you know, when 50 percent of trials fail because of enrollment difficulties, you can actually do it and some things better than nothing.

My follow-up comment is just to echo what Marshall stated about this. It works in the context of having the right outcomes, and there, I think we just need to be very careful.

So, if you've got a hard outcome, placebo control doesn't -- you know, shouldn't really change survival or mortality, shouldn't change certain

lab values.

Considering that in study design, I think in this context, where we have a lot of off-label use may be of some benefit. And how that fits in a regulatory context, I think, is worth considering.

Thank you.

DR. FELTMAN: Thank you, Matt.

Skip, did you want to talk about control groups as well?

DR. NELSON: Sure.

We could have a very long conversation of different control groups, and I'm not going to go there.

I do think I say ICH E10, which was published in 2000, is a very important ethical document. I mean, because it talks about different control groups. But it's now 25 years old, so there's a lot more that can be said.

But at its root, the question of a control group is, if we do a scientific project,

whatever that design is, can we draw an inference from it? Can we conclude that if we didn't do "X" versus did "X" that "Y" would or would not have happened?

That's what it's all about. And if you can do that with an open-label, uncontrolled, or external control comparison to something, great, God bless, that would be wonderful.

If you can do it with a patient has their own control, yeah, great, do it. The question is, can you? I mean -- and under the -- the particular circumstances.

You know, the complexity -- you know, I -- I get the anxiety about not knowing what's going on. I mean, I -- I get that. And -- and maybe I'll -- I warned Matt I was going to tweak him a little bit on this question, and so -- and Elliott said he might also have an answer to it.

But let me -- let me frame this. I -- I started thinking about the milrinone versus placebo. Just put it into context.

So, I trained neonatal and pediatric

ICU. Milrinone came out when I was -- during my fellowship -- and we're talking in the late 1980s. And the neonatologists are now getting around to study it? That should tell you there's a problem right there. All right?

I mean, first of all -- yeah, we were using milrinone in the late 1980s, again, in pediatric ICU, cardiac, et cetera. So you know, when I heard it, I said, "Wow. Okay. There's a drug I know."

But my question is this. You know, so you've got a study with a placebo, and the answer is if a parent says, "Well, if I don't get into the trial, what happens?"

And it's, "Well, whatever's going to happen is the wild west of neonatology," meaning this doctor might start it, this doctor might not -- might not start it, et cetera.

But my question would be if in that group, in your unit, or for that matter, any unit where a trial is going, if there's a clinician that really believes that a patient who met the inclusion

criteria of that study ought to be on milrinone, they should have a real problem with that trial in terms of the fact that they then are taking care of a baby who's on placebo.

You know, so it really challenges in my mind -- I mean, I do believe that there's a moral obligation to do research. I might say let's use evidence-based, not off-label, because I mean, there are some things that are evidence-based that aren't on the FDA label.

So, I mean, I'll just say evidence based. And I might say I'm not -- I'm not proposing we use anything off-label. I can't do that as an industry person because that's the -- I can't do that. But it is evidence-based.

So, my question is, I mean, what -- what is that person who really believes that they should be on it, and this patient might be on placebo? I assume it was blinded.

You know, so you got some yellow fluid -- if I recall, milrinone is yellow. You got

some yellow fluid going in that's fake. What's that dynamic like? Because they really should have a problem with the fact that you're doing this study.

I'll get them both going --

DR. RYSAVY: I'll just -- I'll be really quick. I would just like to comment on that word, "uncertainty." That came up a lot before.

In neonatology -- and this is just something -- this is the -- the water we swim in, we're all dealing with uncertainty all the time, and you still got to act.

And so, in that context, you might have a doctor who's prior -- you know, in a Bayesian context, their belief that this helps is 60 percent. You know, so on the odds -- maybe, but am I certain in this? Absolutely not.

You might have another doctor who's 30 or 40 percent. "Oh, I read a couple of interesting papers, but they weren't enough to convince me." And so they choose not to.

And I -- I think that that's the

context that we're talking about, and that's the milieu-- in which it's appropriate to do a trial when there's true uncertainty.

But there could be reasonable variation of practice in the background because people take the same information and might interpret it slightly differently within uncertainty. So nobody's certain enough when enrolling in this trial.

DR. WEISS: And I -- I'll just add that I think this touches on the concept of equipoise, which in the bioethics world is really debated in terms of whether or not this is a useful construct at all.

You know, and what you are defining is like personal equipoise. So, if I feel like Treatment A, a hundred percent is right all the time, and Matt think that Treatment B is a hundred percent right all the time, do I not have equipoise, but perhaps the study does?

It gets very confusing. And it also feels very problematic to put this as the highest

level of evidence because equipoise then gets to decide whether or not it's even ethical to conduct the RCT in the first place.

And so, I'll just say that when we think about equipoise as a criterion or as the criterion for whether you should conduct a study, really, an individual's preference shouldn't matter. It should be, if we're going to use this, it needs to be something like the field.

Even knowing that the field could get it wrong. Twenty years ago, neonatology thought giving exceedingly high doses of steroids was in the best interest of all these babies. And it was fairly agreed upon, and that ended up not being correct.

But an individual strong belief, I don't believe impact -- should impact equipoise as a criteria for whether to conduct a clinical trial.

DR. NELSON: So, I agree with both of what -- what both of you has said, but let me push then.

Because then your answer to the parent

at the bedside in your unit should have been different. It shouldn't be, "Oh, I don't know, maybe you'll get it. Maybe you won't."

It should have been, "Our group has decided that we're not sure that this drug works, and we're doing this trial to answer that question. So, if you don't go in the trial, you will not get it."

DR. FELTMAN: I'm not sure that would be exactly the situation, though, because usual care that's not standardized -- I'm sorry I wasn't even holding up an orange Post-it note, but --

DR. NELSON: Usual care -- the point is, if it's non-evidence-based usual care, what is it? I mean, in other words, it -- it -- but neonatology is that answer, but --

DR. FELTMAN: Right. But I think you would maybe not take it away or proactively give it by policy, as the -- outside of the study.

DR. RYSAVY: I guess I would just add -- but this maybe sounds like some niche issue, but again, the majority of what we do is off-label.

The most common antimicrobials that were exposing babies to, you know, some of the most common analgesics that we expose babies to, these are all off-label.

And no -- no conscientious doctor or thinking doctor would say, "I'm sorry, we don't actually have approved medications to take away your baby's pain. There's nothing I can do. We're just going to let them suffer.

"I'm sorry we don't have, you know, the medications to deal with this particular infection. You know, if -- it's off-label. We -- we know how to treat it in bigger patients, we're just -- they may pass away from this."

Of course, we do something, and that's -- that's the predicament we're in.

DR. NELSON: Let -- let me push you a little bit more just for fun.

So Alison, I think, made a very --

DR. FELTMAN: Okay. One more push and then I'm going to ask the parents to step in--

DR. NELSON: So Allyson made an interesting point about this balance between a protocol and doing what you think is in the best interest of the patient. I mean, it was sort of a -- talking about that tension.

If you have a well-designed protocol, ideally, it should be that the conditions under which that infant meets to go into that protocol would have been the same conditions under which the clinicians who were 60 or higher in their Bayesian approach would have started milrinone.

So I would hope the protocol would actually reflect clinical practice and their willingness then to do it.

So I guess it's -- it's -- you know, and again it's not off -- let's not use -- let's just say evidence-based. Because things could get published and then you'd have an evidence based, it wouldn't end -- end up on the FDA label.

But -- but I'll stop there.

DR. FELTMAN: I'd love to ask and hear

from Lindsey and Jennifer two questions that we -- we don't have figured -- we -- they weren't -- it's -- they're not on the list, but they're just stemming from what's been talked about.

Do you have any -- anything you'd like to share about the idea of being a parent and having a child receive a placebo, and what -- how do you view the ethics of that?

MS. WAHLSTROM: I can jump in here.

So we -- we actually received compassionate use while we were on a trial because -- you talk about the wild west in care, there's the wild west of transplant, and our room was the wildest of the wild west.

We had every single complication that you can have. We had a CMV count that was having log changes every 48 hours. We crested at a million, which made later on her adenovirus CMV -- or sorry, adenovirus PCR count made that look like child's play.

And so, I -- I think there is the -- the theoretical framework that we're having the

conversation around of pushing in good scientific evidence, which we absolutely need. And then there's the reality in the room that this child's going to die over the weekend if we don't do something.

And so, we did receive a drug under compassionate use that had not been used in PEDs before to anyone's knowledge.

And it -- it halved her count, and it -- it broke her fever of 105 that I've been sitting there for three weeks, despite sleeping on ice and despite having cooling packs packed around her, in two days.

And so, I hope -- I will not name names because I don't know that the company knows she was given the drug -- but I do hope that we can -- we can think about the theoretical frameworks.

And then also understand that if we're trying to get medications approved and through, we also need to be -- be treating patients and keeping them alive so we can see if we can get to the other side of endpoints.

And so for me, that was our personal experience with compassionate use. And I -- and I think as a parent -- as a parent, I would not have said yes to a placebo.

We did actually try the standard of care. It did not work for us. And so, we went into a trial. You don't take transplant on willy-nilly. You put a lot of thought into that decision.

But as a practitioner in the field, I -- I'm heartened by platform trials and -- and other mechanisms that we're starting to see more of. Plausible pathways, great.

Because I -- I think there's a larger ethical question of can we -- if the standard of care is nothing or the standard of care is nothing great, and there's the potential for something, is it even ethical to -- to run the placebo or to run -- to run that outside of a parent's consent?

So I -- I would push a little bit in that direction too.

DR. FELTMAN: Thank you, Lindsey.

Jennifer, did you want to add anything?

MS. DEGL: She spoke beautifully. I'll just save a little time and wait for the next question.

DR. BATEMAN-HOUSE: Can I just jump in for one second?

DR. FELTMAN: Sure.

DR. BATEMAN-HOUSE: So when we're giving someone a product that has not been proven safe and effective for use in that particular person, it seems to me -- and -- and yes, we have some terminology floating around here.

It is like, has it been proven safe and effective? You know, is it evidence-based? Is it standard of care? So the devil is in the details, but let's just, you know, forget the details for one second and just talk generically.

If I'm giving someone a medication, a drug, a intervention that has not yet been proven safe and effective for that person, there may be very reasonable reasons for doing it.

However, in my opinion, you also have a very good argument for, and I would say moral obligation, to collect data. Because someone else is going to be in that exact same situation soon.

And if you have already given someone that product, I believe you have a responsibility to learn from it so that when it comes to the next person, you're not starting again with a blank slate. You are saying, you know, well, this did happen once, and -- and here is what happened.

You know, that doesn't mean it's going to happen that way all the time, but it at least gives us something to work from in terms of thinking about what side effects we should be looking at or, you know, et cetera.

So to me, there really is this obligation that when you do these individual treatments, which may be experimental, you want to collect the data and try to get more value out of it, not necessarily for that individual patient, but for the whole population of patients like that individual.

That's my opinion.

DR. FELTMAN: Thank you for this robust discussion. It's my guilty pleasure to be able to say we don't have time enough and there's still so much to talk about, but we should probably switch gears to our next question. And I hope you all can continue to talk after -- after the panel is over and tomorrow.

I'd like to ask how do we -- so we know that parents are the final decision-makers as far as giving -- providing informed consent for their children, whether they're going to be in the study or not.

But we've been talking today a -- a lot about the value of integrating parental voices earlier in the process. So how do we protect and empower parents in the design of the study for a therapeutic for a patient with rare disease or a neonatology patient?

Jennifer, do you want to start?

MS. DEGL: Yes.

So, in general, all studies need to

focus on clinically meaningful endpoints.

But I can tell you, as a mother of a 23-week micro preemie who was born at 575 grams and participated in two clinical trials, what is clinically meaningful to a parent may be different than what is clinically meaningful to the industry and research.

So, what are some of those things that are -- that are clinically meaningful to families and parents? From a NICU parent perspective, the studies should include and place emphasis on improvement and outcomes that parents can observe and understand in daily life.

Some of those things would be the ability to breathe with less support, improve feeding tolerance or growth trajectories, reduced hospital length of stay or less readmissions, developmental milestones that are appropriate for a corrected age.

Again, from a NICU parent perspective, studies should focus on demonstrating reduction of harm, less invasiveness, or treatment burden.

And some of those would include, as I would like to hear as a mom during a study, fewer invasive procedures, less blood draws, lower incidents of adverse events, reduced need for sedation restraints or painful interventions, and shortened time on mechanical ventilation or IV therapies.

And again, from a NICU parent perspective, studies should collect direct input from parents as validated study data.

Some of those would be parent-reported symptom improvement or stability, parental stress, anxiety, and decision regret scores -- which is something that Ashley was alluding to before. I believe that's important -- clarity of communication and understanding of the study.

And then studies should also include direct input from parents and, you know, on outcomes that extend beyond discharge or just short-term survival because oftentimes those aren't talked about enough.

And some examples would be

neurodevelopmental outcomes as defined by follow-up intervals and visits, the need for ongoing medical technology or therapies after discharge, functional independence over time. And that was being discussed earlier as well. And health-related quality of life for the child and family.

And I believe all of those things should be important and included in study design as -- as best you can by including the parent input on those.

Now, as a NICU parent, enrolling your child in a study is never a clinical decision. It is really just a deeply personal act of trust, and it takes a lot to get there.

What wasn't mentioned, I -- I would have mentioned before, a lot of it is in the approach and the timing, and I -- that was mentioned before.

You know, myself having placenta percreta, I was in the hospital for six weeks and almost lost my life four times, and that was before I had my daughter.

So I gave birth to her, having had all of that -- you know, hysterectomy, 30 units of blood, all of these things, and then we had her, and then I'm being approached to make these very important decisions.

Now me, you know, being a scientist, being -- working in education, it's different. But for someone that has no experience like that, I would imagine it would be very, very frightening.

And I can tell you that it is from my time working as a NICU parent mentor in the program that I -- I run in my daughter's old hospital. So the consent and the approach process is -- is really, really critical.

But families are empowered when the research is designed around outcomes that will protect their child's safety and that they're told that, that will reflect real-life impact and honor the parents as essential, you know, partners, and that their input is both respected and welcomed.

And if they feel that way, you're much

more likely to have a successful study, not only enrollment, but also have the parent remain engaged in that study, you know, for a much longer time.

And I'll -- and I'll also add, you know, from a parent perspective, if you can offer parents the opportunity to hear about the conclusion of the study, if they wish to, and continue their participation, they can feel that they contributed to something greater, if they wish to, should be an option.

And even following up with them for updated contact information to keep them engaged, if it's a -- you know, a long-term study that's very beneficial.

And I do apologize, I actually have to go to catch a flight in a moment. I'm so sorry I can't be here for questions, but I left some business cards on that table where I was sitting, if you want to reach out and ask me any questions. Sorry.

DR. FELTMAN: Thank you, Jennifer, and safe travels when you have to go.

Elliott, could you talk a little bit about representation of -- of different parents' perspectives?

DR. WEISS: Yeah.

I -- I first want to comment on some of the things Jennifer said. In particular, this idea of our research outcomes being made for and by researchers and not for or by clinicians or for parents is exceedingly important and something that I think neonatology has been realizing and trying to figure out what to do with in the last decade.

And I really think we still haven't figured it out, and lots of work is needed to be done.

I'll -- I'll briefly talk about two things in terms of kind of who is at the table and what is within scope when we think about getting different viewpoints. You know who should be at the table?

There's advocacy groups. These have incredible power. There're also kind of social construct, very disease specific. They tend towards

illnesses and populations that have resources and money.

Other parents who are not -- who have children with diseases that are not represented by advocacy groups need to somehow be at the table too.

Clinicians, researchers, the public, taxpayers, funders, including nonprofits, industry and the government -- and it's not that any of these should have necessarily a veto power, but all of them deserve to be heard and these decisions impact what's done downstream.

And when we think about engagement of these different groups, I might typically -- for example, I might convene a NICU parent panel after a project on leading has been grant-funded and the protocol already made. I think what we need to do is include people before and after that.

What areas of study should we prioritize? By what methods? What's the target population? Who drafts the RFA? Where does industry choose to put its money? And then afterwards, as

well, the interpretation of findings.

When I do interview studies, I try to come back to families who are on my panel and say, "Here's what I came up -- we came up with as a team. Does this seem feasible in terms of -- make sense with your experience as well?"

Do they help decide what's getting published and what doesn't? Do they -- who designs the next project, picks the next RFA, or designs what the next RFA is?

And so, I think both who is at the table and what is within scope to be discussed could benefit from being much wider than is traditionally included in thinking about stakeholder engagement.

DR. FELTMAN: Thank you, Elliott. A lot of great questions to think about there.

DR. BATEMAN-HOUSE: Could I respond to that?

DR. FELTMAN: Yes, please.

DR. BATEMAN-HOUSE: I completely agree with what you just said. Right? All stakeholders

should be engaged and -- and, you know, at points where they actually can really impact what happens as opposed to just giving it a rubber stamp afterwards.

But I want to play devil's advocate for just a second. So, all of that takes time and money.

So how do we justify when there's limited amounts of time and limited amounts of money diverting -- not diverting it but -- but spending it on advisory panels or the such, as compared to other things we could be doing with that same amount of money that would perhaps be of more interest to the community in terms of, you know, supporting additional trials or what have you?

DR. WEISS: I would say that's a -- you know, it's a prioritization. It's a decision that we as researchers and other groups need to make.

Like, it's clearly -- for a small, funded study, you're not going to be able to do all these steps.

And still thinking about what could possibly be done and then really deliberately making

the choice of when and how to bring people in, in a way that's appropriate for that project, or that set of project or that entire portfolio of institute, is, I think, something we need to do.

And this will look differently and it will cost money and take time. And all of those are competing resources, and they should be kind of thought about. But I think too frequently it's just not done because it's not thought about.

DR. FELTMAN: Lindsey, I would love to hear from you both in your work and as a personal -- you know, from your personal experiences as a mom and a research participant. I know you talk a lot about the informed consent process.

MS. WAHLSTROM: I do.

I'd like to echo what Jen said about the endpoints. I think one of the more illuminating conversations I had as part of our research experience was shortly before Rona's death -- and I was having a a -- a back and forth with her provider, who kept saying, "We're going to get the graft. We're going to

get the graft."

And I said, "Time out. I'm not talking about the graft. I'm talking about survival." And the response was, "Oh, well, that doesn't look as good." And so I think when we're thinking about research, and we're thinking about endpoints, it's really having those conversations.

And I would push a little bit on the exchange that just happened too. Ron Bartak is in the room. FARA was hugely instrumental in getting new therapies approved for FA-- I think a lot of what we're seeing in the rare disease space are parents and caregivers who, both pre and post the loss of their children, are pushing forward this work.

So yes, genetic testing, precision medicine, all of those things have really unlocked the technology that enables it.

But rest assured that rests on the shoulders of hard work by parents who organized, who gathered the data, who created the registries, who are collecting the information that we need to really have

those natural history studies, to be able to understand causal pathways to start, to see how maybe those pathways are the same, not in their presentation, in their -- in their phenotypes, but in but in the genotypes, right?

So I think there's a lot of work to do there. So when I think about research, and I think about informed consent, I'm very pro-research. Obviously, I continue to work in it even after Rona's death.

I do think we sell hope a lot. And I think especially with the cell and gene boom, we're selling hope of cures a lot and the data aren't quite there yet to back up that sales.

I -- I think if we can think about focusing on selling two things, we're selling an option when one doesn't exist because 95 percent of rare diseases still do not have an FDA-approved treatment.

And we're selling the opportunity to do something meaningful and give back to the disease

community, which is -- is a huge motivator for clinical trial participation across all disease indications.

So, when we talk about ethics, for me it's less about coercion and -- and we'll -- issuing a payment to a family that maybe covers, I don't know, a week in a hotel close to the hospital where their kid's going to be treated for six months -- if that's coercive -- and really thinking about design and understanding.

It's communication. And -- and I think that's where we're really falling short as a -- as a industry, I should say. FUN LAB is actually an acronym for six principles for doing better pediatric care and research.

Most of them are related to design and how we are communicating and making sure that families understand. So Alison's point earlier about parents as experts -- I many times -- I was called the "momatologist," not because they loved me, but because I knew more than the residents.

For a while, they were not allowed in my room because I was tired of teaching when I wanted to just be a mom. So in rare it makes sense to hold those expertise in a similar spirit, especially pre-protocol lock.

That's a critical time period because your complexity for IE criteria and your -- your ability to actually fill a trial and answer your questions is determined at that moment in time. So that's -- that's a really important thing.

And so for me, with informed consent, I think as someone who has done the recruitment and the engagement, I've often treated informed consent as a finish line. But now having lived it, I see it's the starting point. And it's the starting point for an ongoing conversation.

It is an agreement that does not allow parents to negotiate, but it is an agreement that we hold with you as the practitioner about what we can expect and what is going to be happening to our children.

And -- and so we anchor on this forum, and the forum is for you all. It's for the regulators. It's for the lawyers. It's for your compliance folks.

It's not for the families. Because you're not absorbing 50 pages of detailed information with lots of legalese included to make sure that your I's are dotted and your T's are crossed.

So, we need to be thinking a little bit more about how we are balancing the need for that legal component while also creating space for families to truly understand what's coming at them.

Because the existence of an opportunity to do something in the face of nothing is inherently coercive to some extent, maybe not for everyone, sure was for me. And so making space for that and making space for that in the IRBs as well.

When we went into transplant, we were told for every ten kids I transplant, two won't walk out of the room. No one wants to be the two, but two families have to be that. You have to be.

And so when you're thinking about your IRB composition, I think it's important to have one person from the eight and one person from the two or whatever -- whatever similarity that might be for the condition that you're in -- because the understanding of what is ethical from someone who has seen -- seen the worst of it -- and I hold this to be true, that Rona's last breath was not the worst thing that I saw.

So, someone who has seen the worst of it is going to be very different than the understanding of someone who's in the thick of it, fighting for their child. So, when we're talking about parent engagement, having those two viewpoints is really, really critical.

And then the last piece is I will always advocate for having palliative care providers involved in research when pediatric critical illness is involved. I think they are really good at communicating.

I've met a lot of very smart providers who are so brilliant who I'd want on my team, but I

would never want doing my informed consent or to explain anything to me or to be at the bedside when I'm stressed out. Look at -- they're laughing, they know.

But palliative care providers can balance those mental health protections and the physical health protections. And in addition to that, they are adept at having -- oh, look at that, pun not intended. But they are adept at having conversations that help to get care teams and parents on the same page.

And that I think is the most critical thing when we're thinking about ethics. It's really, we're going into this, we are entrusting the most precious things. You could tell me I was going to win the lottery if I joined the clinical trial, and I still wouldn't do it if it wasn't the right choice for my child. Right?

So, when we're thinking about ethics, it's are we explaining things so people understand what they're getting into?

And I would argue we're not because I -- I was blindsided and I read that form 15 times and I talked to people and I was in the parent support group, and I met and interviewed multiple practitioners and I did not understand what some of those things meant.

So, I think for me, when we talk about informed consent, that's where we have the most room to grow.

DR. FELTMAN: Thank you, Lindsey. I couldn't have asked for a better closer to this panel than a pun about adept and as well as your thoughtful comments, so thank you.

So this ends our ADEPT 10 session for tonight. And tomorrow morning, looking forward to a great day of discussions. Thank you again.

DR. MASSARO: Great. Thank you.

And we stayed on time, which is a miracle. So, thank you to our panelists and our speakers today. It was a wonderful opening to our meeting.

We will reconvene tomorrow at 8:30 in the morning, and we look forward to seeing you there for continued discussion. Thank you.

(Whereupon, the meeting concluded at 4:58 p.m.)

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I, RICHARD LIVENGOOD, 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.

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