

1 Drug Development Considerations for the Treatment of
2 Neonatal Enterovirus Infection and Congenital
3 Cytomegalovirus Infection
4 Virtual Public Workshop
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8 Moderated by Sunita Shukla

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<p>1 APPEARANCES</p> <p>2 List of Attendees:</p> <p>3 Jeffrey Hincks, Ph.D., ViroDefense, Inc.</p> <p>4 Kevin Messacar, M.D., Ph.D., University of Colorado</p> <p>5 David Byron, AntiVirus Therapeutics</p> <p>6 Corey Farley, AV Support</p> <p>7 Marcus Washington, AV Support</p> <p>8 Yodit Belew, M.D., FDA</p> <p>9 Prabha Viswanathan, M.D., FDA</p> <p>10 An Massaro, M.D., FDA</p> <p>11 Kunyi Wu, Pharm.D., FDA</p> <p>12 Betsy Pilon, Hope for HIE</p> <p>13 Yeruk Mulugeta, Pharm.D., FDA</p> <p>14 John Concato, M.D., MPH, FDA</p> <p>15 Natalie Pica, M.D., Ph.D., FDA</p> <p>16 Amy Rosenfeld, Ph.D., FDA</p> <p>17 Miranda Delahoy, Ph.D., CDC</p> <p>18 Mark Abzug, M.D., University of Colorado</p> <p>19 Aimee Hodowanec, FDA</p> <p>20 Matthew Vogt, M.D., Ph.D., UNC Chapel Hill School of</p> <p>21 Medicine</p> <p>22 Tatiana Lanzieri</p>	<p>1 CONTENTS</p> <p>2 PAGE</p> <p>3 Dr. Yodit Belew 5</p> <p>4 Dr. Prabha Viswanathan 12</p> <p>5 Dr. An Massaro 31</p> <p>6 Dr. Kunyi Wu 50</p> <p>7 Betsy Pilon 59</p> <p>8 Dr. Yeruk Mulugeta 75</p> <p>9 Dr. John Concato 91</p> <p>10 Dr. Natalie Pica 112, 166</p> <p>11 Dr. Amy Rosenfeld 112</p> <p>12 Dr. Miranda Delahoy 122</p> <p>13 Dr. Mark Abzug 131</p> <p>14</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p>
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<p>1 APPEARANCES (Cont'd)</p> <p>2 List of Attendees:</p> <p>3 Robert Debiasi</p> <p>4 Wendy Carter</p> <p>5 David Kimberlin, M.D., University of Alabama at</p> <p>6 Birmingham</p> <p>7 Mark Schleiss, M.D.</p> <p>8 Steve Oberste, Ph.D., CDC</p> <p>9</p> <p>10</p> <p>11</p> <p>12</p> <p>13</p> <p>14</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p>	<p>1 PROCEEDINGS</p> <p>2 DR. BELEW: Good morning, everyone. It</p> <p>3 is my honor to welcome our speakers, panelists, and</p> <p>4 audience to this important workshop on the topic of</p> <p>5 drug development for the treatment of neonatal</p> <p>6 enteroviral infection and congenital CMV infection.</p> <p>7 It is also my privilege to present the</p> <p>8 opening remark and set the stage for what I hope will</p> <p>9 be a productive and valuable workshop.</p> <p>10 Next slide, please.</p> <p>11 My name is Yodit Belew. I am the</p> <p>12 Associate Director for Therapeutic Review in the</p> <p>13 Division of Antivirals, Office of Infectious Diseases,</p> <p>14 CDER, FDA.</p> <p>15 Next slide, please.</p> <p>16 So about this time last year, the WHO,</p> <p>17 among others, put out a disease-outbreak news alert</p> <p>18 due to -- regarding a severe enteroviral infection in</p> <p>19 infants and neonates, leading to many</p> <p>20 hospitalizations, including ICU admissions.</p> <p>21 Unfortunately, at least one infant died due to this</p> <p>22 outbreak.</p>

<p style="text-align: right;">Page 6</p> <p>1 Next slide, please.</p> <p>2 Congenital CMV infection is the leading</p> <p>3 infectious cause of birth defects and</p> <p>4 neurodevelopmental disabilities, including deafness.</p> <p>5 The CDC estimates that 1 out of every 200 babies is</p> <p>6 born with congenital CMV, with majority being</p> <p>7 asymptomatic at birth.</p> <p>8 With adoption of universal screening</p> <p>9 similar to what Minnesota has introduced, one can</p> <p>10 expect that many more neonates with congenital CMV</p> <p>11 will be identified at birth.</p> <p>12 Next slide, please.</p> <p>13 Both CMV infection and neonatal</p> <p>14 enteroviral infection can be serious and potentially</p> <p>15 life-threatening. More specifically, severe neonatal</p> <p>16 enteroviral infection and symptomatic congenital CMV</p> <p>17 are associated with higher risk of morbidity and</p> <p>18 mortality.</p> <p>19 Based on the literature and epi data,</p> <p>20 these conditions can be considered rare; and to</p> <p>21 provide some regulatory context, Section 526(a)(2)(A)</p> <p>22 of the Federal Food, Drug, and Cosmetic Act defines a</p>	<p style="text-align: right;">Page 8</p> <p>1 adequate and well-controlled trials, which include</p> <p>2 clear stated objectives or hypothesis of the trial</p> <p>3 well before the trial is initiated, a comparator-</p> <p>4 treatment group for quantifying or for qualitative</p> <p>5 assessment of efficacy, clearly defined eligibility</p> <p>6 criteria, ensuring that the population has the disease</p> <p>7 of interest, steps to minimize bias, well-defined</p> <p>8 endpoints for assessing treatment effect, and sound</p> <p>9 statistical-analysis plan.</p> <p>10 Next slide, please.</p> <p>11 As many here might be familiar, there</p> <p>12 is also an alternative pathway for establishing</p> <p>13 substantial evidence of effectiveness in the pediatric</p> <p>14 population.</p> <p>15 That is to say that efficacy of a</p> <p>16 product can be extrapolated from adults to pediatric</p> <p>17 population if there already is an adequate and well-</p> <p>18 controlled clinical trial in adults, demonstrating</p> <p>19 substantial evidence of effectiveness.</p> <p>20 This extrapolation principle is applied</p> <p>21 only when the agency has concluded that the course of</p> <p>22 the disease and the drug's effect are sufficiently</p>
<p style="text-align: right;">Page 7</p> <p>1 rare disease or condition in part as a disease or</p> <p>2 condition that affects less than 200,000 persons in</p> <p>3 the United States.</p> <p>4 As we are all aware, there are no FDA</p> <p>5 approved antiviral products for the treatment of</p> <p>6 enteroviral infection or congenital CMV infection in</p> <p>7 neonates or infants. So why is that?</p> <p>8 Next slide, please.</p> <p>9 If we step back and think about the</p> <p>10 regulatory framework, there is a specific evidentiary</p> <p>11 requirement for establishing efficacy. Sponsors of</p> <p>12 drug products are required to establish safety and</p> <p>13 efficacy in both adult and pediatric populations</p> <p>14 before a product can be approved.</p> <p>15 And how they demonstrate substantial</p> <p>16 evidence of effectiveness is through adequate and</p> <p>17 well-controlled clinical trials on the basis of which</p> <p>18 it could fairly and responsibly be concluded that the</p> <p>19 drug will have the effect it purports to have under</p> <p>20 the condition of use.</p> <p>21 Next slide.</p> <p>22 Outlined here are the elements of</p>	<p style="text-align: right;">Page 9</p> <p>1 similar between adults and pediatric populations to</p> <p>2 permit extrapolation from adult efficacy data to</p> <p>3 pediatric patients.</p> <p>4 Next slide.</p> <p>5 So to bring us back full circle,</p> <p>6 because congenital CMV infection and neonatal</p> <p>7 enteroviral infection are unique or distinct</p> <p>8 conditions limited to infants and neonatal</p> <p>9 populations, adult data cannot be leveraged to</p> <p>10 establish effectiveness.</p> <p>11 And conducting adequate and well-</p> <p>12 controlled clinical trials in these populations, while</p> <p>13 necessary, is undoubtedly very challenging for many</p> <p>14 reasons.</p> <p>15 To name a few characteristics, we have</p> <p>16 poorly understood or not well-characterized natural</p> <p>17 history; potential challenges with designing well-</p> <p>18 powered studies due to small population size; and</p> <p>19 challenges in trial designs, including selection of</p> <p>20 endpoints.</p> <p>21 Next slide, please.</p> <p>22 And that is essentially why we are here</p>

<p style="text-align: right;">Page 10</p> <p>1 today, to discuss the challenges and identify the 2 needed additional scientific work to advance drug 3 development for the treatment of neonatal enteroviral 4 infection and congenital CMV infection. 5 FDA Public Workshop is intended to 6 facilitate exchange of ideas among stakeholders to 7 identify research gaps and help advance the field to 8 address unmet medical need. 9 To clarify, FDA Public Workshops are 10 not advisory to the agency; and the agency will not 11 provide drug-development advice. It is not for 12 regulatory decision-making; and all opinions, 13 recommendations, and proposals are unofficial and 14 nonbinding on FDA or other participants. 15 Next slide, please. 16 So I look forward to a discussion both 17 today and tomorrow. We hope this workshop will move 18 us closer towards our shared goal of advancing drug 19 development to address these unmet needs. You should 20 have full access to the agenda online, but I wanted to 21 briefly highlight the key segments. 22 So the workshop will begin with several</p>	<p style="text-align: right;">Page 12</p> <p>1 disclosures are also available on the meeting website 2 under "Meeting Materials." 3 For the general audience, please note 4 that your microphone and video are automatically 5 turned off. Please submit questions using the Q-and-A 6 feature at the bottom center of your screen and Zoom 7 platform. 8 Next slide, please. 9 And we are honored to have with us this 10 morning Dr. Prabha Viswanathan, Dr. An Massaro, Dr. 11 Kunyi Wu, Ms. Betsy Pilon, Dr. Lily Mulugeta, and Dr. 12 John Concato to kickstart the workshop. 13 Next slide. 14 And it is my pleasure to introduce 15 formally our first speaker, Dr. Prabha Viswanathan, 16 Deputy Director of Office of Pediatric Therapeutics. 17 Dr. Viswanathan's presentation will focus on ethical 18 considerations for pediatric clinical trials. Thank 19 you. 20 DR. VISWANATHAN: Good morning, 21 everyone. It's a privilege to be here, and thank you 22 for your attendance. We'll be beginning Session 1</p>
<p style="text-align: right;">Page 11</p> <p>1 presentations on the general principle of pediatric 2 and neonatal drug development. 3 After we return from about a 20-minute 4 break, the rest of the day will focus on neonatal 5 enteroviral infection with presentations during 6 Session 2 and panel discussion during Session 3. 7 Lunch break will be from 12:20 to 1:00 p.m., and we 8 will adjourn today at around 3:30 p.m. 9 Next slide, please. 10 Day 2 will be entirely dedicated to 11 congenital CMV infection with presentations during the 12 morning session and panel discussion during the 13 afternoon. Again, lunch break will be from 12:20 to 14 1:00 p.m.; and the workshop will conclude at 3:30 p.m. 15 Next slide, please. 16 And before I introduce our morning 17 speakers, let me run through a few housekeeping items. 18 So, one, this meeting is being recorded. Speaker 19 slides, transcripts, and recordings will be available 20 on the meeting's website in the coming weeks. So 21 please check this page regularly for updates. 22 Speaker and panelist affiliations and</p>	<p style="text-align: right;">Page 13</p> <p>1 with a brief overview of ethical considerations for 2 pediatric clinical trials. 3 Next slide, please. 4 I have no disclosures. 5 Next slide, please. 6 So just an overview of what you can 7 expect this morning, this is going to be a high-level 8 30,000-foot view of pediatric ethics. 9 We'll begin with a discussion of the 10 general ethical framework that we use to analyze our 11 protocols, and then we'll see how that ethical 12 framework leads into the regulations that govern the 13 inclusion of children in research, and I'll be really 14 stressing four key concepts. 15 The first is the prospect of direct 16 benefit, followed by the assessment of risk, the 17 component analysis of risk, and finally the need for 18 parent and guardian permission; and then we'll end 19 with a discussion about how these considerations 20 impact our development for the two conditions that are 21 the subject of this workshop. 22 Next slide, please.</p>

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<p>1 So let me take you back in time to 2 begin with the late 1970s, where the National 3 Commission was convened to discuss the structuring of 4 an ethical framework that really has two main concepts 5 it is considering: one, the fact that children are 6 vulnerable and require additional safeguards, 7 balancing that with the fact that pediatric research 8 is necessary to safeguard and improve the health and 9 wellbeing of children.</p>	<p>1 this slide, but you'll see on the left that the 2 National Commission report that I referenced as long 3 as the -- as well as a Belmont report that were both 4 put together in the late 1970s gave rise to 5 regulations that are both at the FDA level in 21 CFR 6 and the DHHS level in 45 CFR.</p>
<p>10 Next slide, please.</p>	<p>7 And these are parallel in their 8 structure, but I'm going to focus on the right-upper 9 area that's circled with the additional safeguards for 10 children in clinical investigations, which is 21 CFR</p>
<p>11 So this commission convened and filed a 12 report, and this is a very simplistic view about what 13 they found. So in essence and in a summary, there are 14 four key concepts: first, ensuring necessity; second, 15 limiting risks; third, preventing disadvantage; and 16 fourth, obtaining permission; and I will briefly go 17 into these individually.</p>	<p>11 50 Subpart D, which I will be referring to as Subpart 12 D for the remainder of this presentation. 13 Next slide, please. 14 So the Subpart D regulations are really 15 broken into five areas, two of which are really 16 relevant for this discussion of the development of 17 antiviral drugs for treating a clinical condition.</p>
<p>18 So first with ensuring necessity, 19 because children cannot consent to participate in 20 clinical trials, we should only enroll subjects when 21 it is necessary to enroll these younger subjects to be 22 able to meet the scientific objective of the trial.</p>	<p>18 A therapeutic such as an 19 investigational antiviral drug would be considered an 20 intervention by and large that confers more than 21 minimal risk to research subjects and therefore must 22 be bound for the prospect of direct benefit for the</p>
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<p>1 Secondly, when we think about risks, we 2 think about how the risks correlate with the benefits 3 that the child might experience in the trial; and this 4 is going to be unique for every circumstance.</p>	<p>1 subjects. 2 That's 50.52, and then 50.55 is -- is 3 the element about permission and assent. So we will 4 only be focusing on those two today.</p>
<p>5 Third, preventing disadvantage, when 6 children are enrolled in a trial, they should neither 7 be exposed to excessive risks due to the interventions 8 they -- they experience in the trial, nor should they 9 be placed at a disadvantage by being unable to access 10 care that they would otherwise receive outside of that 11 setting.</p>	<p>5 Next slide, please. 6 So let me just describe 50.52 for a 7 moment. This is the balance of benefit and risk. 8 This is what we do in clinical practice all the time 9 and -- at the -- the bedside level as well as the 10 population level.</p>
<p>12 And finally, obtaining permission is a 13 critical aspect. Again, because children cannot 14 consent for themselves, they must have parents or 15 guardians that can act as a proxy to provide that 16 consent.</p>	<p>11 So when we're evaluating a clinical 12 protocol, we're looking for some key elements. So 13 does this intervention involve greater than minimal 14 risk? For the most -- by and large for candidate 15 antivirals, that would be true.</p>
<p>17 Next slide, please.</p>	<p>16 Does it provide that prospect of direct 17 benefit to the individual subject? And we'll be 18 talking about the definition of that shortly. And are 19 the risks justified by the anticipated benefit to the 20 subject?</p>
<p>18 So next I'm going to transition into a 19 discussion of how this ethical framework led to the 20 regulations that we currently use today.</p>	<p>18 talking about the definition of that shortly. And are 19 the risks justified by the anticipated benefit to the 20 subject?</p>
<p>21 Next slide, please.</p>	<p>21 Secondly and equally importantly, is 22 that anticipated benefit, the risk balance, at least</p>
<p>22 I won't bore you with every detail of</p>	<p>22 that anticipated benefit, the risk balance, at least</p>

<p style="text-align: right;">Page 18</p> <p>1 as favorable as any available alternatives, including 2 those that are available to the patient outside of 3 clinical research? 4 Next slide, please. 5 So I'm going to provide some 6 definitions. You'll have heard me use these -- these 7 exact phrases more than once, such as "prospect of 8 direct benefit"; and so first, I want to talk about -- 9 what does it mean to be direct? 10 So the benefit that a child experiences 11 really needs to be felt by the individual subject, not 12 the -- the study population in general. Each subject 13 should have some benefit through their participation 14 in the trial; and secondarily, that benefit needs to 15 be arrived -- derived from the intervention under 16 study. 17 So the simple benefit of increased 18 access to healthcare and potentially enhanced 19 monitoring on themselves do not equate to that direct 20 benefit. 21 Second, I want to stress that the 22 assessment for the prospect of direct benefit is</p>	<p style="text-align: right;">Page 20</p> <p>1 of -- of minimal risk, which is the risk that normal 2 healthy children encounter in their daily lives and in 3 routine healthcare. 4 The other distinction that is made in 5 the regulations is a minor increase over minimal risk. 6 Again, there is some latitude here for interpretation; 7 but this is somewhat more than what the child would 8 experience in daily life. 9 Again, a healthy child would experience 10 in daily life but does not have a longstanding threat 11 to that child's health or wellbeing; and when a risk 12 falls into this category, there's an additional 13 requirement that the knowledge gained by exposing a 14 child to this risk must be generalizable to that 15 child's disorder or condition. 16 Next slide, please. 17 Now, to -- until now, I've really been 18 focused on the risk and benefit that derive from the 19 study intervention; but when we are looking at a 20 clinical-study protocol, we're looking at every 21 intervention that is part of that protocol. 22 So there's the -- the drug under study</p>
<p style="text-align: right;">Page 19</p> <p>1 really based on the data that support the activity and 2 the ability of this intervention to modulate the 3 clinical outcome but also how that intervention is 4 used in the trial. 5 So proof-of-concept data that derive 6 from either clinical human data or nonclinical data, a 7 combination thereof, can support the -- the activity 8 of the drug and the ability for that drug to lead to a 9 change in clinical outcome, but the way that drug is 10 deployed in the trial also must be advantageous. 11 So the doses that are used and the 12 duration of the treatment should be sufficient to 13 achieve the outcome. There is always the temptation 14 to start low and slow, so to prevent toxicity; but 15 sub-therapeutic doses would not be considered ethical 16 by and large. 17 Next slide, please. 18 So that was a discussion of benefit, 19 and now I want to turn to risk, and measuring risk is 20 -- is not easy, and -- and the language in our 21 regulations is not incredibly clear. 22 So first of all, we have the definition</p>	<p style="text-align: right;">Page 21</p> <p>1 but all the other interventions that come with it, and 2 we do the same benefit-risk assessment for each and 3 every one of those. 4 To -- to analyze those, we use the same 5 framework that we would for the -- for the main 6 intervention under study. 7 So if that intervention or procedure -- 8 and for example, we could use a blood draw. If it 9 does not hold out a prospect of direct benefit, then 10 it should be restricted to more than -- more -- no 11 more than a minor increase over minimal risk. 12 On the contrary, if that intervention 13 does have some prospect of direct benefit for the 14 child, then we have a little bit more risk tolerance; 15 and again, a risk-benefit analysis is -- is conducted 16 there. 17 Next slide, please. 18 I just want to highlight a few examples 19 of where this is challenging, and -- and some of these 20 things that we don't always think about as elements of 21 the protocol, not all of which are relevant to the 22 discussion here; but some of them might be.</p>

<p style="text-align: right;">Page 22</p> <p>1 So for example, biopsies that might be 2 done in a clinical investigation either for diagnostic 3 purposes or for measuring outcomes, some of them are 4 simple like a muscle biopsy that might be considered a 5 minor increase or -- or just minimal risk. Others 6 that are invasive -- solid-organ biopsies -- are in a 7 different category. 8 The same with diagnostic imaging, you 9 have to consider both the risk of the radiation, how 10 many times a child might be undergoing diagnostic 11 imaging. The risk of contrast agents that might be 12 administered and -- and related to imaging in some 13 ways is also nontherapeutic procedural sedation. 14 So we know there are inherent risks to 15 nontherapeutic procedural sedation. It may be 16 allowable in certain circumstances, but we really look 17 at these closely and -- and determine whether the -- 18 you know, each of these components is -- has both a 19 prospective benefit and a reasonable risk-benefit 20 ratio. 21 Next slide, please. 22 I want to just spend a few minutes</p>	<p style="text-align: right;">Page 24</p> <p>1 And second, it is also acceptable to 2 use placebos when we have an established effective 3 intervention but the administration of that might 4 obscure the treatment and confound the 5 interpretability of the trial and if we could either 6 delay or not provide that drug for a certain amount of 7 time during the clinical-protocol duration and 8 introduce mitigation procedures that -- that prevent 9 that child from experiencing harm during the time that 10 they're exposed to placebo. 11 Next slide, please. 12 We will pivot now from the discussion 13 of benefit and risk in the 50.52 regulations to the 14 50.55 regulations for parent and guardian permission, 15 and the main concept to really drive home here is that 16 -- is, this is a hard time for parents and caregivers 17 when they are caring for a critically ill infant. 18 And so you might have to come back more 19 than one time to really provide an opportunity for 20 parents to ask questions, understand all the 21 dimensions that are affecting their child's 22 participation; and they should receive follow-up as</p>
<p style="text-align: right;">Page 23</p> <p>1 talking about placebo. 2 And this is the -- the discussion about 3 placebo from an -- from an ethical standpoint, 4 acknowledging that there are going to be many opinions 5 about placebo that are offered over the course of the 6 next two days both from pragmatic and acceptability to 7 caregivers and -- and providers; but this, again, is 8 really from the ethical standpoint. 9 So when we look at a placebo-controlled 10 trial, the first thing we look at is -- what is the 11 risk of the placebo itself? How is it administered? 12 What is its composition? How long is it going to be 13 given? And make an assessment about that in and of 14 itself. 15 Second, what are the implications for 16 that child receiving placebo instead of something else 17 in the controller of a trial. So by and large, if 18 there is an established and effective intervention, 19 then all participants in a trial should receive that. 20 However, placebos are an important tool 21 that we use first when there is no established 22 ineffective intervention.</p>	<p style="text-align: right;">Page 25</p> <p>1 the -- as the trial goes on, if things were to change, 2 if knowledge has been gained. 3 There are specific requirements for 4 what the documentation looks like, which is available 5 in the references on the slide; but I -- I won't go 6 into those details for this presentation. 7 Next slide, please. 8 So I'm going to turn now to how this 9 ethical framework impacts drug development for the two 10 conditions that we're discussing today, enterovirus 11 infection in neonates and congenital CMV infection. 12 Next slide, please. 13 And I'm going to go back to the ethical 14 framework that we laid out before, these four core 15 principles: ensuring necessity, limiting risk, 16 preventing disadvantage, and obtaining permission. 17 Next slide, please. 18 We'll begin with ensuring necessity, 19 and I think Dr. Belew has already addressed this quite 20 a bit in her opening remarks, but we know that 21 congenital CMV and enteroviral infections in neonates 22 and very young children are -- are unique to this</p>

<p style="text-align: right;">Page 26</p> <p>1 population.</p> <p>2 It's a population that has an unmet</p> <p>3 medical need, and efficacy cannot be extrapolated</p> <p>4 because there is no corollary disease in other</p> <p>5 populations, including in children.</p> <p>6 And so the scientific and public-health</p> <p>7 objectives cannot be met without enrolling the target</p> <p>8 population of neonates and young children; and so this</p> <p>9 element of the ethical framework is satisfied.</p> <p>10 Next slide, please.</p> <p>11 Second, we'll turn to limiting risks;</p> <p>12 and this will be possibly a topic for the -- for the</p> <p>13 next two days. So clinical trials that evaluate most</p> <p>14 candidate antivirals will need to meet the</p> <p>15 requirements of 50.52, as I outlined.</p> <p>16 Just in summary, clinical and</p> <p>17 nonclinical data can be used to support the prospect</p> <p>18 of direct benefits; and then we will be looking at the</p> <p>19 investigational drug, the risk that is conferred from</p> <p>20 that as well as the other interventions and being --</p> <p>21 making a risk-benefit assessment there about what</p> <p>22 level of risk might be incurred.</p>	<p style="text-align: right;">Page 28</p> <p>1 there's no established effective intervention or if</p> <p>2 the administration of an active control would make the</p> <p>3 study data uninterpretable and withholding that</p> <p>4 treatment can be done safely for the participant.</p> <p>5 A reminder that adjunctive treatments</p> <p>6 should be provided if they are considered standard of</p> <p>7 care. So for example, in a critically ill neonate,</p> <p>8 all supportive care measures would be standardized</p> <p>9 across treatment arms.</p> <p>10 Ongoing therapy, you have -- in the</p> <p>11 case of both enteroviral sepsis as well as congenital</p> <p>12 CMV, such as physical or occupational therapy and</p> <p>13 early-intervention services, would be deployed,</p> <p>14 regardless of treatment assignments.</p> <p>15 Next slide, please.</p> <p>16 So last, obtaining permission -- and</p> <p>17 the key message here is that informed consent is a</p> <p>18 process. It is not a document. The parents and</p> <p>19 caregivers in the -- in the neonatal intensive-care</p> <p>20 unit are signing consent all the time for blood</p> <p>21 transfusions, for small procedures.</p> <p>22 So it's important to differentiate</p>
<p style="text-align: right;">Page 27</p> <p>1 A reminder that the study design is</p> <p>2 important in this benefit-risk assessment; and</p> <p>3 characteristics of the patient population, the risk-</p> <p>4 mitigation strategies that are deployed are -- are an</p> <p>5 important part of the assessment.</p> <p>6 Next, the component analysis, so the</p> <p>7 risk-benefit assessment is not limited to that</p> <p>8 investigational product. We'll be looking at the</p> <p>9 benefit and risk of every intervention in the</p> <p>10 protocol.</p> <p>11 This might include lumbar punctures,</p> <p>12 lab studies, diagnostic imaging, and -- and other</p> <p>13 assessments that -- that the child undergoes either</p> <p>14 for clinical care or for research purposes.</p> <p>15 Next slide, please.</p> <p>16 Third, preventing disadvantage, again,</p> <p>17 this -- I'm not offering solutions or answers here but</p> <p>18 just food for thought to frame the discussion that is</p> <p>19 sure to -- sure to -- to take place over the next two</p> <p>20 days.</p> <p>21 So placebo-controlled trials are</p> <p>22 acceptable if certain criteria are met: first, if</p>	<p style="text-align: right;">Page 29</p> <p>1 enrollment in a clinical trial from all of the other</p> <p>2 informed-consent procedures that they are -- all the</p> <p>3 procedures that they're -- they're asked to consent</p> <p>4 for.</p> <p>5 Consider strategies that help parents</p> <p>6 and caregivers really comprehend what they are signing</p> <p>7 up for, training videos, parent feedback groups, et</p> <p>8 cetera; and I'll just put a thought in mind that</p> <p>9 although the focus of this -- of this discussion is</p> <p>10 really on our very young, our neonates and young</p> <p>11 infants.</p> <p>12 If there was to be studies for these</p> <p>13 populations as they age and -- and the -- the</p> <p>14 possibility of antiviral therapy modulating their</p> <p>15 disease at an older age, then assent may be required</p> <p>16 in the participation of older children.</p> <p>17 Next slide, please.</p> <p>18 I'll just end with some resources. So</p> <p>19 the FDA publishes guidance documents to -- to</p> <p>20 summarize our views about a number of things, and</p> <p>21 these four guidance documents all touch on ethical</p> <p>22 aspects of -- of studies enrolling children.</p>

<p style="text-align: right;">Page 30</p> <p>1 Next slide, please.</p> <p>2 I'm going to skip my summary because I</p> <p>3 believe I have mentioned all of the points on the</p> <p>4 slide.</p> <p>5 Next slide, please.</p> <p>6 And I'll just end with some</p> <p>7 acknowledgements of my colleagues in the Office of</p> <p>8 Pediatric Therapeutics; to Dr. Melanie Bhatnagar, who</p> <p>9 has provided -- provided a lot of the content for this</p> <p>10 presentation; our director, Dr. Dionna Green; and all</p> <p>11 of the Pediatric Ethics staff, both past and present,</p> <p>12 who also have contributed to the content of this</p> <p>13 presentation. Thank you so much.</p> <p>14 DR. BELEW: Thank you, Dr. Viswanathan.</p> <p>15 Next I'd like to introduce Dr. An</p> <p>16 Massaro, Supervisory Medical Officer.</p> <p>17 Next slide, please, Corey.</p> <p>18 Supervisory Medical Officer for the</p> <p>19 Neonatal and Rare Pediatric Disease Team in the Office</p> <p>20 of Pediatric Therapeutics at FDA, she will be speaking</p> <p>21 about clinical and regulatory considerations for</p> <p>22 neonatal antiviral drug development.</p>	<p style="text-align: right;">Page 32</p> <p>1 that are inherent in neonatal clinical trials with a</p> <p>2 focus on considerations that may be relevant to the</p> <p>3 development of antiviral products for treatment of</p> <p>4 congenital infections but also provide some resources</p> <p>5 that can be later referenced for both medical-product</p> <p>6 development in neonates and some considerations for</p> <p>7 rare diseases in pediatric populations.</p> <p>8 Next slide, please.</p> <p>9 For background, in the U.S., pediatric</p> <p>10 drug development is largely driven by pediatric-</p> <p>11 specific drug legislations.</p> <p>12 This includes the 2002 Best</p> <p>13 Pharmaceutical Acts for Children or BPCA, which is a</p> <p>14 voluntary-incentive program for pediatric clinical</p> <p>15 studies, and the 2003 Pediatric Research Equity Act or</p> <p>16 PREA, which gave the FDA the authority to require</p> <p>17 pediatric studies for certain drug and biological</p> <p>18 products.</p> <p>19 Together these laws have led to a</p> <p>20 significant increase in the number of pediatric</p> <p>21 studies conducted and a subsequent increase in the</p> <p>22 number of pediatric-labeling changes for drugs and</p>
<p style="text-align: right;">Page 31</p> <p>1 Thank you, Dr. Massaro.</p> <p>2 DR. MASSARO: Thank you.</p> <p>3 And thank you to the meeting organizers</p> <p>4 for inviting me to participate, and I hope to set the</p> <p>5 stage in the next 10 to 15 minutes or so and provide</p> <p>6 some context from the neonatology perspective that may</p> <p>7 be relevant to all of our discussions over the next</p> <p>8 two days.</p> <p>9 Next slide, please.</p> <p>10 These are my disclosures. My talk</p> <p>11 today will represent my views on these topics, but</p> <p>12 they don't -- I don't plan to discuss any specific</p> <p>13 medical products.</p> <p>14 I'll just acknowledge that ensuing</p> <p>15 discussions may involve off-label use of medications,</p> <p>16 as this is common practice in the NICU, which is</p> <p>17 something we hope to change through efforts like this</p> <p>18 workshop.</p> <p>19 Next slide, please.</p> <p>20 This is an outline of my presentation.</p> <p>21 As noted, my goal is to provide a high-</p> <p>22 level overview of considerations and challenges really</p>	<p style="text-align: right;">Page 33</p> <p>1 biologics over the past several decades.</p> <p>2 Next slide, please.</p> <p>3 In September of 2022, the FDA announced</p> <p>4 the historic milestone of achieving over 1,000</p> <p>5 medicines that include evidence-based pediatric</p> <p>6 information and product labeling.</p> <p>7 This milestone represented the</p> <p>8 collaborative effort of the FDA and multiple other</p> <p>9 stakeholders, who played a real important role in</p> <p>10 informing the current approach to developing medicines</p> <p>11 for children.</p> <p>12 It's notable that the majority of these</p> <p>13 labeling changes occurred in the therapeutic area of</p> <p>14 infection diseases, as you can see highlighted here on</p> <p>15 the right side of the slide. This is very much in</p> <p>16 part due to the work of the divisions involved in the</p> <p>17 planning of this meeting.</p> <p>18 Next slide, please.</p> <p>19 While it's clear that progress has been</p> <p>20 made with regard to pediatric-labeling changes and</p> <p>21 drug development in pediatric patients in general,</p> <p>22 it's also clear that progress in the neonatal</p>

<p style="text-align: right;">Page 34</p> <p>1 population has lagged.</p> <p>2 In the NICU, we continue to practice in</p> <p>3 a setting where, as I mentioned, the majority of</p> <p>4 medications we prescribe to neonates are done so off</p> <p>5 label, meaning that they haven't undergone sufficient</p> <p>6 investigation to establish safety and effectiveness in</p> <p>7 the neonatal population.</p> <p>8 Despite what I had shown you in the</p> <p>9 prior slides, which is, as I noted, now over 1,000</p> <p>10 pediatric labeling changes, only about 5 percent of</p> <p>11 those have been -- have included studies or</p> <p>12 indications in neonates.</p> <p>13 So we really have a scientific and</p> <p>14 legislative mandate to address this gap both by</p> <p>15 conducting clinical studies in neonates for</p> <p>16 medications that are approved in adults and older</p> <p>17 pediatric patients when that's appropriate but also by</p> <p>18 developing new treatments for conditions that are</p> <p>19 specific to the neonate.</p> <p>20 Next slide, please.</p> <p>21 There are many reasons for the limited</p> <p>22 study of drug products in neonates.</p>	<p style="text-align: right;">Page 36</p> <p>1 triggered after separation from placental support.</p> <p>2 Finally, due to many of these factors</p> <p>3 that characterize the immaturity of the neonate, they</p> <p>4 are vulnerable to comorbidities and disease conditions</p> <p>5 across organ systems, making assessment of the safety</p> <p>6 and efficacy of a drug product particularly</p> <p>7 challenging to discern.</p> <p>8 Next slide, please.</p> <p>9 With that general background, I'm going</p> <p>10 to review a few regulatory considerations for neonatal</p> <p>11 drug development. As discussed by Dr. Belew, there's</p> <p>12 a regulatory standard for establishing substantial</p> <p>13 evidence of effectiveness with adequate and well-</p> <p>14 controlled studies.</p> <p>15 However, this approach is often very</p> <p>16 challenging and in some cases not feasible in some</p> <p>17 neonatal conditions.</p> <p>18 The other important regulatory concept</p> <p>19 relevant to our conversations in the need to establish</p> <p>20 substantial evidence of effectiveness with regard --</p> <p>21 is considering that this is with regard to a</p> <p>22 clinically meaningful endpoint. That is a measure of</p>
<p style="text-align: right;">Page 35</p> <p>1 These studies are inherently</p> <p>2 challenging, not only because the -- of the relative</p> <p>3 rarity of the disease conditions in the neonatal</p> <p>4 patients, compared to adults, but also because of the</p> <p>5 added complexity of clinical factors that can impact</p> <p>6 evaluation of a drug administered to a neonate.</p> <p>7 These include the rapid maturation of</p> <p>8 organs and tissues that occurs late in gestation, a</p> <p>9 period that occurs in the ex-utero environment in the</p> <p>10 case of the pre-term infant; and there's continued</p> <p>11 significant maturation after term birth and into early</p> <p>12 infancy or childhood.</p> <p>13 Developmental maturation at the</p> <p>14 cellular and biochemical level also represents a</p> <p>15 challenge, as many enzymes, receptors, transporters,</p> <p>16 and other signaling molecules are expressed</p> <p>17 differently with age.</p> <p>18 Physiological changes associated with</p> <p>19 the transition from the in-utero to ex-utero</p> <p>20 environment after birth must also be considered, as</p> <p>21 changes in circulation; oxygen tension; and function</p> <p>22 of organ systems, such as the lungs and GI tract, are</p>	<p style="text-align: right;">Page 37</p> <p>1 how a patient feels, functions, or survives.</p> <p>2 This can be challenging in the neonate,</p> <p>3 as I'll discuss in the next few slides; but first I</p> <p>4 want to address the concept of pediatric</p> <p>5 extrapolation, as it was also introduced by Dr. Belew</p> <p>6 in her introductory comments.</p> <p>7 You see here in this figure where</p> <p>8 extrapolation is best leveraged is when there's a</p> <p>9 clinical and pathophysiological overlap between the</p> <p>10 neonatal and adult disease condition, denoted here by</p> <p>11 the red area -- arrow.</p> <p>12 While the areas where extrapolation has</p> <p>13 been most successfully used to support substantial</p> <p>14 evidence of effectiveness in neonates are in anti-</p> <p>15 infectives and antivirals, as you saw in my prior</p> <p>16 slide that high number of labeling changes in the</p> <p>17 infectious-disease space is a testament to the</p> <p>18 successful leveraging of pediatric extrapolation in</p> <p>19 this therapeutic area, however, the use of</p> <p>20 extrapolation is limited when conditions occur</p> <p>21 exclusively in neonates or in conditions where the</p> <p>22 natural history or pathophysiology of the condition as</p>

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<p>1 it manifests in neonates is distinct from the adult-</p> <p>2 disease correlate.</p> <p>3 And as Dr. Belew mentioned -- and I'll</p> <p>4 just re-emphasize here -- in general, I would consider</p> <p>5 the conditions we are focused on for this meeting,</p> <p>6 congenital CMV and neonatal enterovirus that fall into</p> <p>7 this category, infections with distinct manifestations</p> <p>8 and clinical sequelae specific to neonates that limit</p> <p>9 the use of extrapolation.</p> <p>10 Next slide, please.</p> <p>11 So as noted, I wanted to spend some</p> <p>12 time discussing why measuring clinical benefit is not</p> <p>13 straightforward in the neonatal population.</p> <p>14 And many of these points are very</p> <p>15 relevant to the discussions we'll have during this</p> <p>16 meeting when we think about how we will establish</p> <p>17 whether a drug, quote/unquote, "works" or not for</p> <p>18 these infections where the clinical sequelae may not</p> <p>19 manifest until much later, after treatment in the</p> <p>20 neonatal period.</p> <p>21 As we'll hear from our patient and</p> <p>22 family advocates during the meeting, not everyone</p>	<p>1 Next slide, please.</p> <p>2 Those concepts translate into real</p> <p>3 challenges when defining clinical endpoints for</p> <p>4 neonatal trials. We're often looking for that unicorn</p> <p>5 -- what I'll call a unicorn endpoint that reflects an</p> <p>6 outcome that's common, assessed in a short time frame,</p> <p>7 and precisely measured.</p> <p>8 Unfortunately for most neonatal</p> <p>9 conditions, we're assessing rare events that occur</p> <p>10 often late after exposure to a therapeutic agent; and</p> <p>11 apart from outcomes such as mortality, morbidity,</p> <p>12 definitions in the neonate represent a challenge.</p> <p>13 As I noted earlier, the paradigm of</p> <p>14 feels, functions, and survives becomes difficult in a</p> <p>15 neonate. A patient -- it's a patient who can't really</p> <p>16 describe of course how they feel, and functional</p> <p>17 assessments in neonates often rely then on clinical or</p> <p>18 caregiver observations or other tools that may not be</p> <p>19 well-validated or fit for purpose.</p> <p>20 Next slide, please.</p> <p>21 So since I've spent a lot of time</p> <p>22 describing challenges without a lot of solutions, I do</p>
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<p>1 values the same outcomes similarly.</p> <p>2 And the field of neonatology has</p> <p>3 numerous examples where therapies demonstrated to have</p> <p>4 positive short-term benefits were later</p> <p>5 counterbalanced by longer-term toxicities or loss of</p> <p>6 effective -- effect or seeing that benefit in the long</p> <p>7 term.</p> <p>8 While this may point to the need for</p> <p>9 longer-term assessments for any investigational</p> <p>10 therapeutic agent, we'll acknowledge that this</p> <p>11 approach can lead to potential delays in getting</p> <p>12 effective drugs through the developmental pipeline to</p> <p>13 patients.</p> <p>14 And there's also inherent complications</p> <p>15 with these longitudinal type studies for attrition and</p> <p>16 intercurrent events that can impact the confidence we</p> <p>17 have in the assessment of long-term drug effects.</p> <p>18 While this may point to the need for</p> <p>19 surrogate endpoints for trials, timeliness and</p> <p>20 efficiency may be counterbalanced with uncertainty,</p> <p>21 depending on the reliability of the surrogate endpoint</p> <p>22 and its relationship to the outcome of interest.</p>	<p>1 want to highlight a lot of ongoing work that's trying</p> <p>2 to address some of these challenges in defining</p> <p>3 outcomes for neonatal studies.</p> <p>4 I've included some references here on</p> <p>5 several recent coordinated multistakeholder efforts to</p> <p>6 build core outcome steps for neonatal clinical trials</p> <p>7 in general, and there's even more ongoing work in</p> <p>8 specific disease area -- areas.</p> <p>9 So one consideration for us in our</p> <p>10 discussions is whether congenital CMV or enterovirus</p> <p>11 would benefit from such an effort, and that may start</p> <p>12 with some of the discussions at our -- at this</p> <p>13 meeting.</p> <p>14 Next slide, please.</p> <p>15 Equally challenging to establishing</p> <p>16 substantial evidence of effectiveness is collection of</p> <p>17 adequate safety data for drugs studied in neonates.</p> <p>18 The size of the safety database needed</p> <p>19 may depend on several factors, including experience</p> <p>20 with the drug itself or similar drugs in adults or</p> <p>21 older children or even previously studied neonatal</p> <p>22 subpopulations; the serious infrequency of adverse</p>

<p style="text-align: right;">Page 42</p> <p>1 reactions observed in other populations, such as 2 those; the rarity of the condition; the potential for 3 unique susceptibility of the neonate to particular 4 adverse events. 5 For example, when we're talking about 6 an investigational product targeting congenital CMV 7 with the aim to improve long-term sensorineural or 8 neurodevelopmental outcomes, that would clearly 9 warrant long-term evaluation from an efficacy 10 standpoint. 11 But even when a drug is intended for a 12 short-term effect, this may still warrant assessment 13 for neuro -- long-term neurodevelopmental safety. 14 And the expectation may be to assess 15 potential safety issues longer than may be potentially 16 expected for -- in a drug development in adults, for 17 example, especially if that drug is known to cross the 18 blood-brain barrier and be associated with high 19 exposure to the developing brain, again, a unique 20 susceptibility to the neonatal population. 21 Next slide, please. 22 These are some additional study</p>	<p style="text-align: right;">Page 44</p> <p>1 workflow for physicians and nurses in the ICU, these 2 are all big challenges. 3 So multistakeholder input is really 4 needed early in the design process to ensure that 5 these studies are feasible and acceptable to both 6 clinicians and families. 7 Finally, safety data should be 8 systematically collected. I already mentioned that 9 the size of the safety database may be based on 10 several different factors, but it's important to 11 ensure that attention is also paid to how adverse 12 events are collected. 13 For example, an adverse event such as 14 hypertension is obviously defined with a different 15 physiological range in the neonate than an adult; and 16 other adverse events may be completely specific to the 17 neonate, such as the occurrence of prematurity-related 18 comorbidities. 19 So I'll refer you to a tool developed 20 by the International Neonatal Consortium to define and 21 grade severity for neonatal adverse events, and the 22 reference can be seen here on this slide.</p>
<p style="text-align: right;">Page 43</p> <p>1 considerations. It's important to sure -- ensure that 2 studies are designed to include a spectrum of relevant 3 clinical variability in the neonatal population of 4 interest, and I'll discuss more about this on my next 5 slide. 6 Another point to emphasize is to 7 remember that the absolute blood volume of a neonate, 8 especially a pre-term neonate, is very small. 9 So limitations in neonatal blood 10 sampling need to be considered when we're designing 11 our clinical studies, especially when we're 12 considering that we'll need blood for sampling for 13 PK/PD endpoints but also laboratory and safety 14 monitoring in conjunction to routine clinical 15 monitoring. 16 It's important to remember the 17 environment also that these studies are occurring -- 18 occurring. 19 As we'll hear from our patient and 20 family advocates, conducting, studies in the NICU, 21 obtaining consent from parents during a stressful 22 time, incorporating study procedures amongst the busy</p>	<p style="text-align: right;">Page 45</p> <p>1 Next slide, please. 2 As I alluded to on the prior slide, 3 there's a wide clinical heterogeneity that 4 characterizes the neonatal population. Using a common 5 language can allow for methods to stratify patients 6 based on characteristics that can greatly impact the 7 analysis of PK and dose-response data. 8 This can allow for assurance that the 9 product is evaluated across the range of gestational 10 age, postmenstrual age, or postnatal age, as 11 appropriate. 12 While of course we recognize that some 13 of these variables may be highly correlated, such as 14 gestational age and birth weight, it's important to 15 recognize that they're all different conceptually, as 16 you can see on this slide; and the information they 17 provide to characterize the neonate are not 18 interchangeable. 19 Next slide, please. 20 I've included here additional resources 21 on many of the concepts I've introduced, including 22 tools developed by the International Neonatal</p>

<p style="text-align: right;">Page 46</p> <p>1 Consortium, resources from a meeting we convened in 2 collaboration with Duke-Margolis last year on neonatal 3 -- on measuring neonatal benefit -- benefit in 4 neonatal clinical trials, and several of -- neonatal- 5 specific FDA guidance documents. 6 Next slide, please. 7 I'm going to end my talk on a brief 8 discussion of rare-pediatric-disease-drug development, 9 as these considerations may also be relevant to our 10 discussions for enterovirus and congenital CMV. 11 Work to advance drug development in 12 rare diseases is supported by legislation, expedited- 13 review pathways, and voucher incentives. I'm going to 14 focus my comments -- my few comments on the orphan- 15 drug-designation and rare-pediatric-disease- 16 designation programs. 17 Next slide, please. 18 So prior to a sponsor receiving a rare 19 pediatric disease, prior to a review voucher, 20 determination must be made that the drug or biologic 21 is actually for a rare pediatric disease. 22 So a request for a rare-pediatric-</p>	<p style="text-align: right;">Page 48</p> <p>1 awarding of priority vouchers. 2 And I just want to emphasize that this 3 is an important distinction when we discuss 4 enterovirus or congenital CMV as, quote/unquote, "rare 5 diseases." We'll be hearing a lot of epidemiologic 6 information over the course of the meeting. 7 And it's true, and while it -- I'll 8 note that it's true that prevention of congenital CMV 9 infection following primary CMV infection in pregnant 10 women and treatment of symptomatic enteroviral 11 infection in the neonate have been -- indications have 12 been granted orphan-drug designations in the past. 13 Whether these programs, the Orphan Drug 14 Program or the RPD Program, may be leveraged for a 15 particular development program for an investigational 16 product to treat these infections really depends on 17 several factors or eligibility criteria. 18 And reviewing all of these nuances in 19 criteria are beyond the scope of my talk today, but 20 I'll refer you to some resources that are available to 21 guide this on my next slide. 22 You can go to the next slide, please.</p>
<p style="text-align: right;">Page 47</p> <p>1 disease designation includes the data to support that 2 the proposed mechanism of action of the drug or -- of 3 the drug or biologic in that drug is intended to treat 4 a rare pediatric disease. 5 And that's defined as a disease with 6 serious or life-threatening manifestations that 7 primarily affect individuals from birth to 18 years 8 and that the total prevalence of the disease affects 9 fewer than 200,000 people. 10 The rare -- RPD-designation portion of 11 the Priority Review Voucher Program is administered by 12 the Office of Orphan Products Development or OOPD in 13 collaboration with our office and the Office of 14 Pediatric Therapeutics within the Office of the 15 Commissioner at the FDA. 16 Next slide, please. 17 So I've noted here -- and as Dr. Belew 18 also mentioned -- the statutory definition of a rare 19 disease, as defined by the Orphan Drug Act; and as we 20 just discussed, there's also a definition for a rare 21 pediatric disease; and it has its own statutory 22 definition for the purposes of RPD designation and</p>	<p style="text-align: right;">Page 49</p> <p>1 And here you'll find the relevant links 2 to additional information on the programs I mentioned, 3 as well as this first link here is a recently 4 published review of the RPD Program. That has a lot 5 of information about this first ten years of -- of 6 this program being in existence. 7 Next slide, please. 8 So I'll wrap up and say in summary that 9 drug development in neonates faces unique challenges 10 due to rapid developmental changes and vulnerabilities 11 that are really specific to neonates. 12 The FDA and really multiple other 13 sources have resources to promote and support drug 14 development for neonates and for rare pediatric 15 diseases. So with that, I will turn back to the 16 organizers. Thank you. 17 DR. BELEW: Thank you, Dr. Massaro. 18 Next I'd like to introduce Dr. Kunyi 19 Wu, Clinical Pharmacology Team Leader in the Division 20 of Infectious Disease Pharmacology at FDA. Dr. Wu 21 will be discussing clinical pharmacology 22 considerations for dose selection in pediatric</p>

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<p>1 patients.</p> <p>2 Thank you, Dr. Wu.</p> <p>3 DR. WU: Thank you.</p> <p>4 So today I'm going to share the</p> <p>5 clinical pharmacology considerations for dose</p> <p>6 selection in pediatric patients.</p> <p>7 Next slide.</p> <p>8 This is the outline for my talk.</p> <p>9 First, I will talk about three broad approaches to</p> <p>10 pediatric drug development; and then I'll talk about</p> <p>11 modeling and simulation and the clinical pharm</p> <p>12 considerations for dose selection in pediatric</p> <p>13 patients.</p> <p>14 Then I will use one example to</p> <p>15 illustrate how to use animal data to select</p> <p>16 initiatives in pediatric clinical trials and then</p> <p>17 follow up with challenges and opportunities.</p> <p>18 Next slide.</p> <p>19 This slide lists three broad approaches</p> <p>20 to pediatric drug development. First, when disease or</p> <p>21 disease progression is unique to pediatric patients,</p> <p>22 then PK, Safety, and Efficacy Approach is used.</p>	<p>1 and Safety Approach is not applicable.</p> <p>2 So the sponsor may need to come to us</p> <p>3 to discuss before they initiate their clinical</p> <p>4 program.</p> <p>5 Next slide.</p> <p>6 Modeling and simulation plays an</p> <p>7 important role in pediatric drug development. I</p> <p>8 borrowed this figure from a publication from FDA back</p> <p>9 to 2019. In this publication, it illustrates the</p> <p>10 MIDD, Model Informed Drug Development Program, in</p> <p>11 Pediatric Program.</p> <p>12 And they form three parts: first,</p> <p>13 leverage knowledge; second, dose selection and</p> <p>14 optimization; third, informing clinical-trial design.</p> <p>15 So in Infectious Disease Pediatric Program, usually</p> <p>16 before that we already accumulate some data from</p> <p>17 adults or other indications.</p> <p>18 So a model can help to leverage</p> <p>19 knowledge, and the model also can help to compare the</p> <p>20 exposure-response relationship in pediatric patients</p> <p>21 versus adults. Model can help to select initiatives</p> <p>22 in pediatric-development programs, and the model also</p>
<p>Page 51</p> <p>1 The second scenario is when disease or</p> <p>2 disease progression is similar in pediatric patients</p> <p>3 and adults but the exposure response, ER, relationship</p> <p>4 in peds may be different from adults; and now the PK,</p> <p>5 Safety, and PD/Efficacy Approach is used.</p> <p>6 The third scenario is when adults and</p> <p>7 peditrics share a sufficiently similar disease course</p> <p>8 and response to intervention. Then PK and Safety</p> <p>9 Approach is used. The third approach, which is the PK</p> <p>10 and Safety Approach, is the most frequently used</p> <p>11 approach in infectious-disease pediatric-development</p> <p>12 programs.</p> <p>13 Next slide.</p> <p>14 Valganciclovir is an example to use PK</p> <p>15 and Safety Approach to select and approve those adult,</p> <p>16 one month, and older, based on similar ganciclovir</p> <p>17 exposure in pediatric patients versus adults.</p> <p>18 As multiple speakers already mentioned</p> <p>19 previously, for the two disease types we discussed in</p> <p>20 this workshop, which is congenital CMV infection and</p> <p>21 the neonatal enteroviral infection, those two disease</p> <p>22 types are unique in pediatric patients; and this PK</p>	<p>Page 53</p> <p>1 can incorporate pediatric ontogeny in infants and the</p> <p>2 neonates.</p> <p>3 Sometimes model can help to select</p> <p>4 model, and the simulation can help to select sample</p> <p>5 size and the PK sampling scheme in the program.</p> <p>6 Next slide.</p> <p>7 Maribavir is an example to use</p> <p>8 published PK model to select pediatric dose in</p> <p>9 adolescents. Even without PK data, this dose has been</p> <p>10 approved. Of course, most studies are required in</p> <p>11 adolescents to confirm the simulation results.</p> <p>12 Next slide.</p> <p>13 So I want to use the rivaroxaban case</p> <p>14 to illustrate the learning and the confirming cycle in</p> <p>15 the modeling-simulation practice. Rivaroxaban is an</p> <p>16 anticoagulant, and it has been approved based on</p> <p>17 similar drug exposure in pediatric patients versus</p> <p>18 adults.</p> <p>19 And the -- the study design -- the</p> <p>20 clinical study design is age staggered from older</p> <p>21 children to younger children. So in older-children</p> <p>22 cohort, it's older than 6 months. The study dose was</p>

<p style="text-align: right;">Page 54</p> <p>1 predicted by using PBPK model, physiologically based 2 pharmacokinetics model. 3 And interestingly, the observed 4 exposure was way lower than the predicted exposure. 5 So based on this observation, the sponsor increased 6 dose regimen from QD to BID and then matched the 7 exposure in adults. 8 And also based on this observation, 9 sponsor selected higher than PBPK-model-predicted dose 10 in younger cohort, which is younger than 6 months. 11 However, the observed exposure still though was way 12 lower than the predicted exposure. 13 Then the sponsor increased the dose 14 regimen again from BID to TID and then matched adult 15 exposure. At the end of the day, all the PK data were 16 incorporated into the population PK model; and the 17 clinical PK data and the population PK model analysis 18 results were used to select dose in pediatric 19 patients. 20 I hope this example illustrates the 21 practice in modeling simulation as prediction, 22 learning, and confirming the cycle.</p>	<p style="text-align: right;">Page 56</p> <p>1 means their body size, their body surface area, their 2 weight changes on a daily basis, especially in 3 neonates and infants. 4 So when we think about dosing regimen, 5 we need to think about whether we want to use weight- 6 based dose, which is milligram-per-kilogram dose or we 7 want to use flat dose or we want to use weight-based 8 dose. 9 Sometimes we also need to think about 10 local drug concentrations. For example, for CNS 11 penetration, central-nervous-system penetration, so if 12 CNS is the target organ, then it is an efficacy 13 concern if it is -- it is not, then it becomes a 14 safety concern. 15 However, it's very hard to get a PK 16 sample in CSF, cerebrospinal fluid; and even when we 17 get a PK sample, it's very sparse and with high 18 variability. 19 Another example is for hearing loss. 20 For hearing loss, we need to consider the inner-ear 21 penetration -- drug-inner-ear penetration. However, 22 it's almost impossible for us to get a sample -- PK</p>
<p style="text-align: right;">Page 55</p> <p>1 Next -- next slide. 2 This slide lists some clinical 3 pharmacology considerations for dose selection in 4 pediatric patients. 5 First, route of administration, for 6 very young children and very sick children, the 7 parenteral-administration route is preferred over oral 8 because for the oral route first we have to have age- 9 appropriate formulation, which takes time; and second, 10 age may have impact on absorption. 11 So for different formulations, very 12 young children -- absorption in very young children 13 may be different from adults. However, most viability 14 -- viability studies are conducted in adults. So that 15 increased uncertainty for predict -- for -- for dose 16 prediction in very young children. 17 And also, disease may have impact on 18 absorption. For example, for enteroviral infection, 19 then it impacts GI tracts; and that may have an effect 20 on absorption. 21 We also view pediatric population as a 22 very dynamic, very heterogeneous population, which</p>	<p style="text-align: right;">Page 57</p> <p>1 sample in clinical trials for inner-ear penetration. 2 So animal models may become helpful in this case. 3 When we consider drug distribution and 4 elimination, we need to think about organ maturation, 5 enzyme maturation, receptor-transporter maturation. I 6 have to admit we still have a knowledge gap in this 7 area. 8 Next slide. 9 I want to use one example, which is 10 lucinactant's case, to illustrate how to use animal- 11 study results to select initial dose in pediatric 12 clinical trials. So lucinactant has been approved for 13 the prevention of respiratory distress syndrome, RDS, 14 in premature infants because those children -- they 15 cannot produce enough surfactant in their lungs. 16 So lucinactant is a synthetic 17 surfactant. So because of the unique indication in 18 this population, we don't have any PK data from 19 adults, any clinical adults for -- from other 20 indications. So the initial dose in neonates was 21 directly selected based on premature monkeys and a 22 premature-rabbit model.</p>

<p style="text-align: right;">Page 58</p> <p>1 And a range of doses were evaluated in 2 animal models, and three doses moved -- moved on to 3 clinical trials; and eventually, one dose was 4 approved. 5 Next slide. 6 We already know for the PK -- PBPK in 7 animal models have been used in pediatric clinical 8 programs. However, the daily challenge we encountered 9 is with the decrease of age in younger cohorts we have 10 fewer data. 11 So additional data, especially in very 12 young children, will help us understand the physiology 13 in -- in young children and help us to better predict 14 and use the modeling-simulation practice or use some 15 other approaches to estimate, predict, evaluate the 16 dose in pediatric populations. 17 Next slide. 18 I want to use this opportunity to thank 19 all the individuals listed on this slide and also 20 thank my colleagues in the DIDP and the DAV in FDA for 21 their help to develop those slides and also 22 stimulating discussions. Without them, this</p>	<p style="text-align: right;">Page 60</p> <p>1 might be walking in with. 2 So, please, next slide. 3 So families come in with something 4 traumatic happening at birth often, whether it was 5 planned or unplanned, depending on what -- you know, 6 what their situation was. 7 And they have a lot of questions and a 8 lot of trauma regardless because acute care itself, 9 especially when you're expecting a baby and -- and 10 going through this experience, you know, is definitely 11 not in anyone's plan or hopes and dreams for -- for 12 their child and their -- their parenthood. 13 Plus, you have to think about the other 14 baggage that people have along the way regarding 15 social determinants of health, regarding any sort of 16 other, you know, developmental trauma or systemic, you 17 know, impact and marginalization that may occur. 18 Next slide, please. 19 So this -- this is my story. Max was 20 born 12 years ago actually last week -- or 2 weeks ago 21 now, and he was my first pregnancy. Everything was 22 normal and typical until it wasn't at 37 weeks.</p>
<p style="text-align: right;">Page 59</p> <p>1 presentation would not happen. Thank you for your 2 attention. 3 DR. BELEW: Thank you, Dr. Wu. 4 Next I'd like to introduce Ms. Betsy 5 Pilon, Executive Director for Hope for Hypoxic 6 Ischemic Encephalopathy. Ms. Pilon's talk is entitled 7 "Life of a NICU Parent: Decision-Making in Clinical 8 Trial Enrollment." 9 Thank you, Ms. Pilon, for being here 10 today and sharing your perspectives and experiences 11 with us. 12 MS. PILON: Thank you so much for 13 having me. 14 Next slide, please. 15 So I'm going to talk a little bit about 16 the NICU experience from both my perspective and being 17 a part of a community that very often starts in the 18 NICU. 19 And I just want to ask everyone what 20 you virtually walked into this room today and what 21 kind of baggage. You know, it varies; and I want you 22 to think in the context of the NICU what families</p>	<p style="text-align: right;">Page 61</p> <p>1 So the HIE community is a little bit 2 unique in that the majority of our families are full 3 term, but I know that there -- I'm very familiar with 4 the CMV community as well and hope that this is, you 5 know, applicable to the discussion points today as 6 well. 7 He was born in the community-hospital 8 setting, transferred to Downtown Detroit at Henry Ford 9 Hospital for therapeutic hypothermia. We had no idea 10 that this was even a possibility. 11 You know, the messaging and 12 representation still remains heavily skewed towards 13 preemies; and, you know, typically, families are 14 counseled that if you get past 36 weeks you should be, 15 quote/unquote, "in the clear." 16 And any full-term babies that I knew 17 were there for transient observation, maybe a 18 bilirubin level, something that -- that was very 19 transitional and not something neurologically focused. 20 For our -- for our journey, as you can see on the 21 bottom, you know, we did get transferred to the NICU. 22 So that was a layer of complexity.</p>

<p style="text-align: right;">Page 62</p> <p>1 I was luckily transferred down a few 2 hours after Max was. Max got into the cooling process 3 -- you can see the little graphic at the bottom there 4 -- on full EEG umbilical line. He was on the 5 oscillator, very, very sick, getting transferred down; 6 and we had to be separated because he was, you know, 7 delivered by emergency C-section.</p> <p>8 And then he went through his cooling 9 for hypothermia, which is a 72-hour process, cooldown, 10 warmup, and then on Day 5 received an MRI; and at that 11 time, you know, the MRI, like many hospitals, was on 12 the other side of the moon, it felt like; and they so 13 had to pack him up, reintubated him for stability at 14 that time.</p> <p>15 I hope and believe and have heard that 16 a lot of practices have changed over the past 12 17 years, always the case.</p> <p>18 And -- but it was a very stressful time 19 for us; and everyone kept, you know, talking about how 20 MRI day was going to be the sentinel day of 21 information for us to figure out if this was kind of a 22 transient encephalopathy or if this was more</p>	<p style="text-align: right;">Page 64</p> <p>1 physician what it meant. I flagged him down a little 2 bit; and he said, "Well, it just means it has to do 3 something with the brain; but don't go home and Google 4 it."</p> <p>5 So for me, that was a dissatisfier not 6 knowing what, you know, a diagnosis was for my child, 7 what this could mean, what life might look like across 8 a very wide variety -- spectrum of outcomes with HIE. 9 It is very heterogeneous in all ways, I believe.</p> <p>10 And I feel strongly about now 11 connecting with over 10,000 families worldwide with 12 Hope for HIE and hearing so many different stories. 13 So, you know, me as a family member, we -- we left the 14 NICU without any connection to any support. I had 15 asked for support. I had asked for other families to 16 be connected to.</p> <p>17 So obviously, that was a very isolating 18 and frustrating time; and just the NICU in general is 19 really -- it's a slog, regardless of if you're there 20 for 1 day or 100 days. It's -- it's a very complex 21 acute-care environment. 22 In our situation, you know, Max was,</p>
<p style="text-align: right;">Page 63</p> <p>1 associated with HIE.</p> <p>2 But HIE at that time was not named to 3 us. It was just talking about general brain injury, 4 and so we did have MRI day. It showed moderate damage 5 to the occipital, parietal, and frontal lobes; and we 6 were kind of thrust into what everyone in our 7 community called the dreaded HIE wait and see.</p> <p>8 Wait and see how he's going to develop. 9 Wait and see if he'll eat. Wait and see if suck, 10 swallow, gag, you know, coordinates and comes together 11 or if he'll need a feeding tube.</p> <p>12 We had no mention 12 years ago of HIE 13 until there was one day where we had non-family- 14 centered rounds and overheard the term encephalopathy.</p> <p>15 So I had worked for the health system 16 in marketing and communications, had written a lot of 17 patient-education materials, and had been exposed to a 18 lot of different medical terms; and that was not one 19 that I had been -- that I had been familiar with.</p> <p>20 So I reached out to my sister-in-law, 21 who's a pediatric physical therapist. I had asked her 22 what encephalopathy meant. I asked the -- the</p>	<p style="text-align: right;">Page 65</p> <p>1 like, the only really sick full-term baby. So that 2 was very isolating; and then when trying to talk to 3 people about the fact that he was full term in the 4 NICU, you know, there was just a lot of downplay or, 5 you know, of course well -- well-meaning but very much 6 -- you know: "He'll be fine. He's full term."</p> <p>7 Or even in NICU support groups that we 8 initially connected with, you know, we were told, 9 like, many -- by fellow parents that had been -- there 10 was nothing to worry about 'cause our baby was only in 11 the NICU for three weeks.</p> <p>12 So, you know, there's just a lot of 13 interesting things; and when we talk about today -- 14 next slide, please.</p> <p>15 The topic at hand, which is neonatal 16 clinical trials -- you know, and in this context of 17 HIE and other -- other very difficult, harrowing 18 potential experiences, there's lots of variables that 19 work against research and -- researchers and families.</p> <p>20 Now, Max was born in 2012; and that was 21 at a period of time with cooling in particular that 22 that was becoming standard of care; but it was not</p>

<p style="text-align: right;">Page 66</p> <p>1 fully expanded standard of care.</p> <p>2 And so we were very fortunate that</p> <p>3 Henry Ford was a part of the NRN cooling trials and</p> <p>4 that everyone was very aware that this was a treatment</p> <p>5 available and that they had the treatment available,</p> <p>6 you know, not only at Henry Ford.</p> <p>7 But obviously, I'm in metro Detroit.</p> <p>8 There's lots of -- you know, lots of good sites that</p> <p>9 are -- that we had a lot of great research and -- and</p> <p>10 access to good care, but the disparity of care is</p> <p>11 certainly variable out there.</p> <p>12 And so, you know, with HIE, in</p> <p>13 particular with cooling, you need to initiate it</p> <p>14 within six hours and get the baby started cooling down</p> <p>15 for biggest chance at efficacy; and I think back to</p> <p>16 the families that I'm connected to through our</p> <p>17 organizational support where there -- we have families</p> <p>18 that participated in the original cooling trials.</p> <p>19 And I think about what a science-</p> <p>20 fiction, you know, discussion that sounds like to, you</p> <p>21 know, do an experimental treatment to cool a baby down</p> <p>22 for three days. You can't touch them, can't -- you</p>	<p style="text-align: right;">Page 68</p> <p>1 causing a lot of mistrust. It is trauma.</p> <p>2 And then we also come across on the</p> <p>3 clinical side -- there is -- is and can be bias,</p> <p>4 gatekeeping, and misperception of families and</p> <p>5 systemic inequity, so a lot of things -- a lot of big</p> <p>6 factors from the family perspective of -- and the</p> <p>7 clinical perspective of -- of trying to enroll</p> <p>8 families into clinical trials in the context of the</p> <p>9 NICU.</p> <p>10 But we must accept finite</p> <p>11 disappointment but never lose infinite hope for that.</p> <p>12 So next slide, please.</p> <p>13 We're going to talk a little bit about</p> <p>14 the exciting work of the -- that is going on with</p> <p>15 researchers and families. So on HIE in particular,</p> <p>16 'cause that's what I know and can talk about, you</p> <p>17 know, there's 30-plus years of research with HIE.</p> <p>18 We've explored cooling with head cooling versus whole</p> <p>19 body.</p> <p>20 People have done additional, you know,</p> <p>21 studies with longer, quicker, colder gestational</p> <p>22 modifiers to really explore all facets of cooling.</p>
<p style="text-align: right;">Page 67</p> <p>1 know, have to keep stimuli low. At least, that was</p> <p>2 what the -- the experience of -- of us and those that</p> <p>3 went through those trials.</p> <p>4 So it's, you know, very high stakes</p> <p>5 and, again, time sensitive. Resource variability I</p> <p>6 mentioned a little bit. You know, with HIE and a lot</p> <p>7 of neonatal clinical trials, there's the mother-baby</p> <p>8 health and separation aspects.</p> <p>9 So I mentioned I'm very lucky that I</p> <p>10 was transferred, you know, with Max; but many people</p> <p>11 are not; and mother's health is often very impacted as</p> <p>12 well, depending on the causation.</p> <p>13 There's an overwhelming well-</p> <p>14 intentioned and necessary consent that's insisted by</p> <p>15 the -- you know, the IRBs out there; and you have to</p> <p>16 really build quick health-literacy lessons to build</p> <p>17 consent to have informed consent. You know, with --</p> <p>18 with HIE or many others, something didn't go right.</p> <p>19 So a lot of times there's that, you</p> <p>20 know, fight or flight or freeze in -- in the midst of</p> <p>21 trauma. That can create a mistrust, and there's just</p> <p>22 a lot of medical misinformation out there that's</p>	<p style="text-align: right;">Page 69</p> <p>1 There's a PCORI study going on right now called COOL</p> <p>2 PRIME looking at mild HIE in cooling, which was not</p> <p>3 originally included in the -- the original underlying</p> <p>4 cohorts.</p> <p>5 And then the HEAL study is another</p> <p>6 landmark study that now has very powerful secondary</p> <p>7 analyses going on. There's also -- the Gates</p> <p>8 Foundation has a preclinical pipeline with various</p> <p>9 small and large animal models and human organoid.</p> <p>10 And they're really trying to look at</p> <p>11 equity for LMIC because HIE in particular impacts LMIC</p> <p>12 far more than high-income countries, but -- and -- and</p> <p>13 cooling is just not something that's feasible for many</p> <p>14 around the world or effective, given some updated</p> <p>15 information.</p> <p>16 And on the horizon, there's novel and</p> <p>17 repurposed medication possibilities; and this is where</p> <p>18 I know the FDA and other regulatory agencies come in.</p> <p>19 People are talking about stem cells, peptides,</p> <p>20 biologics, and even melatonin and looking at what</p> <p>21 could -- caffeine, there's all sorts of things that</p> <p>22 are being explored.</p>

<p style="text-align: right;">Page 70</p> <p>1 And things -- you know, what I -- what 2 I was really struck by, by a previous speaker was 3 looking at, you know, the -- the existing medications 4 that are approved and what could be repurposed and 5 getting also people outside of a specific area. 6 For HIE, it's very obviously 7 neonatology and neurology focused; but, you know, we 8 have a lot of innovation going on that -- I've heard a 9 story of, you know, innovation going on from 10 infectious-disease immunology as well, you know, in 11 looking at multiple factors. So multidisciplinary 12 collaboration is really essential for this. 13 And so the next slide, please. 14 Gap areas to consider from my 15 perspective, silos, bias, and impact to the enrollment 16 -- you know, centering the community that you're 17 studying and avoiding tokenization for funding, that 18 does happen across HIE and other -- and other disease 19 areas. 20 Having early multidisciplinary 21 stakeholder involvement, thinking outside neonatology 22 -- neonatology, as I mentioned early in the trial-</p>	<p style="text-align: right;">Page 72</p> <p>1 bias that does exist is that families can't understand 2 or they're not educated. So help us be educated and 3 understand so we can also translate that back to 4 communities. 5 And then looking at longitudinal 6 engagement and support and looking at proactive 7 communication planning, that should be formalized 8 throughout the entire study, so looking at how your 9 intention -- the intentionality, the key messages, 10 working with a communication consultant. 11 I -- I can't emphasize -- emphasize 12 that enough to use best practices for patient and 13 family engagement with those considerations for 14 building health literacy and include longitudinal 15 support resources for enrolled families. 16 Families -- you know, two years is a 17 long time. There's a lot that goes on. You're in the 18 acute period in a neonatal trial in the NICU; but then 19 afterwards you have to figure out life with what 20 you've gone through and process and, you know, deal 21 with whatever impacts might be long-lasting from the 22 NICU.</p>
<p style="text-align: right;">Page 71</p> <p>1 design process -- and site training for communication 2 is essential to enrollment success, making sure that 3 people really are building training resources in 4 collaboration with families that have gone through 5 clinical trials to, you know, really, you know, 6 implement best practices in consistency and also have 7 mechanisms of trying to just, you know, find ways to 8 answer common questions to optimize enrollment 9 measures, develop measures that matter. 10 I know this was alluded to by An 11 earlier. Composite, there's a lot of work being done 12 right now in multiple areas, which is really exciting 13 versus lumping death and disability, which is kind of 14 the comment of, you know, mortality and morbidity. 15 And NDI in particular is such an 16 interesting definition that I think we're seeing a lot 17 of work that's being done, and Jean Vie [ph] up in 18 Canada and others are looking at what we can do to 19 move to that composite and then looking to help 20 patient and family stakeholders understand those 21 biomarkers too. 22 We want to be educated. A lot of the</p>	<p style="text-align: right;">Page 73</p> <p>1 Families need those supports so we can 2 decrease attrition rates and make sure that they're 3 really engaged in these studies. So, you know, we've 4 tried to do that with several of the studies that our 5 families have been a part of; and, you know, the HEAL 6 study is a great example. 7 There's a ton of secondary analyses. I 8 am communicating those back to our community as they 9 come out and continuing to have families be engaged in 10 that process to build this community culture of 11 research. 12 Next slide, please. 13 And just to give my own example of 14 Max's journey to share where a lot of these clinical 15 trials stop, you know, so Max's developmental-impact 16 journey, vision concerns early on, 3 months, you know, 17 we were pushed -- we pushed to wean him off 18 phenobarbital, which is now -- there's evidence behind 19 that practice change over the past decade, which is 20 fantastic. 21 You know, at 9 months old, he got -- 22 received an official cerebral palsy diagnosis. At 2</p>

<p style="text-align: right;">Page 74</p> <p>1 years, he got corrective vision surgery. You know, he 2 was in PT and OT and has been for his entire life. He 3 has a slew of specialists down there -- you can see -- 4 from 6 months onward. 5 Then you can see the black line, and 6 this is where most clinical trial ends because of data 7 and funding and needing to accelerate things through; 8 but of course, kids hopefully go on to live lives; and 9 with Max, he began walking at age 3. At 5 years, he 10 had some delays and suspected ADHD. At 8, he had 11 confirmed inattentive ADHD. 12 At age 8 and a half, we had epilepsy 13 join our lives, onset at the sleep-wake cycle; 10 14 years, an anxiety diagnosis; and at 11 years, just 15 this past year, an official CVI diagnosis and had a 16 pretty intensive surgery that he's been doing an 17 amazing recovery with. 18 For medications, like I mentioned, he 19 was on phenobarb when he was born, which is very 20 standard of care to control seizures, although he had 21 no noted subclinical or clinical seizures; and -- but 22 when epilepsy rejoined, he was on Trileptal -- or he</p>	<p style="text-align: right;">Page 76</p> <p>1 And, Betsy, really thank you for that 2 family perspective, such an important component of 3 what I'll be discussing. 4 Again, I'm Lily Mulugeta. I'd like to 5 thank Yodit Belew and the rest of the organizers for 6 inviting me to participate in this workshop today. 7 Again, my talk will focus on leveraging 8 pediatric-trial networks to facilitate pediatric drug 9 developments. In addition, I will briefly touch on 10 some global collaborations in advancing pediatric drug 11 developments. 12 Next slide, please. 13 I have no financial conflicts to 14 disclose. 15 Next slide, please. 16 So perhaps I'm preaching to the choir a 17 bit here, but I do want to take a minute to remind us 18 of the important principles of pediatric therapeutics' 19 development. So much of what we will be discussing 20 today and tomorrow will be based on these principles. 21 So firstly, I hope we recognize that 22 it's imperative that pediatric patients similar to</p>
<p style="text-align: right;">Page 75</p> <p>1 is continually on Trileptal. 2 He has a rescue med. He's on Adderall. 3 He was on baclofen until last year's surgery. So 4 we've been able to take that one off. So just looking 5 at the medication cocktail, what impact does that 6 have? It's really important to families to understand 7 the pharmacokinetics behind that as well. 8 And that is -- I have the next slide; 9 and I am happy to take questions or connect at any 10 point; but again, I want to thank you for the 11 opportunity to speak today. 12 DR. BELEW: Thank you, Ms. Pilon. 13 Next I'd like to introduce Dr. Lily 14 Mulugeta, Associate Director for Policy and Research 15 for the Division of Pediatric and Maternal Health at 16 FDA. Dr. Mulugeta's talk is entitled "Facilitating 17 Neonatal and Pediatric Drug Development: Leveraging 18 Pediatric Trial Networks and Global Collaboration." 19 Thank you, Dr. Mulugeta. 20 DR. MULUGETA: Thank you for that 21 introduction. 22 Good morning, everyone.</p>	<p style="text-align: right;">Page 77</p> <p>1 adults have access to products that have undergone 2 rigorous evaluation. One way to do this is to ensure 3 that pediatric studies are incorporated early into 4 product-development programs when appropriate. 5 There's also growing recognition that 6 incorporation of regulatory standards into pediatric 7 clinical research really strengthens the quality of 8 the research. 9 Next slide, please. 10 So moving on to the challenges in 11 pediatric drug development -- and I think you've heard 12 some of these challenges earlier; but really to 13 emphasize, one of the most persistent issues is the 14 lag between adult approval and pediatric labeling. 15 This delay, which often averages around 16 seven years, means that children may not have timely 17 access to treatments that have deemed to be safe and 18 effective in adults. Patient-accrual difficulties 19 also pose a significant challenge in pediatric drug 20 development and account for nearly 40 percent of study 21 discontinuations. 22 Factors contributing to these</p>

<p style="text-align: right;">Page 78</p> <p>1 difficulties may include the small size of the 2 pediatric patient population for certain conditions, 3 the willingness of clinicians to use therapeutics off 4 label, and inefficiencies in conducting pediatric 5 clinical trials. 6 These challenges, which are 7 particularly pronounced in neonates and infants, can 8 result in insufficient evidence to support pediatric 9 product labeling, which really leaves healthcare 10 providers with limited guidance on the use of new 11 therapeutics in children. 12 Next slide, please. 13 So the evolution in pediatric drug 14 development over the last really couple of decades 15 represents a paradigm shift; right? It's no longer 16 about protecting children from research but really 17 rather protecting them through research. 18 And this shift in mindset really 19 recognizes that evaluating both new and existing drugs 20 in pediatric patients requires collaborations across 21 various stakeholders, and I think Betsy really 22 illustrated that very nicely as well.</p>	<p style="text-align: right;">Page 80</p> <p>1 academia, industry, and regulators are also crucial 2 under -- in driving collaborative efforts. 3 These partnerships can also enable the 4 development of innovative trial designs that overcome 5 the many limitations of neonatal and pediatric 6 development, including the small sample sizes and the 7 acceptability of the pediatric trial design. 8 Additionally, which is really the focus 9 of my talk today, pediatric-research networks can play 10 a pivotal role in facilitating the setup and execution 11 of pediatric clinical trials; and I'll talk a bit more 12 about this in the next several slides. 13 Next slide, please. 14 So the roles of pediatric-research 15 networks are really multifaceted. Networks in general 16 -- not limited to pediatric networks, but networks in 17 general have been identified as a promising approach 18 to overcome inefficiencies in clinical research, which 19 is particularly important for the pediatric 20 population. 21 These networks facilitate collaboration 22 among stakeholders who may not have traditionally</p>
<p style="text-align: right;">Page 79</p> <p>1 So it has to include patients, 2 families, patient organizations, academic researchers, 3 community practitioners, regulators, and industry 4 partners. 5 The FDA, for instance, has really 6 demonstrated its commitment to improving the 7 efficiency of pediatric clinical trials through 8 collaborative initiatives; and I'll touch upon some of 9 these in my talks; but really this workshop is another 10 example of many collaborations that are aimed at 11 advancing pediatric drug development. 12 Next slide, please. 13 So opportunities really for 14 collaboration in pediatric drug development are 15 abundant. One key opportunity lies in precompetitive 16 collaborations where various stakeholders can share 17 preclinical data, tools, and resources without 18 compromising their competitive interests. 19 These collaborations not only foster 20 innovation but also streamline the drug-development 21 process and ultimately benefit patients, which is 22 really our goal. Consortia and partnerships between</p>	<p style="text-align: right;">Page 81</p> <p>1 worked together -- right -- such as researchers from 2 different institutions, industry sponsors, regulators. 3 And so by pooling resources -- and that 4 may include data or expertise or both -- these 5 networks can accelerate research and development in 6 pediatric patients. 7 They can also encourage innovation, 8 which is highly desirable in the -- in pediatric drug 9 development by supporting the implementation of novel 10 trial designs, use of registries, modeling studies, 11 and platform trials. 12 And lastly, pediatric-research networks 13 enable the conduct of multicentered trials; and I'm 14 sure I don't have to say too much about this to this 15 group. I just really need to emphasize that this is 16 an essential component for recruiting larger and more 17 diverse pediatric-trial populations. 18 Next slide, please. 19 So there is a variety of pediatric- 20 research networks with different organizations -- 21 organizational structures and levels of activities. 22 Some of these networks are based around</p>

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<p>1 clinical specialties really focusing on optimizing 2 patient outcomes while other networks operate across 3 geographical locations and really focusing on 4 addressing barriers and inefficiencies in the conduct 5 of clinical research.</p> <p>6 And really ideally, these networks are 7 highly integrated -- right -- combining the strengths 8 of clinical specialty-focused approaches really with 9 the broader reach of geographically diverse networks. 10 and I'll provide some examples in the next few slides.</p> <p>11 Next slide, please.</p> <p>12 So pediatric-research networks have the 13 potential to significantly impact discussion-making 14 throughout the drug-development life cycle, and I 15 think this is really an important emphasis.</p> <p>16 In the early phases, these networks can 17 provide valuable insight -- insights into disease 18 prevalence, treatment patterns, patient heterogeneity, 19 and even potential biomarkers that may be specific to 20 the pediatric population of interest.</p> <p>21 In later phase stages, pediatric- 22 research networks can influence key aspects of trial</p>	<p>1 pediatric-research networks abound -- right -- 2 showcasing diverse models and approaches to pediatric 3 drug development. There's no way that in my 15-minute 4 talk I'll be able to provide an exhaustive list of 5 these networks, but I do -- would like to highlight a 6 few examples.</p> <p>7 One example is the Pediatric Trials 8 Network or the PTN, which was established in 2010 with 9 funding from the NIH. This was specifically to 10 fulfill a mandate under BPCA. The PTN collaborates 11 with academic institutions, industry sponsors, and 12 regulators to provide infrastructure and support for 13 both designing and conducting pediatric trials.</p> <p>14 And what's interesting, this network's 15 contribution also includes submission of the collected 16 data to the FDA to update product labeling 17 specifically for off-patent drugs; and you'll hear 18 more about this network from my colleague Rachel 19 Greenberg tomorrow.</p> <p>20 Similarly, other collaborative 21 initiatives, such as the Collaborative Antiviral Study 22 Group, bring together multiple centers to conduct</p>
<p>1 design; and this can include inclusion-exclusion 2 criteria, treatment duration, collection of 3 supplementary safety data and considerations around 4 data extrapolation from either older children or 5 adults.</p> <p>6 And in addition, by collaborating with 7 these networks, sponsors can also potential optimize 8 trial conduct by identifying potential trial 9 candidates, engaging qualified sites, and -- and 10 investigators as well.</p> <p>11 Lastly, pediatric-research networks 12 play -- can play a vital role even in the post- 13 approval stage.</p> <p>14 And this can be a mechanism to 15 contribute to the expansion of the product labeling to 16 other pediatric populations, generating supplementary 17 safety data, and potential even addressing long-term 18 safety considerations that may not be really fully 19 understood at the time of its initial approval in 20 adults or approval in pediatric patients.</p> <p>21 Next slide, please.</p> <p>22 So examples of successful active</p>	<p>1 clinical trials, evaluating new antiviral therapies. 2 So these really multicenter 3 collaborations, which often can be funded by 4 government agencies or public private partnerships, 5 play a crucial role in accelerating the development 6 and evaluation of both new and old treatments for 7 pediatric patients.</p> <p>8 Next slide, please.</p> <p>9 I know this is really a busy slide, and 10 I really don't expect you to read what's -- all the 11 information that's in this slide, but it's really to 12 emphasize that the landscape of pediatric drug 13 development is enriched by a multitude of 14 collaborative initiatives and research networks.</p> <p>15 Each of these contribute uniquely to 16 the advancement of pediatric therapeutic innovation.</p> <p>17 As you can see, some of these networks 18 around -- are modeled around clinical specialties, 19 such as IMPAACT, for example, while others include 20 multiple specialties and focus on addressing 21 inefficiencies in the conduct of pediatric clinical 22 research; and that includes C4C, iACT, and others that</p>

<p style="text-align: right;">Page 86</p> <p>1 are listed on here.</p> <p>2 In addition, the range of activities of</p> <p>3 these networks may also vary; and it could include</p> <p>4 anywhere from protocol development for evaluation of</p> <p>5 novel therapies to providing collaborative clinical-</p> <p>6 trial infrastructure, assistance with regulatory</p> <p>7 submission, and development of consensus and treatment</p> <p>8 guidelines.</p> <p>9 It's also important to note that these</p> <p>10 networks are increasingly broadening to a global and</p> <p>11 patient-centered approach, which, you know, given</p> <p>12 Betsy's presentation, it's clear that this approach</p> <p>13 will yield to better and efficient pediatric research</p> <p>14 and development programs.</p> <p>15 Next slide.</p> <p>16 And just to briefly touch upon networks</p> <p>17 that are unique to neonates, there are neonatal</p> <p>18 networks. An example is the International Neonatal</p> <p>19 Consortium or the INC, which plays a vital role in</p> <p>20 addressing the unique challenges associated with</p> <p>21 neonatal drug development.</p> <p>22 Many of these challenges were mentioned</p>	<p style="text-align: right;">Page 88</p> <p>1 collaboration and cooperation in therapeutics</p> <p>2 development.</p> <p>3 The ICH fosters alignment among both</p> <p>4 regulatory authorities and industry experts, and the</p> <p>5 recent milestone in this collaborative journey is the</p> <p>6 recent publication of the ICH E11A Guideline, which</p> <p>7 provides a harmonized global framework for</p> <p>8 extrapolation of data, both PK efficacy and safety and</p> <p>9 pediatric drug development.</p> <p>10 And this guideline is really grounded</p> <p>11 in scientific rigor but also provides regulatory</p> <p>12 harmonization and really exemplifies the synergistic</p> <p>13 potential inherent in global collaborations when aimed</p> <p>14 at enhancing therapeutics development for children.</p> <p>15 Next slide, please.</p> <p>16 There are clearly many international</p> <p>17 regulatory collaborations. I've just listed a few.</p> <p>18 Some are solely focused in pediatrics, while others</p> <p>19 are broader but address pediatric regulatory-related</p> <p>20 issues.</p> <p>21 Initiatives such as the Monthly</p> <p>22 Pediatric Cluster Conference, which was established in</p>
<p style="text-align: right;">Page 87</p> <p>1 by my colleagues earlier this morning. So really by</p> <p>2 leveraging multidisciplinary expertise and</p> <p>3 collaborative frameworks, neonatal networks like INC</p> <p>4 aim to develop consensus-driven approaches that can</p> <p>5 enable feasible and practical trials in neonates.</p> <p>6 This concerted effort has been</p> <p>7 particularly -- particularly impactful, for example,</p> <p>8 in neonatal seizures. This is a space where</p> <p>9 regulatory waivers for required pediatric studies in</p> <p>10 neonates were previously granted due to perceived</p> <p>11 impracticality.</p> <p>12 And as a result of the -- all the work</p> <p>13 that was done by the INC and the consensus</p> <p>14 recommendations that were developed, it has really</p> <p>15 allowed the FDA to require neonatal studies for anti-</p> <p>16 epileptics on a case-by-case basis.</p> <p>17 Next slide, please.</p> <p>18 So moving on to global collaborations,</p> <p>19 one that I would like to mention is the International</p> <p>20 Council for Harmonization or the ICH, which stands as</p> <p>21 an example of concerted efforts to harmonize</p> <p>22 regular -- regulatory standards and promote global</p>	<p style="text-align: right;">Page 89</p> <p>1 2007, for example, facilitate ongoing dialogue and</p> <p>2 information exchange among regulatory agencies. This</p> <p>3 one particularly includes FDA, EMA, PMDA, Health</p> <p>4 Canada, and TGA.</p> <p>5 So these collaborative forums really</p> <p>6 serve as catalysts for sharing scientific insights,</p> <p>7 discussing policy considerations, and addressing</p> <p>8 pediatric-specific regulatory challenges, ultimately</p> <p>9 with the goal of ensuring that pediatric drug-</p> <p>10 development programs are efficient and practical.</p> <p>11 Next slide, please.</p> <p>12 So really in summary, given all the</p> <p>13 presentations today and hopefully from some of the</p> <p>14 information I've shared with you, I hope it's evident</p> <p>15 that the landscape of pediatric drug development is</p> <p>16 characterized by significant achievements stemming</p> <p>17 from collaborative efforts and multidisciplinary</p> <p>18 approaches.</p> <p>19 Collaborative networks that continue to</p> <p>20 expand globally are instrumental in driving progress,</p> <p>21 fostering innovation, and addressing challenges</p> <p>22 inherent in pediatric and neonatal therapeutics</p>

<p style="text-align: right;">Page 90</p> <p>1 development.</p> <p>2 And as we look towards the future,</p> <p>3 really continued emphasis of -- on inclusion of</p> <p>4 voices, such as Betsy's, of patient outcomes, data</p> <p>5 transparency, regulatory harmonization, and policy</p> <p>6 development will be paramount in sustaining the</p> <p>7 momentum of therapeutic innovation for pediatric</p> <p>8 patients.</p> <p>9 Next slide, please.</p> <p>10 Again, I would like to thank the</p> <p>11 organizers for giving me an opportunity to speak</p> <p>12 today, as well as my colleagues from the FDA at PTN</p> <p>13 who contributed to these slides; and I look forward to</p> <p>14 the rest of the presentations and discussions. Thank</p> <p>15 you so much.</p> <p>16 DR. BELEW: Thank you, Dr. Mulugeta.</p> <p>17 Next I'd like to introduce our last</p> <p>18 speaker of the session, Dr. John Concato. Dr. Concato</p> <p>19 is the associate director for Real-World Evidence</p> <p>20 Analytics in the Office of Medical Policy at FDA. Dr.</p> <p>21 Concato will be speaking about real-world data and</p> <p>22 real-world evidence in drug development.</p>	<p style="text-align: right;">Page 92</p> <p>1 to, to evaluate the potential use of real-world</p> <p>2 evidence to support a new indication for a drug</p> <p>3 already approved or to satisfy post-approval study</p> <p>4 requirements.</p> <p>5 We also have issued a draft framework</p> <p>6 within two years and guidance for industry starting</p> <p>7 within five years and -- and continuing through just a</p> <p>8 couple of months ago.</p> <p>9 An important note at the bottom of this</p> <p>10 slide, our standard for substantial evidence to</p> <p>11 approve drugs and biologic products is unchanged. We</p> <p>12 owe that to patients, whether they be adults or</p> <p>13 neonates. We have to be sure that the drugs are safe</p> <p>14 and effective.</p> <p>15 Next, please.</p> <p>16 This is a screenshot of our 2018 real-</p> <p>17 world-evidence framework. I wanted to with this slide</p> <p>18 mention that what I'll be discussing applies to the</p> <p>19 Center for Drugs, the Center for Biologics, and the</p> <p>20 Oncology Center of Excellence.</p> <p>21 We coordinate with our Center for</p> <p>22 Devices and Radiological Health, but they have their</p>
<p style="text-align: right;">Page 91</p> <p>1 Thank you, Dr. Concato.</p> <p>2 DR. CONCATO: Thank you.</p> <p>3 Hello, everyone.</p> <p>4 And next slide, please.</p> <p>5 The views and opinions expressed are my</p> <p>6 own and should not be attributed as official FDA</p> <p>7 policy. I do not have any conflicts of interest</p> <p>8 related to this presentation; and when I mention</p> <p>9 commercial product, it's not an actual or implied</p> <p>10 endorsement.</p> <p>11 Next, please.</p> <p>12 I'll be providing a high-level</p> <p>13 overview, starting with a background on real-world</p> <p>14 evidence and then moving onto selected aspects of</p> <p>15 FDA's Real-World Evidence Program, including guidance</p> <p>16 development and demonstration of research projects,</p> <p>17 and then moving on to real-world data and real-world-</p> <p>18 evidence activities related to neonatal healthcare.</p> <p>19 Next.</p> <p>20 Let's start with the 21st Century Cures</p> <p>21 Act of 2016 and mandates met. I need to convey that</p> <p>22 we have established the program, as Congress asked us</p>	<p style="text-align: right;">Page 93</p> <p>1 separate regulations, and they've covered a real-</p> <p>2 world-evidence program with a lot of cross-</p> <p>3 communication and cross-specialization.</p> <p>4 Back to drugs and biologics, our</p> <p>5 program can be thought of informally in the taxonomy</p> <p>6 of: one, internal agency processes, such as providing</p> <p>7 consultation to review divisions; number two, external</p> <p>8 stakeholder engagement listed in sections or even</p> <p>9 today's workshop and tomorrow -- and tomorrow's</p> <p>10 workshop; number three, demonstration of research</p> <p>11 projects -- I'll give an example later -- and last but</p> <p>12 not least, number four, guidance development.</p> <p>13 Next, please.</p> <p>14 Just to mention, because there is a bit</p> <p>15 of ambiguity, if not confusion in the -- in the field,</p> <p>16 in the ecosystem, real-world data are data related to</p> <p>17 patient-health status or delivery of healthcare</p> <p>18 routinely collected from a variety of sources.</p> <p>19 And then real-world evidence is</p> <p>20 clinical evidence regarding the benefits and risks of</p> <p>21 a medical product, defined simply as being derived</p> <p>22 from analysis of real-world data, regardless of the</p>

<p style="text-align: right;">Page 94</p> <p>1 study-design type.</p> <p>2 Next, please.</p> <p>3 So why all the attention focused on --</p> <p>4 let's say "hype" -- on real-world evidence? This is</p> <p>5 somewhat simplified, but interest in real-world</p> <p>6 evidence can be attributed at least in part to</p> <p>7 improved access to -- and the ability to be rapidly</p> <p>8 analyzed -- information in the era of so-called big</p> <p>9 data.</p> <p>10 In addition, research over the past</p> <p>11 actually several decades has shown that observational</p> <p>12 studies -- while they have a more challenging time</p> <p>13 addressing sources of bias, they can under certain</p> <p>14 circumstances generate valid results.</p> <p>15 Certainly, the 21st Century Cures Act</p> <p>16 asking the -- the U.S. FDA to evaluate the potential</p> <p>17 use of real-world evidence for medical-product</p> <p>18 approvals is relevant.</p> <p>19 And then simply and perhaps and</p> <p>20 sociologically, the popularity of "real-world" as a</p> <p>21 term and other factors, unfortunately something like</p> <p>22 the COVID-19 pandemic, which focused attention on</p>	<p style="text-align: right;">Page 96</p> <p>1 Next, please.</p> <p>2 Just in case it helps going forward in</p> <p>3 general, not just limited to neonatal healthcare, one</p> <p>4 misconception is that RWD and RWE are new concepts.</p> <p>5 In reality, sources of data and types of study design,</p> <p>6 as I mentioned, haven't fundamentally changed.</p> <p>7 They might evolve, but it's really the</p> <p>8 electronic access to more detailed clinical data</p> <p>9 evolution as well as the data becoming more</p> <p>10 reliable -- relevant and reliable, is what's making a</p> <p>11 difference.</p> <p>12 The second misconception is that</p> <p>13 there's a simple dichotomy of, quote, "randomized</p> <p>14 trials versus observational studies," close quote,</p> <p>15 again, a misconception. In reality, clinical trials</p> <p>16 are defined by assignment of treatment according to an</p> <p>17 investigational protocol.</p> <p>18 So if you think about it, single-arm</p> <p>19 trials face challenges similar to those of</p> <p>20 observational studies in determining whether</p> <p>21 differences in clinical outcomes -- in that case</p> <p>22 compared to an external control group -- represent</p>
<p style="text-align: right;">Page 95</p> <p>1 different methods of evidence generation -- but I do</p> <p>2 want to point that with -- without invoking the terms</p> <p>3 "real-world data" or "real-world evidence," we can</p> <p>4 actually talk about types of data sources and study</p> <p>5 designs.</p> <p>6 And those terms aren't new but are</p> <p>7 totally sufficient to convey the intended message.</p> <p>8 Next slide, please.</p> <p>9 Moving forward to more recently from a</p> <p>10 couple of years ago, a colleague, Jacqueline Corrigan-</p> <p>11 Curay, and I published on where are we now with regard</p> <p>12 to real-world evidence; and the main content of the</p> <p>13 article -- the main issue being addressed -- excuse me</p> <p>14 -- was that the terms "RWD" and "RWE" were being used</p> <p>15 inconsistently and interchangeably.</p> <p>16 So the content of our article addressed</p> <p>17 two common misconceptions, provided a conceptual</p> <p>18 overview of study design, described our guidance and</p> <p>19 demonstration projects, highlighted a couple of</p> <p>20 approvals, and offered a path forward. My next two</p> <p>21 slides will cover the first two of these five content</p> <p>22 areas.</p>	<p style="text-align: right;">Page 97</p> <p>1 actual treatment effects.</p> <p>2 Next slide.</p> <p>3 These same issues are shown in this</p> <p>4 figure. I will not go through each word on the page.</p> <p>5 But at the upper portion of the box in</p> <p>6 the middle of this slide, as methodologists, we talk</p> <p>7 about randomized interventional studies, nonrandomized</p> <p>8 but still interventional studies, and then</p> <p>9 nonrandomized and noninterventional studies, a little</p> <p>10 bit jargon-y; but the next one down is more shoptalk</p> <p>11 in our line of work.</p> <p>12 We've had traditional randomized</p> <p>13 trials, which might use real-world data to help plan,</p> <p>14 such as to assess enrollment criteria and assess trial</p> <p>15 feasibility or select sites. We have trials in</p> <p>16 practice settings, such as point-of-care trials where</p> <p>17 the outcome might be pulled from health-record data.</p> <p>18 We have externally controlled trials,</p> <p>19 and then we have observational studies, which is what</p> <p>20 many people think of when they hear the term "real-</p> <p>21 world evidence."</p> <p>22 But at the bottom of that simple box,</p>

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<p>1 note that the generation of real-world evidence can 2 start with randomized trials. It certainly includes 3 externally controlled trials; and of course, it 4 includes observational studies. 5 This is a bit technical, but I think 6 it's relevant, whether we're talking about neonatal 7 medicine or geriatric medicine or anywhere in between. 8 Next slide, please. 9 Here is where the guidance that FDA has 10 published is -- is summarized. I know there's a lot 11 of rows in this slide, but we chose a modular 12 approach, a suite of guidance so that it's one-stop 13 shopping when you have a question as a sponsor or any 14 -- or an investigator. 15 I'll summarize this slide by saying the 16 first two rows are real-world-data sources, Electronic 17 Health Records and Claims, as well as Registry or Data 18 Standards. In the third row, regulations were 19 developed, assuming clinical trials would be the basis 20 of evidence submissions. So we had to account for the 21 real-world-data differences. 22 "Regulatory Considerations" speaks for</p>	<p>1 multiple phases of the life cycle of" -- Microsoft 2 changed "EHR" to "HER." I apologize for not spotting 3 that typo. 4 And the figure on the right basically 5 shows the complexity. 6 Not to go through this dataset, but 7 unlike clinical trials, where the data come in ready 8 to be analyzed, we don't -- we don't blame the 9 clinicians at the bedside for taking care of the 10 neonatal patient and not necessarily knowing that the 11 electronic health record will be pulled later to do 12 our research analysis. 13 Next slide, please. 14 So what does FDA do -- CDER and CBER 15 and OCE in particular -- when evaluating real-world 16 evidence? This is a very high-level overview; but 17 when going to look down, we consider whether the real- 18 world data are fit for use, a major issue. 19 And by "fit for use," we mean whether 20 they're reliable, accurate, complete, and traceable 21 and whether they're clinically relevant. 22 We also determine whether the study</p>
<p>Page 99</p> <p>1 itself. Our regulations didn't anticipate nonclinical 2 trials; and then the next three, Externally Controlled 3 Trials, Noninterventional Studies, and Trials in 4 Practice Settings, are design-consideration guidances. 5 Last but not least, we have a 6 Submitting Real-World Evidence guidance, which allows 7 sponsors to help us to help them if they accurately 8 identify what they're doing with regard to real-world 9 data and real-world evidence. 10 The link at the bottom provides all the 11 information you might want in general to see these 12 guidances as well as to see summaries of them. 13 Next slide, please. 14 Just to give a little bit of detail on 15 our guidances, this is a screenshot of the Assessing 16 Health Records and Medical Claims or HR Claims 17 guidance that was issued in draft several years back. 18 Next slide, please. 19 A little bit more in detail, excerpts 20 from "Real-World Data" on the left: "The process for 21 examining the quality of data is not a one-time 22 assessment. Rather, it's an ongoing process in</p>	<p>Page 101</p> <p>1 design generated adequate scientific evidence to 2 answer -- help answer the regulatory question; and 3 then last but not least, the study conduct has to meet 4 FDA regulatory requirements to ensure the -- the 5 safety and efficacy of the product. 6 Next slide, please. 7 So here is an example actually approved 8 for both adult and -- and pediatric patients based on 9 so-called real-world evidence. 10 PROGRAF, tacrolimus, had been approved 11 for the prophylaxis of organ rejection in patients 12 receiving liver and later kidney and heart transplants 13 based on traditional randomized control trial 14 evidence; and the drug was used widely in clinical 15 care, including for lung transplantation. 16 But RCTs were not done or at least not 17 submitted to the agency for approval. Later on a 18 sponsor submitted a supplemental New Drug Application 19 for FDA with an observational real-world-evidence 20 study. 21 The study data and design were 22 evaluated according to FDA standards. We heard in the</p>

<p style="text-align: right;">Page 102</p> <p>1 introductory talk about our 314.126 regulation section 2 that determines what is an adequate and well- 3 controlled investigation. 4 And in -- in this case, approval for 5 preventing rejection/death in lung transplant, again 6 for both adults and pediatric patients, was granted in 7 2021. 8 Next slide, please. 9 I don't want to leave you all with the 10 idea that working with real-world data is an easy 11 task. These are representative challenges with the 12 real-world data or real-world evidence that cover a 13 wide slot of submissions, and most submissions fall 14 short at least at this time. 15 It's not always a sponsor's fault. I 16 would say in the first category of real-world-data 17 sources sometimes the data are just not reliable and 18 relevant enough; or again, a clinical trial might have 19 datapoints at certain intervals of weeks or months, 20 whereas in clinical care it's more driven by other 21 factors. 22 We heard earlier about endpoints. The</p>	<p style="text-align: right;">Page 104</p> <p>1 world-data and real-world-evidence work on neonates. 2 This is a screenshot from a website that is still on 3 the FDA page, "Advancing Standards and Methodologies 4 to Generate Real-World Evidence from Real-World Data 5 through a Neonatal Pilot Project." 6 The U01 Award at the top is a 7 cooperative research agreement through Health and 8 Human Services. This was a competitive procedure or 9 process whereby the International Neonatal Consortium, 10 part of the Critical Path Institute, was awarded a 11 project. 12 Basically, it -- the point is to -- to 13 develop a real-world-data analytics platform, and that 14 has been very successful to date. 15 Next slide, please. 16 I won't go into the details. I'll 17 leave that for my C-Path colleagues, but this 18 commentary from 2023 in the Journal of Pediatrics on 19 "Real-World Evidence for Neonatal Drug Development: 20 Challenges and Opportunities" mentioned that the 21 challenges surrounding the use of real-world data are 22 substantial but not insurmountable.</p>
<p style="text-align: right;">Page 103</p> <p>1 suitable capture of endpoints isn't always feasible in 2 real-world-data sources, and sometimes there's a need 3 for linkage with other data sources. Excuse my voice 4 today, I'm asking. 5 Certainly, the design and 6 interpretation of nonrandomized studies presents 7 problems, such as confounding. An underappreciated 8 problem is problems with index date or zero time -- I 9 don't have time to get into that -- or the use of an 10 inappropriate comparator. 11 And then last but not least, in the 12 category of conduct, unlike clinical trials, where 13 everything is done prospectively, in -- in this case, 14 we want to be sure that the analysis was prespecified. 15 If it's not, there could be some cherry-picking going 16 on that makes the drug look better than it actually 17 is. 18 And then last but not least, we do 19 require access to patient-level data and the ability 20 to inspect real-world-data sources. 21 Next slide, please. 22 Part of our footprint includes real-</p>	<p style="text-align: right;">Page 105</p> <p>1 And real-world-evidence-driven drug 2 development represents an evolution in scientific 3 methodology as well as a renewed commitment to 4 advancing neonatal health on a global scale. 5 Next slide, please. 6 I'll wrap up by saying that the FDA 7 remains committed to robust policy development aligned 8 with the 21st Century Cures Act while we maintain our 9 evidentiary standards in honoring our obligation to 10 protect and promote public health. 11 Focusing on the distinction between 12 interventional studies and noninterventional studies 13 can help us all understand and describe the relevant 14 methodologic issues that might be holding us back; and 15 certainly, getting more experience, including the 16 conduct of rigorous noninterventional studies, will 17 help to advance drug development. 18 Next slide, please. 19 So hopefully, I've conveyed these 20 summary points. One is that, in addition to the 21 randomized trial paradigm, not in lieu of it, not to 22 replace it, the availability of big data and passage</p>

<p style="text-align: right;">Page 106</p> <p>1 of the 21st Century Cures Act reflect and contributed 2 to the emergency of real-world evidence. 3 Our Real-World Evidence Program for 4 drugs and biologics is advancing, as we outlined in 5 our 2018 framework, including guidance documents and 6 demonstration projects, as I've given a couple of 7 examples of. 8 And please, again, appreciate that CDER 9 approves drugs and biological products based on 10 existing evidentiary standards, including when 11 evaluating real-world evidence. 12 But as the earlier slides have 13 indicated and presentations, we -- we all hope for a 14 better future and the appropriate use of real-world 15 data and real-world evidence can advance neonatal drug 16 development in ways that we're not entirely sure -- 17 sure of yet but that we can look forward to seeing in 18 the future. 19 Next slide, please. 20 Thank you very much. 21 DR. BELEW: Thank you, Dr. Concato. 22 That concludes the presentations for</p>	<p style="text-align: right;">Page 108</p> <p>1 know how the drug is going to be metabolized, 2 excreted. We don't know what the concentrations are. 3 Would it be possible to develop a study 4 that has a range -- simultaneously enrolls a range of 5 -- of doses, some of which are modeled to be 6 therapeutic, not yet proven, some of which are 7 deliberately less than that, subtherapeutic or maybe 8 even homeopathic, in a way that then would be able to 9 -- we'd be able to say: "Look. Everybody gets 10 drugged, but we do have a range of -- we anticipate a 11 range of benefit that could be looked at with an 12 adequate sample size"? 13 So that -- that -- that's the question. 14 Is that something that FDA could be open to? 15 DR. BELEW: Dr. Kimberlin, thank you so 16 much for the question. I think your first question 17 about placebo -- I think we'll talk more about this 18 during the panel session. As to your second question, 19 we could also perhaps talk about this during the panel 20 as well, unless Dr. Wu has any comments to make. 21 DR. WU: Yeah. This is Kunyi. I 22 can -- I can give a try and get started, and I think</p>
<p style="text-align: right;">Page 107</p> <p>1 Session 1 of our agenda. We're running a bit behind, 2 but we now have a few minutes to take clarifying 3 questions related to the presentations we have heard 4 this morning. 5 Panelists, please raise your hand in 6 Zoom if you wish to ask a question. 7 And, members of the public, you may 8 enter your questions in the Q-and-A box. 9 Dr. Kimberlin, do you have a question? 10 DR. KIMBERLIN: I -- I do, and I'm not 11 sure if it will fit with this particular section or 12 not. I was struck by a couple of things with -- 13 across the presentations, which were all really good. 14 One is the comment about the challenge 15 of placebo and -- and the acceptance of -- of a 16 placebo-controlled trial on the one hand and then the 17 -- the need for some sort of comparator -- a good 18 comparator on the other hand, Point Number 1. 19 Point Number 2, even with the modeling 20 that we can do from older children and adults with a 21 given antiviral, if it's not being used in babies, we 22 don't know what the ontogeny is going to be. We don't</p>	<p style="text-align: right;">Page 109</p> <p>1 we can discuss more in the panel discussion. 2 But for modeling simulation, just from 3 a technical perspective, if this drug is repurposed 4 and then we know the PK of the drug, just based on our 5 understanding -- it -- it's case by case of course. 6 But based on our understanding on the 7 ontogeny, on the enzyme maturation, on the receptor- 8 transporter maturation, we may or may not be able to 9 predict those in the neonatal and infant population; 10 and then, again, it's case by case. So this is a 11 technical challenge and difficulties. 12 And then for your second question, I 13 think you asked, you know, simultaneously enrolled -- 14 so that's, you know, beyond my knowledge; and then we 15 have to discuss. I'd just defer to other disciplines 16 to answer this question. 17 DR. VISWANATHAN: Hi, Dr. Kimberlin. 18 This is Prabha Viswanathan again. I -- just to 19 briefly touch on the ethical aspect of your -- of your 20 question, if I heard it correctly, about whether it 21 would be acceptable to enroll subtherapeutic doses and 22 -- we never say "never" in ethics. It's all really</p>

<p style="text-align: right;">Page 110</p> <p>1 about context.</p> <p>2 But prolonged doses of a -- of a -- or</p> <p>3 multiple doses of -- of a -- of a drug that's known to</p> <p>4 not offer that prospect of direct benefit to the</p> <p>5 participant is something that would need to be</p> <p>6 justified. So I think that's something that we can</p> <p>7 dig into, into the panel a little bit more.</p> <p>8 DR. BELEW: And, Dr. Abzug, I think you</p> <p>9 had a clarifying question as well?</p> <p>10 DR. ABZUG: Thank you.</p> <p>11 And I want -- first of all, want to</p> <p>12 thank everybody for the excellent presentations that</p> <p>13 we've heard thus far. I also want to pick up on -- on</p> <p>14 David's question a little bit about the issue of a</p> <p>15 placebo.</p> <p>16 It seems to me there's a tension</p> <p>17 between the standard of direct benefit to all</p> <p>18 participating subjects and having a placebo group,</p> <p>19 which is the gold standard for a randomized control</p> <p>20 trial because in most circumstances placebo recipients</p> <p>21 are not expected to have a direct benefit from the</p> <p>22 intervention.</p>	<p style="text-align: right;">Page 112</p> <p>1 enterovirus epidemiology and background.</p> <p>2 (Off the record.)</p> <p>3 DR. PICA: Welcome back. We will now</p> <p>4 begin Session 2, which will focus on enterovirus</p> <p>5 epidemiology and background. We are delighted to have</p> <p>6 Dr. Amy Rosenfeld, Dr. Miranda Delahoy, and Dr. Mark</p> <p>7 Abzug here this morning.</p> <p>8 Next slide, please.</p> <p>9 It is now my pleasure to introduce our</p> <p>10 first speaker, Dr. Amy Rosenfeld, Principal</p> <p>11 Investigator in the Division of Viral Products in the</p> <p>12 Office of Vaccines, Research, and Review at FDA. Dr.</p> <p>13 Rosenfeld's talk is entitled "Picornaviruses and</p> <p>14 Neonatal Sepsis."</p> <p>15 Thank you, Dr. Rosenfeld.</p> <p>16 DR. ROSENFELD: Thank you very much for</p> <p>17 inviting me to speak to you this morning about</p> <p>18 picornaviruses and neonatal sepsis.</p> <p>19 Next slide.</p> <p>20 So picornaviridae is a family of</p> <p>21 viruses. These are single-stranded positive-sense RNA</p> <p>22 viruses that are nonenveloped; and the viral family is</p>
<p style="text-align: right;">Page 111</p> <p>1 So I -- I'd like to hear a little bit</p> <p>2 more about how that tension is -- is addressed or</p> <p>3 should be addressed in -- in study design. Thank you.</p> <p>4 DR. BELEW: Thank you, Dr. Abzug. I</p> <p>5 think that those are really important comments, and</p> <p>6 we're -- we're hoping to cover that more in the panel.</p> <p>7 DR. VISWANATHAN: Yeah. I -- I can</p> <p>8 just provide a very brief response, and I -- I do</p> <p>9 think it merits more discussion during the panel. We</p> <p>10 acknowledge that the placebo control doesn't receive</p> <p>11 benefit. The -- the trial needs to be designed in</p> <p>12 such a way that risks are minimized for all patients,</p> <p>13 regardless of their subject assignment.</p> <p>14 Ultimately, it is a complex issue. So</p> <p>15 I -- I do think it probably deserves a little bit more</p> <p>16 discussion from all the different contributors a</p> <p>17 little bit later in the afternoon, but thank you for</p> <p>18 the question.</p> <p>19 DR. BELEW: Great. Thank you all for</p> <p>20 those questions and to our speakers for providing</p> <p>21 answers. We're now going to take a break; and we'll</p> <p>22 reconvene at 11:20 for Session 2, when we will discuss</p>	<p style="text-align: right;">Page 113</p> <p>1 composed of 40 genera; and today we're going to talk</p> <p>2 about 2 of the genera, which is the enterovirus genus</p> <p>3 and the parechovirus genus.</p> <p>4 And the enterovirus genus is composed</p> <p>5 of 11 -- of 14 species, plus Rhinoviruses A through C,</p> <p>6 whereas the parechovirus genus is composed solely of</p> <p>7 one species, parechovirus, which is then subdivided</p> <p>8 into A and B.</p> <p>9 And we're going to talk about the A --</p> <p>10 viruses in A's, which is Parechovirus 1, 3A, and 6,</p> <p>11 which are associated with neonatal-sepsis infection,</p> <p>12 as well as members of Species B of the enterovirus</p> <p>13 genus, which are Echoviruses 11, 30, and Coxsackie A.</p> <p>14 Additionally, there are additional</p> <p>15 coxsackieviruses that also associate with the</p> <p>16 development of neonatal sepsis.</p> <p>17 Next slide, please.</p> <p>18 So the picornaviruses all have a</p> <p>19 similar structure. They're composed of, as I said, a</p> <p>20 nonenveloped particle, which is composed of three</p> <p>21 viral capsid proteins. Viral Capsid Proteins 1</p> <p>22 through 3 are on the exterior surface of the particle,</p>

<p style="text-align: right;">Page 114</p> <p>1 and Viral Capsid Protein VP0 is on the inner surface 2 of the particle.</p> <p>3 The difference between parechoviruses 4 and enteroviruses is a maturation cleavage, VP0 into 5 VP2 and 4 for enteros, which occurs after the particle 6 is egressed from the infected cell. So it is a 7 cleavage that is thought to be catalyzed by the ion 8 genome in the particle. That occurs after the virus 9 is released.</p> <p>10 So capsid proteins are 11 cotranslationally proteolytically processed and self- 12 assembled, and they self-assemble into pentamers, 13 which are on the right, which are five protomers of 14 each viral protein. This gives rise to an icosahedron 15 particle, which has the signature threefold, fivefold, 16 and twofold axes of symmetry.</p> <p>17 And here, if you look at the particle 18 on the side, the pentamer, you can see VP4 in green 19 lines the interior surface. Not all particles form a 20 canyon, which is a crevice that surrounds the fivefold 21 axis of symmetry.</p> <p>22 For many enteroviruses, including</p>	<p style="text-align: right;">Page 116</p> <p>1 These viruses all replicate within the 2 cytoplasm of the infected cell. So they attach to a 3 cell-surface protein, which is known as the receptor. 4 Many of these receptors have not been identified.</p> <p>5 Once the particular attaches to the 6 cell protein, the surface protein, it is internalized 7 in an endosome; and depending upon the enterovirus or 8 even parechovirus, un-coding and release of the viral 9 genome is a pH-dependent process. So it's regulated 10 by the acidification of this endosome.</p> <p>11 The RNA is released. It's immediately 12 engaged by ribosomes. It's translated into the 13 polypeptide. The final approach -- the final enzyme 14 of this polypeptide is the RNA-dependent RNA 15 polymerase and -- which regulates and is required for 16 replication, which -- of the viral genome, which goes 17 through a negative-strand intermediate.</p> <p>18 Once the viral genome is replicated, it 19 is immediately encapsidated by the viral procapsid 20 precursors. They are -- the virus particle is 21 assembled. It is released; and for enteroviruses, as 22 I said, there's the maturation cleavage of VP0 into</p>
<p style="text-align: right;">Page 115</p> <p>1 poliovirus and rhinoviruses of the major group, this 2 is a receptor-binding site. However, once again, this 3 canyon is not present on the surface of parechoviruses 4 and many other echo -- and many other enteroviruses.</p> <p>5 Next slide.</p> <p>6 All of these viral genomes are -- have 7 the same organization. They're all linked to viral 8 genome -- viral-protein-linked genome, which is VPG at 9 the five-prime end. This is removed or -- upon 10 release of the viral genome into the cytoplasm.</p> <p>11 So you have a free five-prime end 12 without the seven-methylguanosine cap to regulate 13 translation initiation, but the viral RNA is 14 immediately engaged by the ribosome and is the mRNA of 15 the genome.</p> <p>16 And once again, it is a single open 17 meeting frame; and this polypeptide is 18 cotranslationally proteolytically processed by viral- 19 encoded proteases into either the mature or immature 20 proteins through the schematic map that I've described 21 beneath.</p> <p>22 Next slide.</p>	<p style="text-align: right;">Page 117</p> <p>1 VP2 and VP4 after egress.</p> <p>2 Next slide, please.</p> <p>3 So the pathogenesis of picornavirus is 4 very interesting. These viruses are species-specific. 5 They are generally spread from one individual or 6 animal to another in an oral-fecal or respiratory 7 mechanism.</p> <p>8 Severe disease does not occur at the 9 primary site of infection. It occurs at the secondary 10 sites of an infection, which can include the central 11 nervous system, the liver, the skin, as well as the 12 heart and thought to pancreas.</p> <p>13 The presence of neutralizing antibodies 14 in the sera of infected patients is the best biomarker 15 for protection for the good development of severe 16 disease, and this is done from studies of patients 17 that were infected with poliovirus as well as many 18 different serotypes of human rhinovirus.</p> <p>19 Next slide, please.</p> <p>20 So in the lab, we measure infectious 21 virus generally by two methodologies. Our lab uses a 22 plaque assay, which is serial tenfold dilutions and we</p>

<p style="text-align: right;">Page 118</p> <p>1 -- of the viral stock or -- or sample, and then we ask 2 whether or not we can see a focus of dead cells by 3 staining the monolayer with a dye -- with a dye that 4 looks for cell viability. 5 You can use -- also use 6 endpoint/terminal dilutions, which are done in these 7 96-well plates; and again, you score for cytopathic 8 effects, as described in the table below. 9 Next slide, please. 10 However, the presence of RNA in the -- 11 so clinically, we don't do this anymore. We generally 12 use an RT-PCR looking for a fragment of the viral 13 genome. This suggests that we're measuring the 14 presence of viral RNA and not infectious virus. 15 And here you can see from studies done 16 by -- on Zika virus that the detection of viral RNA 17 occurs -- can persist much longer than the generation 18 of the infectious virus. 19 So there is a discordance between the 20 presence and detection of RNA as from infectious 21 virus, and we're really only concerned about whether 22 or not you are producing and shedding infectious</p>	<p style="text-align: right;">Page 120</p> <p>1 Next slide. 2 However, there is a caveat to this; and 3 that is the presence of a cross-reactive enterovirus- 4 antibody response, which my lab has been 5 characterizing for many years now. 6 So what we did was, we immunized mice 7 with individual enteroviruses, including islets of EV- 8 D68 and coxsackieviruses as well as rhinovirus and 9 polio; and then we collected the polyclonal sera and 10 used plaque assays to determine whether or not the 11 sera was able to protect cells and culture from the 12 infection -- from infectious virus. 13 And you can see here that when you use 14 polyclonal sera from mice immunized with an 15 Enterovirus D islet -- you can see you're able to 16 protect cells and culture not only from the immunizing 17 virus but as well as from heterologous enteroviruses, 18 including polio as well as different islets of EV-D68 19 and Rhinovirus 1A. 20 Next slide, please. 21 This suggests that when we talk about 22 sera -- results from serosurveys, seroconversions,</p>
<p style="text-align: right;">Page 119</p> <p>1 virus. 2 Next slide, please. 3 One of the important aspects of 4 clinical research or the clinic for enteroviruses was 5 -- is discerning or assessing whether or not you have 6 an active infection, if you have immunity, or if you 7 were priorly exposed to the virus; and for this, we 8 use an ELISA binding assay. 9 And these are described here in the -- 10 in the schematics, as you have a solid support. You 11 have an antibody. You either look for viral antigen 12 or an antibody against the virus, and then you come in 13 with an indicator. 14 So these are generally done by lateral 15 flow and commercially available for many viruses, such 16 as we saw for SARS-CoV-2. 17 And if we want to look at 18 neutralization and say that you have seroconverted and 19 you have a protective immune response, we use a 20 microneutralization assay, which is derived from the 21 endpoint/terminal dilution assay that I just described 22 in the previous slide.</p>	<p style="text-align: right;">Page 121</p> <p>1 sera -- seropositivity studies, we must keep in 2 fact -- keep in mind that there is a presence of a 3 cross-reactive immune response, which may suggest that 4 these studies' conclusions are misleading. 5 And we must try to figure out 6 mechanisms or assays which are more virus-specific, 7 which has been difficult because there's tremendous 8 genomic conservation among these viruses. 9 Next slide, please. 10 And with that, I will end and be happy 11 to take questions. Thank you for inviting me. 12 DR. PICA: Thank you, Dr. Rosenfeld. 13 We'll actually wait for questions at the end of all 14 the speakers, but thank you so much. 15 Next I'd like to introduce Dr. Miranda 16 Delahoy, Senior Epidemiologist in the Acute Flaccid 17 Myelitis and Domestic Polio Team within the Division 18 of Viral Diseases at Centers for Disease Control and 19 Prevention. 20 Thank you for being with us here today, 21 Dr. Delahoy. 22 DR. DELAHOY: Thank you.</p>

<p style="text-align: right;">Page 122</p> <p>1 Good morning, and thanks for the 2 invitation to present today about epidemiologic data 3 and neonatal enterovirus infections, which is 4 collected through national surveillance. 5 Next slide, please. 6 Before presenting national surveillance 7 data on neonatal enterovirus infections, I'll spend a 8 few minutes discussing the surveillance systems that 9 collect these data. Knowing about these systems can 10 help understand data availability as well as 11 limitations of surveillance data. 12 There are three main national- 13 surveillance systems that collect data on enterovirus 14 infections: the National Enterovirus Surveillance 15 System or NES, the National Respiratory and Enteric 16 Virus Surveillance System or NREVSS, and the New 17 Vaccine Surveillance Network, NVSN. 18 Next slide, please. 19 This slide gives an overview about 20 these three systems. NES is a passive laboratory- 21 based surveillance system. Passive surveillance 22 systems rely on voluntary reporting and are likely to</p>	<p style="text-align: right;">Page 124</p> <p>1 across the country. 2 Because NES has the most granular 3 information on enterovirus types and ages of the 4 patients with infections, most of this presentation 5 will focus on data from NES, although I will 6 intersperse some information from NREVSS and NVSN. 7 Next slide, please. 8 I'll now present an analysis of two 9 decades' worth of data from NES. We analyzed data on 10 10,224 non-polio enterovirus infections reported to 11 NES during 2004 to 2022 to assess types and fatal 12 outcomes of neonatal enterovirus infections. Note 13 that the data presented today are considered 14 preliminary. 15 Next slide, please. 16 Among all of the infections, 7 percent 17 occurred among neonates defined in this presentation 18 as being under 1 month old. 19 Next slide. 20 Many enterovirus types were identified 21 among the neonatal infections reported to NES. This 22 graph shows the number of neonatal infections reported</p>
<p style="text-align: right;">Page 123</p> <p>1 miss cases but can cover large areas and be useful for 2 observing infection trends. 3 NES has been collecting reports on 4 enterovirus infections, along with virus-type 5 information, since the 1960s. It covers all age 6 groups, and patient age is reported down to the month. 7 The number of reporting laboratories varies from year 8 to year. In 2022, the CDC lab and labs from four 9 states reported EV-typing data to NES. 10 Scope is limited partly due to the 11 number of laboratories performing EV typing. The 12 other two surveillance systems that collect 13 information on enterovirus infections provide 14 aggregate non-typed data for rhinovirus and 15 enterovirus positivity. 16 These include the National Respiratory 17 and Enteric Virus Surveillance System or NREVSS, which 18 is also a passive system collecting data from more 19 than 90 labs nationally, and the New Vaccine 20 Surveillance Network or NVSN, which also collects 21 aggregated rhinovirus and enterovirus data among 22 children presenting to 7 pediatric-health facilities</p>	<p style="text-align: right;">Page 125</p> <p>1 to NES during the past two decades by virus type. 2 Coxsackievirus B5, Coxsackievirus B3, 3 Echovirus 11, and Coxsackievirus B4 were the virus 4 types most frequently detected among neonates during 5 this time period. 6 Next slide, please. 7 We'll now take a look at some temporal 8 trends in the nine most common virus types or those 9 that each represented more than 5 percent of the total 10 number of neonatal infections. 11 Next slide, please. 12 This graph shows data from NES on the 13 number of reported neonatal infections by year for the 14 most commonly detected enterovirus types among 15 neonates, with each EV type represented by a different 16 color. 17 To give an example of how to read this, 18 in 2004, all the way on the left, the orange segment 19 is the largest and goes from 1 to 16 on the Y axis, 20 representing 15 total infections for Echovirus 9 21 because Echovirus 9 is the one that corresponds to 22 that orange color in the key.</p>

<p style="text-align: right;">Page 126</p> <p>1 It's hard to see; but beneath that, 2 there is one Coxsackievirus B5 infection in the dark- 3 blue color; and above, there are four CVB4 infections 4 in gray and so on. 5 Overall, there was not a single virus 6 type that was most commonly detected and reported each 7 year. Rather, the top virus types among neonates 8 changed over time. Several virus types had peaks in 9 certain years and then periods of low detection 10 between peaks. 11 For example, Coxsackievirus B5, shown 12 in the blue at the very bottom of the stacked graph, 13 had apparent peaks of detection in 2005, 2010, 2014, 14 and 2017 to 2018, whereas CVB3, in the brown color 15 toward the top of the graph, had a large peak in 2014 16 but low detection in other years. 17 Please take caution in interpreting 18 these apparent patterns because of the small numbers 19 of infections represented overall, but I do hope -- 20 hope that this helps to visualize changes in 21 predominant virus types over time. 22 This can also be used to visualize</p>	<p style="text-align: right;">Page 128</p> <p>1 2004 to 2022, the numbers of reported infections were 2 highest during July through October. 3 Next slide, please. 4 Turning for a moment to other data 5 sources, similar seasonal patterns of rhinovirus and 6 enterovirus circulation among respiratory specimens 7 were also observed in NREVSS, with percent positivity 8 peaking in September or October of the past five 9 years. 10 Next slide, please. 11 Similarly, in NVSN, rhinovirus and 12 enterovirus detection peaked in September or October 13 each -- each year among children with respiratory 14 infections. 15 Next slide, please. 16 We'll now turn back to the NES data. 17 Enterovirus infections were detected from a number of 18 specimen types, such as CSF, NP swabs, and stool or 19 rectal swabs. 20 Compared with older patients, 21 enterovirus infections were more commonly detected 22 among CSF for neonatal patients, whereas among persons</p>
<p style="text-align: right;">Page 127</p> <p>1 overall trends in infection. You can see here that 2 the most neonatal enterovirus infections were reported 3 during 2014. 4 Next slide, please. 5 Overall, some virus types were more 6 frequently detected among neonates, compared with 7 older children and adults. These included 8 Coxsackievirus Types B1, B2, B3, B4, and B5 and 9 Echovirus 11. However, EV-D68 and Echovirus 30 were 10 less common among neonates and more frequently 11 detected among persons aged 1 month or older. 12 Next slide, please. 13 We also considered temporal patterns of 14 neonatal enterovirus infections. This graph shows the 15 reported number of neonatal infections reported to NES 16 by month from 2013 to 2022. Enterovirus infections 17 tend to peak in late summer and early fall. Few 18 enterovirus infections were reported during the early 19 COVID-19 pandemic or 2020 and 2021. 20 Next slide, please. 21 Looking at months during which 22 infections were reported summed across the years from</p>	<p style="text-align: right;">Page 129</p> <p>1 aged 1 month or older infections were more commonly 2 detected by throat or NP swabs. 3 Next slide, please. 4 In NES data, only 10 percent of 5 neonates had a known outcome, that is, whether they 6 died. 7 Next slide, please. 8 Among the 35 neonatal patients who had 9 known outcome in NES, 15 -- or 43 percent -- died. It 10 is likely that enterovirus testing and reporting in 11 general as well as reporting of outcome data are 12 biased toward patients with more severe infections. 13 Next slide, please. 14 There are a number of limitations in 15 the analyses presented today. A small number of labs 16 perform and report EV typing, and these labs are not 17 nationally representative. Enterovirus typing and 18 reporting is voluntary and not systematic. 19 It is likely that testing and reporting 20 are biased toward including more severe infections and 21 potential infections among younger patients. In NES, 22 outcome data are often unavailable; and in general,</p>

<p style="text-align: right;">Page 130</p> <p>1 national enterovirus-surveillance systems include 2 little -- limited clinical information. Excuse me. 3 Next slide, please. 4 To summarize our conclusions, 5 enterovirus types detected among neonates differ from 6 those detected among persons aged 1 month or older. 7 Enterovirus infections display a seasonal pattern, 8 typically peaking in late summer; and enterovirus 9 infections can cause severe disease among neonates 10 that can result in death. 11 National data on enterovirus infections 12 can be used to observe seasonal trends and detect 13 signals in year-to-year changes and enterovirus 14 infections. They can also be used to analyze 15 circulating virus types by age. 16 It is our hope that enterovirus 17 surveillance can be strengthened in the United States. 18 Strengthening the capacity for enterovirus typing and 19 surveillance could be beneficial for understanding the 20 burden of disease and clinical manifestations of 21 enterovirus infections and for informing potential 22 treatment options and prevention measures.</p>	<p style="text-align: right;">Page 132</p> <p>1 developing therapies for. 2 Next slide, please. 3 I have no relevant financial 4 relationships with commercial interests. 5 Next slide. 6 So my goal is to do two things. One is 7 to give you a flavor of the clinical challenges that 8 neonatal enterovirus infections present and why we 9 need therapies for them and then to let you know where 10 we are currently as far as treatment options for these 11 infections. 12 Next slide, please. 13 So to give a little bit of broadness to 14 the -- to the -- in context to the discussion, 15 neonatal enterovirus infections are one type of 16 manifestation of a broad canopy of -- of presentations 17 that enteroviruses can -- can produce. 18 Firstly, most infections are likely 19 asymptomatic. Of those that are symptomatic, most of 20 those cause nonspecific febrile illnesses in children 21 or adults. Many cause rashes. For example, Echo 9, 22 as shown here, is a common cause of rash-associated</p>
<p style="text-align: right;">Page 131</p> <p>1 Next slide, please. 2 Thank you all for your attention today 3 and to my CDC team and those who invited us to speak 4 today. I'm happy to take questions during the 5 clarification session. 6 DR. PICA: Thank you so much, Dr. 7 Delahoy. 8 Next I'd like to introduce Dr. Mark 9 Abzug. Dr. Abzug is a professor of pediatrics at the 10 University of Colorado School of Medicine in the 11 Section of Infectious Diseases and Epidemiology and is 12 Vice Chair for Academic Affairs for the Department of 13 Pediatrics. 14 His title is -- his talk is entitled 15 "Neonatal Enterovirus Infections: Challenges and 16 Opportunities." 17 Thank you, Dr. Abzug. 18 DR. ABZUG: Thank you. 19 And thanks to the organizers for the 20 opportunity to speak with you today. My role is to 21 now present over the next 20 minutes or so a clinical 22 overview of the infections that we're talking about</p>	<p style="text-align: right;">Page 133</p> <p>1 illness. 2 Coxsackie A Viruses are associated with 3 herpangina, which is shown in the picture just 4 immediately to the left with vesicles -- small 5 vesicles in the posterior oropharynx. This is often a 6 highly febrile illness. 7 Hand-foot-mouth disease is similar but 8 with slight differences. Here you can see on the 9 right-hand side the ulcerations more commonly in the 10 anterior oropharynx but also involving the peripheral 11 extremities. This is often associated with Coxsackie 12 A16, also with Coxsackie A6, and in the context of 13 pandemics of Enterovirus A71. 14 Hemorrhagic conjunctivitis can cause -- 15 be caused by a number of serotypes. That also may be 16 neurotropic, and that picture is depicted on the lower 17 left, and in the last decade has emerged respiratory 18 illness associated with Enterovirus D68. 19 Next slide, please. 20 Coxsackie B Viruses in particular are 21 important causes of myocarditis and pericarditis and 22 account for up to about a third of cases of viral</p>

<p style="text-align: right;">Page 134</p> <p>1 myocarditis with a proven etiology. Enteroviruses 2 cause a range of neurologic syndromes, including 3 meningitis, encephalitis, acute disseminated 4 encephalomyelitis, and Reye's syndrome. 5 They can cause paralytic disease with 6 polioviruses or acute flaccid myelitis with 7 Enterovirus D68. Enterovirus A71 is a type of 8 enterovirus that's common in cause of pandemics of 9 brain-stem encephalitis, particularly in Asia. 10 Enteroviruses can cause a number of 11 severe infections in immunocompromised hosts, 12 including chronic CNS infection as well as 13 disseminated infections. We're going to talk more 14 about perinatal and neonatal viral sepsis. 15 And then I'll also mention that there 16 are some data linking enteroviruses in a persistent or 17 chronic form with a number of chronic conditions, as 18 shown here. Those data are really not that 19 definitive. 20 Next slide, please. 21 So for neonatal enteroviruses, as we 22 focus in on them, this slide is really just meant to</p>	<p style="text-align: right;">Page 136</p> <p>1 of severe myocarditis in newborns associated with 2 Coxsackie B3 and B4 infections and, as been mentioned 3 earlier, reports from France and elsewhere in Europe 4 of Echovirus 11 infections causing severe neonatal 5 hepatitis and coagulopathy. 6 Next slide, please. 7 Transmission to the newborn of 8 enteroviruses may occur in a minority of cases 9 prenatally, and that's evidenced by retrieval of virus 10 from products of conception or by evidence of clinical 11 illness and/or viremia in the baby as early as within 12 a couple of hours after birth to a couple of days 13 after birth. 14 But the majority of babies when they 15 acquire an enterovirus acquire it intra- or post- 16 partum most often from the mothers, occasionally from 17 other family contacts; and we know from epidemiologic 18 studies up to a few percentage of mothers during 19 enterovirus season will shed virus either from 20 respiratory or GI secretions at the time of delivery. 21 If a mother has illness in the week 22 prior to delivery associated with enterovirus, then</p>
<p style="text-align: right;">Page 135</p> <p>1 give you an overview of the epidemiology to say that 2 newborn enterovirus infections are common. 3 Many of them, if not most of them, are 4 asymptomatic; but of the smaller group that are 5 symptomatic, you can see that they're associated with 6 a range of presentations in the newborn: viral sepsis, 7 viral meningitis, myocarditis, or any combination 8 thereof. 9 But overall, if you look across these 10 different articles in the literature -- literature, 11 you'll see that these viruses are a common cause of 12 disease in the newborn period. 13 Next slide, please. 14 The epidemiology of neonatal 15 enterovirus infections mirrors that of enterovirus 16 infections in general that we've just heard about. So 17 we tend to see these infections in the summer and fall 18 in temperate regions; and there's variability year to 19 year and place to place, depending on what types of 20 enteroviruses are circulating locally. 21 And that was really borne out a year 22 ago when we saw these reports from the United Kingdom</p>	<p style="text-align: right;">Page 137</p> <p>1 there's a much higher rate of the baby becoming 2 infected; and babies have been shown to be infected 3 following both vaginal or caesarean delivery. 4 And there's speculation that breastmilk 5 may also transmit virus, at least based on reports of 6 positive culture or positive PCR of breastmilk 7 specimens. 8 There are also reports of sporadic and 9 epidemic spread of enterovirus infections among staff 10 and babies in nursery settings. 11 Next slide, please. 12 The vast majority of newborns who have 13 an enterovirus infection fortunately are asymptomatic 14 infections. Then there's a subset of babies who have 15 -- will have a benign illness often characterized by 16 fever for a few days and some other symptoms for 17 around a week. Sometimes there's a biphasic course. 18 Meningitis that's uncomplicated may 19 occur in some of these babies, generally associated 20 with a good outcome. Fortunately, the disease that 21 we're most concerned about today in this session, 22 severe disease, is the least common of these outcomes</p>

<p style="text-align: right;">Page 138</p> <p>1 but the most worrisome.</p> <p>2 Next slide, please.</p> <p>3 So when we see a baby who may be</p> <p>4 infected by an enterovirus, there are a number of</p> <p>5 features that are evident from the history. Most</p> <p>6 often these babies, even those who have a severe</p> <p>7 infection, are born to mothers with a normal</p> <p>8 pregnancy. The babies are most often full term and</p> <p>9 have had uncomplicated initial courses.</p> <p>10 Prematurity does worsen the outcome</p> <p>11 overall for neonatal enterovirus infections, but it's</p> <p>12 a minority of babies who become sick who were</p> <p>13 premature to start with.</p> <p>14 If there has been a viral illness in</p> <p>15 the mother around the time or preceding delivery,</p> <p>16 which occurs in about 60 to 70 percent, that may be</p> <p>17 associated with a variety of symptoms, including</p> <p>18 fever, respiratory or GI symptoms.</p> <p>19 Severe abdominal pain in the perinatal</p> <p>20 period of the mother also is prominent as a result of</p> <p>21 this infection, and that may mimic chorioamnionitis or</p> <p>22 abruptio and may actually cause an obstetrician to</p>	<p style="text-align: right;">Page 140</p> <p>1 set of symptoms.</p> <p>2 Next slide, please. Next slide,</p> <p>3 please.</p> <p>4 This slide shows the variety of</p> <p>5 manifestations that I characterize under the heading</p> <p>6 of "Severe Disease." The more common are on the left-</p> <p>7 hand side: meningoencephalitis, myocarditis,</p> <p>8 pneumonitis, hepatitis, coagulopathy, and sepsis.</p> <p>9 Some uncommon complications of neonatal</p> <p>10 enterovirus disease are listed on the right-hand side;</p> <p>11 and of note, any of these manifestations may occur in</p> <p>12 -- in -- together as a constellation. So a baby may</p> <p>13 have meningoencephalitis and hepatitis. It may have</p> <p>14 myocarditis and hepatitis and coagulopathy, et cetera.</p> <p>15 Next slide, please.</p> <p>16 Now, this slide is a busy one; and</p> <p>17 it -- and it aims to summarize the most common</p> <p>18 scenarios we see with severe enteroviruses.</p> <p>19 Meningoencephalitis, myocarditis, pneumonitis, and</p> <p>20 hepatitis and coagulopathy all just highlight some of</p> <p>21 the points on this slide.</p> <p>22 Meningoencephalitis may be caused by</p>
<p style="text-align: right;">Page 139</p> <p>1 think that delivery might be needed sooner rather than</p> <p>2 later.</p> <p>3 There's often a history of viral</p> <p>4 symptoms in other family members; and in the baby, the</p> <p>5 viral-illness onset may occur anywhere from the first</p> <p>6 day of life out to a month of life; but severe disease</p> <p>7 most often is associated with onset of illness within</p> <p>8 the first two weeks of life and especially within the</p> <p>9 first week of life.</p> <p>10 Next slide, please.</p> <p>11 This is a listing of symptoms and signs</p> <p>12 that neonates with an enterovirus infection may</p> <p>13 present with, and you can see it's rather broad and</p> <p>14 rather long.</p> <p>15 Often these babies present as</p> <p>16 generically ill newborns with fever or hypothermia,</p> <p>17 irritability, lethargy. They may have anorexia. They</p> <p>18 may be hypoperfused. They may be jaundiced, and they</p> <p>19 may have a variety of rashes, with macular or</p> <p>20 maculopapular rashes being the most common.</p> <p>21 GI involvement is often present, and</p> <p>22 respiratory symptomology is also a frequent presenting</p>	<p style="text-align: right;">Page 141</p> <p>1 echoviruses or Coxsackie B Viruses. It's hallmark is</p> <p>2 in change in consciousness. Seizures may occur.</p> <p>3 Motor abnormalities may occur. On imaging,</p> <p>4 particularly MRI, white-matter injury particularly in</p> <p>5 the periventricular area is not uncommon.</p> <p>6 And these babies have a variable</p> <p>7 prognosis. The majority of them live through their</p> <p>8 infection, but their neurologic prognosis depends on</p> <p>9 how severe their acute-encephalitis picture was.</p> <p>10 Myocarditis most often is caused by the</p> <p>11 Coxsackie B Viruses, and this is often -- often</p> <p>12 associated with a high mortality rate in the order of</p> <p>13 30 to 50 percent, and survivors may either have</p> <p>14 residual cardiac dysfunction or sometimes may go on to</p> <p>15 have no evident long-term sequelae.</p> <p>16 Pneumonitis is a less common presenter</p> <p>17 of severe enterovirus disease. When it occurs, it's</p> <p>18 most often associated with echoviruses, occasionally</p> <p>19 with Coxsackie B Viruses. It may be a primary</p> <p>20 manifestation, or it may be associated with any of</p> <p>21 these other manifestations. It tends to be rapid and</p> <p>22 severe and associated with a very high mortality rate.</p>

<p style="text-align: right;">Page 142</p> <p>1 Hepatitis and coagulopathy for years 2 now have been recognized as primarily associated with 3 echoviruses, with Echo 11 being the prototype; but in 4 more recent reports, Coxsackie B Viruses have also 5 been shown to cause severe hepatitis. 6 And in its most severe form, this 7 syndrome will present as acute hepatic necrosis with 8 acute liver failure with an associated coagulopathy 9 noted by thrombocytopenia and prolonged clotting times 10 and often -- sometimes grave clinical bleeding, 11 including intracranial bleeding. 12 There's a broad range of mortality 13 reported from anywhere from 24 percent to into the 80- 14 percent range. Of survivors, some will have 15 persistent hepatic dysfunction; but because of the 16 regenerative capacity of the liver, many survivors 17 will eventually develop normal liver function once 18 again. 19 Next slide, please. 20 It is hard to give you the answer of 21 what is the mortality rate with neonatal enterovirus 22 disease because we don't have good population-based</p>	<p style="text-align: right;">Page 144</p> <p>1 representative examples. 2 Next slide, please. 3 What we do have from the literature are 4 a number of risk factors or markers that help us 5 identify which babies are the ones most likely to have 6 severe disease. 7 Onset of illness within the first seven 8 days of life -- and especially within the first few 9 days of life -- is a key marker, as is absence of 10 neutralizing antibody in the baby to the serotype of 11 enterovirus that he or she is dealing with. 12 And that likely is also tied to the 13 next risk factor of maternal illness with offset just 14 before or at delivery, meaning mother has had enough 15 time to transmit a lot of virus to baby but not enough 16 time to develop antibody that will be passably 17 transmitted to the baby. 18 As I mentioned earlier, prematurity is 19 not the prototype on presentation; but when babies who 20 are premature develop severe neonatal disease, they 21 tend to do worse, as do males; and babies who have 22 multisystem disease, such as hepatitis plus</p>
<p style="text-align: right;">Page 143</p> <p>1 prospective data. Mostly, what we have are case 2 series in the literature that use a variety of 3 different conclusion criteria. 4 And Dave Byron from AntiVirus 5 Therapeutics put together this graph on the left, 6 which plots out some of the different reported 7 mortality rates in different series in the literature; 8 and you can see that they're really all over the 9 place, reflecting different inclusion criteria used in 10 the different series. 11 But many of the series show quite high 12 mortality rates; and in this plot, somewhere around 40 13 to 50 percent was sort of the average if you take all 14 these reports together. 15 A few years ago we did a query of the 16 PHIS database of 45 children's hospitals; and using 17 diagnostic codes for neonatal enterovirus hepatitis, 18 coagulopathy, or myocarditis, we came up with a 24- 19 percent mortality rate in this database. 20 And then a recent literature review 21 that spanned 20 years identified a mortality rate of 22 30 percent. So that at least gives you some</p>	<p style="text-align: right;">Page 145</p> <p>1 myocarditis, tend to do worse. 2 Severe hepatitis that's caused necrosis 3 and acute liver failure, also a poorer prognosis; and 4 a few lab markers, a positive serum viral culture has 5 been shown to correlate with mortality; and certain 6 serotypes, including Echovirus 11 and some of the 7 Coxsackie B Viruses, are also associated with worse 8 disease. 9 Next slide, please. 10 This is a nice graph because I just 11 think it -- it really exemplifies the importance of 12 timing of onset. This is a review over 10 years from 13 China from now almost more than 20 years ago. 14 But this looked at neonatal enterovirus 15 disease characterized in three different 16 presentations: in the dark bars, nonspecific febrile 17 illness; in the white bars, uncomplicated viral 18 meningitis; and in the bar graph -- or not the bar 19 graph but the -- the line, the solid line, hepatic- 20 necrosis cases. 21 And you can see that the benign 22 presentations, febrile illness and meningitis, really</p>

<p style="text-align: right;">Page 146</p> <p>1 were pretty much scattered over the first month of 2 life, as shown on the X axis.</p> <p>3 But if you look at hepatic necrosis, 4 that line has a really strong peak within the first 5 seven days of life, making the point that it's the 6 babies who present earliest who are generally the ones 7 more likely to develop severe disease.</p> <p>8 Next slide.</p> <p>9 And in my last few minutes with you, I 10 just want to tell you about the current state of 11 therapy and things that are on the horizon for 12 neonatal enterovirus infections. Standard treatment 13 right now includes when a baby presents and is being 14 worked up with the symptomology and the disease 15 manifestations I've shown you.</p> <p>16 They typically are given empiric 17 antibacterial treatment until bacterial infection is 18 ruled out. Likewise, specimens are sent for herpes 19 simplex virus, which can often very much mimic the 20 presentation of neonatal enterovirus disease; and 21 usually, an empiric treatment of aciclovir is given 22 until herpes has been ruled out.</p>	<p style="text-align: right;">Page 148</p> <p>1 enteroviruses, although in variable amounts based on 2 serotype and the specific IVIG lot being addressed.</p> <p>3 So for that reason, this therapy, 4 immunoglobulin, has been used in the newborn setting. 5 Mostly, we have anecdotal or retrospective reports of 6 using either IVIG or maternal convalescent plasma that 7 is hopefully enriched with antibody to the serotype 8 that's infected the mother and her baby.</p> <p>9 And IVIG or plasma has been used both 10 in the treatment setting as well as for prophylaxis. 11 There has been one small randomized study -- really a 12 pilot study that we and others did many years ago now 13 that looked at newborns in the first two weeks of life 14 with neonatal enterovirus disease.</p> <p>15 They were randomized to receive this 16 dose of IVIG or no treatment, and this was a study 17 that was not intended to look at clinical benefit but 18 really to look to see whether there was virologic 19 suggestion that this might be a valid therapy.</p> <p>20 And what we were able to show was that 21 in babies who received an IVIG product that had a 22 neutralizing titer of 1 to 800 or greater to that</p>
<p style="text-align: right;">Page 147</p> <p>1 And then after those two specific 2 interventions, we're really left with supportive care, 3 supporting the respiratory symptoms, the 4 cardiovascular symptoms, admitting -- administering 5 blood -- blood products when needed, supporting kidney 6 function.</p> <p>7 Some babies go on to need ECMO and even 8 left-ventricular-assist devices in the acute setting, 9 and then occasionally transplant of liver or heart is 10 needed if there's been failure of either of those 11 organs.</p> <p>12 Next slide.</p> <p>13 We often talk about immunoglobulin 14 therapy in the context of neonatal enterovirus 15 disease, and there are a number of reasons for that. 16 As has -- has been mentioned, enteroviruses -- a key 17 immune defense against enteroviruses in general is the 18 antibody response.</p> <p>19 We know for the newborn that a lack of 20 neutralizing antibody increases risk of severe disease 21 for that infecting serotype, and we know that in IVIG 22 there is neutralizing antibody to many different</p>	<p style="text-align: right;">Page 149</p> <p>1 baby's own infecting serotype there was faster 2 cessation of viremia and viruria, so at least giving 3 biological plausibility to this therapy.</p> <p>4 And then more recently, we have a 5 retrospective study of babies with hepatitis and 6 coagulopathy due to enterovirus infection; and they 7 showed that IVIG administration within three days of 8 illness onset, as compared to receipt of IVIG more 9 than three days beyond illness onset, was associated 10 with a lower mortality.</p> <p>11 Next slide, please.</p> <p>12 As far as more specific antiviral 13 therapy, I'll mention the capsid-binder approach. 14 These are drugs that inhibit attachment and un-coding. 15 There are three that are in clinical development.</p> <p>16 Pleconaril, that has been evaluated for 17 neonatal enterovirus disease in particular both by 18 reports of individual cases and a randomized control 19 trial that I'll tell you more about.</p> <p>20 Pocapavir is a poliovirus antiviral 21 that's being developed as part of the poliovirus 22 eradication effort. It has variable activity against</p>

<p style="text-align: right;">Page 150</p> <p>1 non-polioviruses but has been used on -- in an 2 expanded-access basis for some neonatal cases of 3 enterovirus disease. 4 And vapendavir is another capsid binder 5 that's in clinical development, primarily thus far 6 being looked at for rhinovirus infections in adults 7 with obstructive pulmonary disease. 8 Next slide, please. 9 So this is the title of the study that 10 a Collaborative Antiviral Study Group did a number of 11 years ago, a randomized double-blind placebo- 12 controlled trial of pleconaril for newborns with 13 enterovirus sepsis. 14 Next slide. 15 This baby -- this study looked at 16 babies who were less than 2 weeks of age who presented 17 with presumed enterovirus infection with at least one 18 of hepatitis, coagulopathy, or myocarditis. They were 19 randomized 2 to 1 to receive pleconaril or placebo for 20 7 days. There were a number of different endpoints, 21 both virological and clinical and other. 22 We enrolled 61 babies; and you can see</p>	<p style="text-align: right;">Page 152</p> <p>1 than the -- than the placebo recipients, and I show 2 you there on the right-hand side the death rates, and 3 that was significant, with a P-value of 0.02. 4 The bottom panel looks specifically at 5 the 70 -- the 70 percent who were infected with 6 enteroviruses; and you can see comparable death rates; 7 but here with the smaller numbers, the difference in 8 survival is no longer statistically significant. 9 Next slide here. 10 Thank you. So this concludes with what 11 our current treatment status is for severe neonatal 12 enterovirus disease, and that really is supportive 13 care as the mainstay of therapy. Many, if not most, 14 babies these days do receive either IVIG or maternal- 15 convalescent plasma. 16 As far as antiviral therapy, pleconaril 17 is not FDA-approved. It is not available in the 18 United States. Individual cases may sometimes be able 19 to receive pocapavir via an expanded-access mechanism. 20 And then I'll just let you know that 21 the Congenital and Perinatal Infections Consortium, 22 which is the next version of the Collaborative</p>
<p style="text-align: right;">Page 151</p> <p>1 the 2-to-1 ratio of pleconaril to placebo recipients; 2 and of the babies enrolled, 70 percent were ultimately 3 shown to be enterovirus infected. 4 Next slide, please. 5 Amongst the enterovirus-infection 6 group, this graph shows the rate or the time plotted 7 to culture negativity for all cultured sites combined. 8 The dark line is the placebo group. The lighter line 9 is the pleconaril group. 10 So then you can see that there was a 11 trend of the pleconaril group becoming culture 12 negative overall faster than those who received 13 placebo. 14 Next slide. 15 And this shows survival of the patients 16 in the study, the subjects in the study. Again, the 17 light line is the pleconaril group. The darker line 18 is the placebo group. 19 The top panel is all treated babies in 20 the study, the intend-to-treat group; and you can show 21 that -- or you can see that the overall survival 22 probability was higher in the pleconaril recipients</p>	<p style="text-align: right;">Page 153</p> <p>1 Antiviral Study Group, is currently conducting a 2 natural-history study to further describe in a 3 prospective manner neonatal enterovirus and 4 parechovirus viral sepsis in newborns to help better 5 define mortality rates in a prospective manner and 6 hopefully identify predictors of morbidity and 7 mortality that will help this -- with the design of 8 clinical trials of antivirals as they become available 9 for study. 10 I will stop there, and I'm happy to 11 address any questions at this time. Thank you. 12 DR. PICA: Thank you, Dr. Abzug. 13 That concludes the presentations for 14 Session 2 of our agenda. We now have a few minutes to 15 take clarifying questions related to the presentations 16 we've just heard; and as a reminder, these questions 17 should be related to the presentation contents 18 specifically. Other topics will be covered during the 19 panel session. 20 Panelists, please raise your hand in 21 Zoom if you wish to ask a question. 22 And, members of the public, you may</p>

<p style="text-align: right;">Page 154</p> <p>1 enter your questions in the Q-and-A box.</p> <p>2 DR. VISWANATHAN: So it looks like we</p> <p>3 already have a question from Dr. Messacar directed</p> <p>4 specifically to Dr. Abzug.</p> <p>5 Dr. Abzug, the question is: "I am</p> <p>6 curious on your thoughts about requiring signs of</p> <p>7 severe enteroviral disease in neonates to enroll them</p> <p>8 in a treatment trial.</p> <p>9 With the risk factors identified, would</p> <p>10 it be more beneficial to try to enroll and treat</p> <p>11 neonates identified with enterovirus earlier in the</p> <p>12 course of disease, who are at high risk for</p> <p>13 progression?"</p> <p>14 So, Dr. Abzug, I'll turn it over to you</p> <p>15 if you have some preliminary comments you want to make</p> <p>16 on -- on this; but again, we're really trying to limit</p> <p>17 this to, you know, just clarification if there's</p> <p>18 something not clear in a presentation; and then some</p> <p>19 of these more deeper discussion points we'll delve</p> <p>20 into in the panel this afternoon.</p> <p>21 But, Dr. Abzug, if you have any initial</p> <p>22 comments, feel free.</p>	<p style="text-align: right;">Page 156</p> <p>1 predict who will go on to have organ disease that</p> <p>2 might portend a more severe outcome.</p> <p>3 And I think if you look at the -- the</p> <p>4 list of risk factors, if you subtract out the clinical</p> <p>5 ones, the ones where there's already hepatitis or</p> <p>6 already myocarditis or already multisystem disease,</p> <p>7 the two most predictive risk factors are early onset</p> <p>8 of illness and lack of neutralizing antibody in the</p> <p>9 baby to the serotype infecting that child.</p> <p>10 I'm not sure that early onset of</p> <p>11 infection is predictive enough.</p> <p>12 If we had a way to rapidly know whether</p> <p>13 the baby has neutralizing antibody to his or her</p> <p>14 particular enterovirus and we coupled that with early</p> <p>15 onset of illness, then I think we may be able to</p> <p>16 enrich that population enough to know that we're</p> <p>17 studying the right group of children that will give us</p> <p>18 the right answer that we want from the study.</p> <p>19 DR. PICA: Thank you so much.</p> <p>20 Are there other clarifying questions</p> <p>21 that people would like to ask?</p> <p>22 I don't think we can hear you.</p>
<p style="text-align: right;">Page 155</p> <p>1 DR. ABZUG: Yeah. Thank you.</p> <p>2 And thanks, Kevin. It's a really,</p> <p>3 really good question on how best to design a study of</p> <p>4 neonatal enterovirus disease.</p> <p>5 The challenge is that a large number of</p> <p>6 -- well, not a large number but of the -- the number</p> <p>7 of babies -- larger number of babies who present with</p> <p>8 enterovirus infections, a modest percentage of them</p> <p>9 will go on to have severe disease.</p> <p>10 The others will have generally a benign</p> <p>11 outcome, usually with a short hospital stay and</p> <p>12 usually without identified long-term sequelae. So the</p> <p>13 value of antiviral therapy in that group is likely to</p> <p>14 be limited.</p> <p>15 So that's why studies have focused on</p> <p>16 the more severe babies, and we focused on babies who</p> <p>17 present already -- have presented already with</p> <p>18 evidence of end-organ disease that predicts a worse</p> <p>19 outcome.</p> <p>20 Kevin's question is: Can we take the</p> <p>21 universe of babies who present with enterovirus</p> <p>22 disease in the newborn period, use risk factors to</p>	<p style="text-align: right;">Page 157</p> <p>1 DR. SCHLEISS: Oh, Mark --</p> <p>2 DR. PICA: There we go.</p> <p>3 DR. SCHLEISS: Can you hear me?</p> <p>4 DR. PICA: Yes. We can now.</p> <p>5 DR. SCHLEISS: Oh, very good. Yeah.</p> <p>6 That was a great presentation from the whole panel.</p> <p>7 I had a question for Mark about</p> <p>8 maternal -- maternal strains. I mean, should we be</p> <p>9 trying to type maternal islets as well in the setting</p> <p>10 of the neonatal disease.</p> <p>11 I -- I'm remembering this interesting</p> <p>12 case report from some years ago now in which they --</p> <p>13 and you cited it briefly in one of your slides or the</p> <p>14 concept anyway of using maternal plasma, which if it's</p> <p>15 a perinatally acquired infection, you know, should be</p> <p>16 highly enriched for neutralizing antibody for that</p> <p>17 baby's islet.</p> <p>18 So maybe this is a question better</p> <p>19 suited for the later-afternoon session; but anyway, I</p> <p>20 -- I just wondered. You know, we -- we -- we're in</p> <p>21 this era now of this great explosion of knowledge</p> <p>22 about neutralizing antibodies and infectious diseases</p>

<p style="text-align: right;">Page 158</p> <p>1 in babies, and I -- I just wondered if you had any 2 thoughts on that -- on that topic. 3 DR. ABZUG: Yeah. The -- the appeal of 4 convalescent plasma is -- is really strong because 5 that -- that's certainly a better way of knowing that 6 you're giving a baby a high titer of antibody to the 7 relevant virus than by picking a lot of IVIG off a 8 pharmacy shelf. 9 The challenges are a couple. One is 10 that of timing. We want a mother to have recovered 11 enough clinically that we're confident that she's not 12 viremic and that we're not giving extra virus as we 13 give mothers plasma. 14 And we want enough time to have elapsed 15 to be confident that there is antibody that's been 16 produced in that and is present in that plasma to give 17 to the baby. So it certainly would be helpful if we 18 had rapid assays to tell us: "Is there still virus in 19 that plasma? Is there a high amount of antibody in 20 that plasma?" 21 And then we just need the logistics to 22 be able to rapidly plasma freeze and -- and have the</p>	<p style="text-align: right;">Page 160</p> <p>1 very slow periods of time when sending things off to 2 reference labs, were a clinician to have a baby in 3 front of them that they suspected had enteroviral 4 sepsis or even had confirmed had enteroviral sepsis. 5 I guess just to clarify -- are there 6 ways to do that, that you know of? "Quickly," I 7 should say. 8 DR. ABZUG: Matt, your question is: 9 Are there ways to quickly identify the amount of 10 antibody in a product being given to a baby? 11 DR. VOGT: Correct. Yeah, for -- for 12 one of these babies with enteroviral sepsis. 13 DR. ABZUG: Yeah. I do not know of a 14 rapid way that's readily available. I'm open to 15 others who -- 16 DR. VOGT: Yeah. 17 DR. ABZUG: -- may -- may know -- know 18 more about that. 19 DR. VOGT: I suspected not, and I'm 20 sure we can talk about it more in the afternoon, but I 21 figured I'd put that out in the clarification time 22 here.</p>
<p style="text-align: right;">Page 159</p> <p>1 product to give to baby; and that can be, depending on 2 where -- where a baby is housed, that could be a 3 challenge, depending on the setting. 4 So it's a -- it's an attractive option; 5 but there are pragmatic obstacles; and if we had some 6 more rapid assays to look at presence of virus, to 7 look at type of virus, and the amount of antibody to 8 it, I think that would put us in -- in better stead 9 for using that therapy more broadly. 10 DR. PICA: Thank you. 11 Dr. Vogt, do you have a question 12 related to this? 13 DR. VOGT: I sure do. I think Mark 14 actually may have already hinted at the answer to it 15 previously. 16 There are -- but -- but, Dr. Abzug, 17 there are more -- or I guess I should say there are 18 not, like, commercial or readily available ways to do 19 the, you know, measuring of neutralizing antibody 20 titer against a specific virus and/or, you know, 21 identifying the virus. 22 All that stuff basically happens in</p>	<p style="text-align: right;">Page 161</p> <p>1 DR. ABZUG: Well, perhaps there are 2 people like you who can make panels of relevant 3 antibodies. 4 DR. VOGT: Agreed. Totally agree. 5 DR. PICA: Dr. Kimberlin, did you have 6 a question as well? 7 DR. KIMBERLIN: Well, yes. 8 I'm going to ask Mark if he can to give 9 us some way of thinking about for antivirals, not for 10 -- not for -- for antibody therapies but for 11 antivirals. 12 How -- how specific do we have to be to 13 say that we need to look for babies infected with 14 Coxsackie B5 and, "Does this antiviral work against 15 that; or does it work against, you know, one of the 16 enteroviruses or, you know, the echoviruses?" 17 Do we have to get virus specific, or 18 can we look at things more across the -- the totality 19 of -- of virus subtypes that -- that infect these 20 babies? 21 DR. ABZUG: Good question, and I'd say 22 it depends a little bit on both the -- the virus and</p>

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<p>1 the drug.</p> <p>2 So there are some enteroviruses like</p> <p>3 poliovirus that seem to have their own particular</p> <p>4 susceptibility to -- to an agent with pocapavir being</p> <p>5 a good example of that being a good polio drug but not</p> <p>6 being as good or at least being more variable against</p> <p>7 other enterovirus serotypes.</p> <p>8 Now, there are other medications,</p> <p>9 pleconaril, which has relatively broad anti-</p> <p>10 enterovirus activity but isn't enriched against the</p> <p>11 polioviruses; and within the spectrum of nonpolio</p> <p>12 enteroviruses, pleconaril may have more or less</p> <p>13 activity against some versus the others.</p> <p>14 But overall, at least for the ones that</p> <p>15 infect newborns primarily, there's reasonably good</p> <p>16 activity.</p> <p>17 Then you have some specialized</p> <p>18 enteroviruses like Enterovirus A71, Enterovirus D68,</p> <p>19 both of which are not major players in the newborn</p> <p>20 period but cause their own severe disease in -- in</p> <p>21 childhood, that seem less susceptible to pocapavir and</p> <p>22 pleconaril.</p>	<p>1 not really work against more current circulating</p> <p>2 islets like islets like nine -- eighteen four nine</p> <p>3 forty-seven, which was isolated from a case in 2014,</p> <p>4 because it doesn't really have a canyon and stuff.</p> <p>5 So you have to have as much knowledge</p> <p>6 as possible, unless you're going to target a</p> <p>7 nonstructural protein like the protease or a 2C, which</p> <p>8 is a -- which is another protease or a helicase of the</p> <p>9 virus, and even that has caveats.</p> <p>10 DR. PICA: Thank you very much, Dr.</p> <p>11 Rosenfeld and Dr. Abzug.</p> <p>12 I think we have time briefly for one</p> <p>13 last question, and we have a Q-and-A from an attendee.</p> <p>14 So the question is: Do you believe that IVIG and</p> <p>15 pleconaril is synergistic? Is there any data</p> <p>16 suggesting synergistic effect?</p> <p>17 So Dr. Abzug, are you -- are you aware</p> <p>18 of any data regarding potential synergy between IVIG</p> <p>19 and -- and pleconaril?</p> <p>20 DR. ABZUG: Good question. I am not</p> <p>21 aware of invitro data that specifically looked at that</p> <p>22 question, not to say that it doesn't exist, and -- and</p>
Page 163	Page 165
<p>1 But there are other agents that are in</p> <p>2 development, particularly protease inhibitors, which</p> <p>3 tend to have a -- can be against those as well as</p> <p>4 really having a broad range of invitro activity.</p> <p>5 So it's hard to generalize, David. I</p> <p>6 think it depends a little bit on the group of</p> <p>7 enterovirus you're talking about and the type of</p> <p>8 agent, some being more selective and some of the</p> <p>9 agents being broader in their spectrum.</p> <p>10 DR. ROSENFELD: Could I just add into</p> <p>11 that?</p> <p>12 DR. ABZUG: Please.</p> <p>13 DR. ROSENFELD: So in fact, actually it</p> <p>14 goes a little bit even more specific than what Mark</p> <p>15 said. So for instance, if you look at EV-D68, some</p> <p>16 particles have canyons and have pocket factors; and</p> <p>17 other particles do not.</p> <p>18 So you really want to have as much</p> <p>19 information about the actual virus that is infecting</p> <p>20 the baby that is possible because, for instance, the</p> <p>21 capsid inhibitor from Rossman's data works against</p> <p>22 Furman, which is the prototype EV-D68 islet, but does</p>	<p>1 maybe some of our pharmaceutical partners who are with</p> <p>2 us today know the answer to that.</p> <p>3 As far as clinical data, I'll mention</p> <p>4 that the randomized study that I showed you some</p> <p>5 graphs from earlier, we included in that a graph that</p> <p>6 looks at -- looked at pleconaril plus IVIG, pleconaril</p> <p>7 without IVIG, placebo with IVIG, and placebo without</p> <p>8 IVIG and plotted the survival in the four groups.</p> <p>9 Keep in mind that although the</p> <p>10 pleconaril and placebo was a randomized intervention,</p> <p>11 IVIG were not -- was not randomized.</p> <p>12 That was up to the individual provider</p> <p>13 to make that decision; but with all those caveats, we</p> <p>14 did show that the survival was highest in the</p> <p>15 pleconaril-IVIG recipients and then sequentially</p> <p>16 lower, with the lowest group being the placebo, no-</p> <p>17 IVIG group, so suggesting at least the potential that</p> <p>18 there might be some clinical synergy, not -- not true</p> <p>19 antiviral synergy per se but clinical synergy between</p> <p>20 IVIG and an antiviral.</p> <p>21 The results in that plot were not</p> <p>22 statistically significant but at least interesting in</p>

<p style="text-align: right;">Page 166</p> <p>1 terms of hypothesis generation.</p> <p>2 DR. PICA: Thank you, everyone, for</p> <p>3 these questions and to our speakers for providing</p> <p>4 answers. We will now take a lunch break, and we'll</p> <p>5 resume at 1 p.m. for our panel discussion on</p> <p>6 enterovirus trial-design challenges. Thank you all so</p> <p>7 much.</p> <p>8 (Off the record.)</p> <p>9 DR. PICA: Hello, everyone. Welcome</p> <p>10 back. We will now start our panel discussion on</p> <p>11 enterovirus trial-design challenges. As discussed</p> <p>12 this morning, there are many challenges related to the</p> <p>13 development of pediatric therapeutics, including</p> <p>14 ethical, scientific, clinical, regulatory, and</p> <p>15 logistical considerations.</p> <p>16 There are also additional challenges</p> <p>17 specific to the development of treatments for severe</p> <p>18 enterovirus infection. We're looking forward to</p> <p>19 discussing these themes and important topics this</p> <p>20 afternoon.</p> <p>21 Next slide, please. Next slide.</p> <p>22 We welcome -- welcome back our speakers</p>	<p style="text-align: right;">Page 168</p> <p>1 We will start by asking our panelists</p> <p>2 to discuss the key challenges in antiviral drug</p> <p>3 development for the treatment of enterovirus infection</p> <p>4 in infants and neonates.</p> <p>5 Please comment on what additional</p> <p>6 nonclinical or basic-science work may be needed to</p> <p>7 help drive therapeutic development of treatment of</p> <p>8 enterovirus infection in infants and neonates.</p> <p>9 Dr. Oberste, do you want to turn on</p> <p>10 your camera and make a comment?</p> <p>11 DR. OBERSTE: Yes. Thanks.</p> <p>12 I think one of the big challenges at</p> <p>13 least from kind of where I sit on CDC and from the</p> <p>14 laboratory perspective is that there are so many</p> <p>15 different enteroviruses. There's over 100 different</p> <p>16 types. They use 7 different receptors.</p> <p>17 And so, as you heard earlier from --</p> <p>18 from Amy, you know, some -- they're even within a</p> <p>19 type. There are some that have different kind of</p> <p>20 surface properties that may affect the efficacy of --</p> <p>21 of things like capsid-binding drugs; and certainly,</p> <p>22 you know, other targets could be affected similarly.</p>
<p style="text-align: right;">Page 167</p> <p>1 from this morning and thank them for participating in</p> <p>2 our panel this afternoon.</p> <p>3 I would also like to welcome some</p> <p>4 additional panelists: Dr. David Byron, Head of</p> <p>5 Research and Development at AntiVirus Therapeutics;</p> <p>6 Dr. Jeffrey Hincks, cofounder and President of</p> <p>7 ViroDefense; Dr. David Kimberlin, professor and Vice</p> <p>8 Chair of Clinical and Translational Research as well</p> <p>9 as Codirector of the Division of Pediatric Infectious</p> <p>10 Diseases at the University of Alabama at Birmingham;</p> <p>11 Dr. Steve Oberste, Acting Director of the Division of</p> <p>12 Viral Diseases at Centers for Diseases Control and</p> <p>13 Prevention; Dr. Matthew Vogt, Assistant Professor of</p> <p>14 Pediatrics in Microbiology and Immunology at UNC at</p> <p>15 Chapel Hill School of Medicine; and Dr. Kevin</p> <p>16 Messacar, Associate Professor of Pediatrics at</p> <p>17 University of Colorado.</p> <p>18 As a reminder, panelists, please raise</p> <p>19 your hand in Zoom if you wish to make a comment.</p> <p>20 Members of the public may enter</p> <p>21 questions in the Q-and-A box.</p> <p>22 Next slide, please.</p>	<p style="text-align: right;">Page 169</p> <p>1 And, you know, one of the issues is</p> <p>2 that, while there are, you know, certain enteroviruses</p> <p>3 that seem to be more highly associated with severe</p> <p>4 disease in neonates, in fact probably most of them can</p> <p>5 cause severe disease at some level.</p> <p>6 You saw the -- the graph that Miranda</p> <p>7 showed with even a fairly small number of cases, and</p> <p>8 there's a long tail of lots of other enterovirus</p> <p>9 types. So that's -- that's, I think, one of the</p> <p>10 biggest challenge -- challenges, and -- and the other</p> <p>11 one is something that Matt brought up this morning</p> <p>12 about rapid ways to -- to type the viruses.</p> <p>13 It's -- it's very difficult. It</p> <p>14 requires sequencing. At least, that's the current</p> <p>15 state-of-the-art test.</p> <p>16 And -- and even though that's much,</p> <p>17 much faster than the old ways of antigenic typing,</p> <p>18 going back, you know, decades, it still takes a lot of</p> <p>19 time; and it's not -- it's not really possible to turn</p> <p>20 that around in a clinically relevant time frame.</p> <p>21 So to me, those are -- those are two of</p> <p>22 the biggest challenges that we have in -- in getting</p>

<p style="text-align: right;">Page 170</p> <p>1 some of the basic information that's needed to -- to 2 drive either drug development or in fact, you know, 3 clinical treatments. Thank you. 4 DR. VISWANATHAN: Yes. And -- 5 DR. PICA: Dr. -- Dr. Abzug, did you 6 want to comment? 7 DR. ABZUG: Yeah. I'll just add to the 8 list that -- that Steve has started us with. I want 9 to put the obvious out there, which is, we're dealing 10 with a relatively rare condition that's devastating 11 but fortunately rare in numbers. 12 And so the incentivization for 13 developing antiviral drugs particularly targeting this 14 population is -- is not presently there and -- and is 15 a major challenge; and with the rarity of the 16 condition, it also means doing the studies of 17 candidate drugs is challenging. 18 And, as was discussed this morning, 19 this is a prime condition where it -- where network 20 studies are really the only way to evaluate new 21 agents. 22 But those network studies have to be</p>	<p style="text-align: right;">Page 172</p> <p>1 prepared to enroll at any time, primarily during the 2 summer and fall but not always. We're seeing some 3 circulation even in, you know, January and February, 4 when we wouldn't used to have seen that before. 5 Climate change is impacting so many 6 ways that infectious diseases circulate or -- or 7 pathogens circulate. So you've got to -- you've got 8 to have sites ready. That means they've got to have 9 warm funding. It's expensive. 10 And -- and I would suggest more 11 expensive than many times we really legitimately 12 compensate them for in -- in terms of being ready to 13 enroll and maybe not getting anybody not for lack of 14 effort but just because -- because the -- the patients 15 were not coming in, which can be a good thing from the 16 standpoint of the -- of the babies but -- but not so 17 good from the standpoint of trying to get to the end 18 of the study. 19 So the rarity of the -- of the disease 20 -- the severe-disease manifestations itself, I think, 21 is -- is one of the very biggest challenges. Another 22 would be -- and this is true for so many diseases</p>
<p style="text-align: right;">Page 171</p> <p>1 set up over a large number of sites because of the 2 rarity condition -- of conditions that represent a 3 rare -- a broad range of geography since what's 4 happening in one community on a given enterovirus 5 season may not be what's happening in another 6 community. 7 And those studies need to be done over 8 time; and by "over time," I mean usually several to -- 9 to more than several years because of the year-to-year 10 variability and unpredictability of which 11 enteroviruses are circulating at any given time. 12 DR. PICA: Yeah. I think that's an 13 excellent point. Dr. Kimberlin, do you have something 14 else to add? 15 DR. KIMBERLIN: Yeah. I would -- I 16 would add to what Mark just said and -- and say that 17 in addition to wanting to do this over several seasons 18 because of variability of -- of circulating strains or 19 types of -- of enteroviruses, it's just by necessity 20 to get enough subjects. They are so few and far 21 between. 22 And -- and so you have to have sites</p>	<p style="text-align: right;">Page 173</p> <p>1 where it's -- it's -- you know, the baby has been 2 healthy and then all of a sudden is -- is not. 3 It's pretty overwhelming to -- to 4 families; and when they hear things about experimental 5 treatments, many of them just shut down and say: 6 "Nope. I'm not doing that for my baby." And that -- 7 that -- that's not unique to neonatal enteroviral 8 sepsis, but it is a challenge. 9 DR. PICA: Dr. Vogt? 10 DR. VOGT: I think this point that I'm 11 going to make also builds off all of the previous 12 points that were made, which is that for this rare 13 disease that is also caused by, as was pointed out, 14 over 100 different viruses that all seem to have the 15 ability to at least cause some of these forms of 16 disease and with all these different disease 17 manifestations like myocarditis or hepatitis or things 18 like that it also becomes hard to just decide, like, 19 what level of preclinical work is needed to advance 20 something into actual clinical trials. 21 So do you need to show evidence 22 against, you know, one just Echovirus 11 -- let's say</p>

<p style="text-align: right;">Page 174</p> <p>1 -- or one -- or Coxsackie B3; or do you need to see, 2 you know, evidence against five clinical syndromes or 3 ten clinical syndromes in preclinical models, with the 4 caveat that all the preclinical models are also models 5 and not humans? 6 So a complication that I think comes 7 even before we get the chance to think about all the 8 other complications that come with the human studies 9 that follow. 10 DR. PICA: Dr. Rosenfeld, do you have a 11 comment? 12 DR. ROSENFELD: I do. As the basic 13 scientist, the basic entero-virologist representative 14 to the panel, I think we -- these are all, I agree, 15 very serious points and concerns. We need to take a 16 step back and say, "Do we actually have models for 17 these diseases?" And we really don't have immune- 18 competent animal models for enteroviruses. 19 And even -- I mean, I was trained by 20 somebody who generated the first model of a human 21 pathogen. He generated the mouse model for poliovirus 22 infection and paralytic disease, but he will also</p>	<p style="text-align: right;">Page 176</p> <p>1 to understand the importance of enteroviruses?" And 2 that seems to be very difficult. 3 DR. PICA: Excellent points. 4 Dr. Abzug, did you want to respond? 5 DR. ABZUG: Yeah. I just wanted to 6 build on a couple of the previous points. 7 You know, I think that the question of 8 incentivization is key; and this really gets to the 9 second bullet that we're supposed to address in this 10 session, which is the collaboration. 11 And this really needs to be an 12 effort -- there really needs to be an effort -- a 13 collaborative effort amongst industry and academia, as 14 -- as mentioned in that bullet, as well as funding 15 agencies to make this a priority. 16 I mean, this is a -- this is a group of 17 viruses which -- although they cause adult morbidity 18 and sometimes mortality, they truly are more 19 pediatric-threatening; and the younger the child, the 20 more threatening they are. 21 And so we're really talking then to a 22 young pediatric population, which is not the kind of</p>
<p style="text-align: right;">Page 175</p> <p>1 acknowledge the fact that it's not true to real 2 disease. 3 Like, you cannot orally infect those 4 mice and have the -- the polio replicate and go 5 through the entire neuroinvasion process. We cheat. 6 We immunize the animals IP, IM. 7 So there is -- we take advantage of the 8 known viremic phase, and that's all based on a lot of 9 autopsies and data generated in the 1930s through the 10 '50s by seminal clinicians like Dorothy Horstmann and 11 David Bodain for polio. 12 We really don't have any of that 13 information for any other entero, and so we need to 14 start off just asking very simple questions and how to 15 develop a model that we can actually test and say, 16 "This is somewhat related to the human disease" with 17 the understanding that the animals are not humans. 18 And that has not been well-funded 19 because these are not considered diseases where people 20 die; and so that leads to the incentivization that 21 Mark was talking about; and that really starts off 22 with, "Can you get the NIH and other granting agencies</p>	<p style="text-align: right;">Page 177</p> <p>1 market that -- that industry thrives on, and it's not 2 necessarily the kind -- type of disease that funding 3 agencies are targeting. 4 But there really needs to be a 5 collaborative effort to try to raise the -- the 6 visibility of these agents and the need for -- for the 7 funding to develop the drugs -- develop drugs with 8 different roots of administration applicable to the 9 children we're talking about, developing the -- the 10 models that Amy is referring to, and then developing 11 the -- the means -- the networks to do these studies. 12 It -- it's really a major, major 13 undertaking. 14 I just want to add a couple other 15 challenges that are -- are at least tangentially 16 related to some that we've mentioned. 17 Kevin Messacar's question earlier 18 mentioned predictors. We have some predictors of who 19 is going to do badly, but they're not so honed down 20 that we can really apply them yet, I think, to the 21 clinical setting or the clinical-trial setting. 22 And if we had real-time laboratory</p>

<p style="text-align: right;">Page 178</p> <p>1 diagnostics that give us serotype, antibody level, 2 that sort of thing, that might help us do that better. 3 And then one other thing just to 4 mention is that within a given newborn with severe 5 enterovirus disease, the disease course can be very 6 variable; and variability makes defining endpoints 7 harder. 8 And it makes having the -- the 9 appropriate end in your study more challenging, and it 10 also makes it harder to predict -- to predict which of 11 the babies you're seeing in front of you are the best 12 candidates for a therapeutic trial. I'll stop there. 13 DR. PICA: Thank you. 14 Well, I think Dr. Schleiss had his hand 15 up. 16 DR. SCHLEISS: Oh, hi, thank you. 17 Yeah. This is a great discussion. I just wanted to 18 ask the panel what their thoughts might be about 19 wastewater surveillance and polio. You know, 20 obviously, that's an enterovirus 'cause it's caused a 21 lot of mortality. 22 And we had that infamous case in New</p>	<p style="text-align: right;">Page 180</p> <p>1 DR. OBERSTE: Yeah. Thanks. I can 2 take that one on since we've been directly involved in 3 the wastewater testing for polio that followed the -- 4 the New York case, and one of the issues for -- in 5 doing wastewater testing for enteroviruses is that 6 they're -- is that they're ubiquitous. There's 7 probably 30 to 50 million cases or infections a year. 8 So if you pick sewage from any -- 9 basically a city, you know, a wastewater-treatment 10 system, it's going to be positive for enterovirus; and 11 so it's not terribly helpful in that way. 12 You would have to do typing and 13 sequencing, which is possible; but of course, you 14 know, it's not just a few people depositing viruses 15 into that sewage system. It's probably many 16 thousands, if not, you know, 100,000 or more; and so 17 sorting out all the different enteroviruses that are 18 there is going to be a huge challenge. 19 And then, again, the vast majority of 20 infections are asymptomatic or very mild; and so which 21 ones actually matter? And so while it's certainly an 22 interesting thought, I think it would be hard to get</p>
<p style="text-align: right;">Page 179</p> <p>1 York State a couple years ago now, I guess; and I -- I 2 think the CDC had actually expanded some of the 3 wastewater surveillance in response to that event. 4 And is there some way to tie in, you 5 know, the kinds of messaging and awareness that Mark 6 was just talking about to vaccine-preventable diseases 7 and sort of package that polio story? Heaven help us 8 if we need therapeutics for -- for wild-type polio. I 9 -- I don't think we're going to get back to that 10 point. 11 But the antivaccine movement, you know, 12 has kind of forced our hand on this issue. So I -- 13 just a sort of general question to the panel, thoughts 14 about wastewater surveillance, as it might relate to 15 enterovirus surveillance and tying the whole topic 16 into polio because that will certainly capture some 17 public attention. 18 DR. PICA: Yeah. Thank you, Dr. 19 Schleiss. I know Dr. Rosenfeld and Betsy had their 20 hands up, but I -- before we hear from them, I welcome 21 the panel -- anyone from the panel to -- to answer Dr. 22 Schleiss' question.</p>	<p style="text-align: right;">Page 181</p> <p>1 any actionable data out of it. 2 You know, we had talked to a number of 3 states about doing some wastewater testing for polio 4 specifically and especially in states that -- that had 5 -- states or cities that had known low-vaccine 6 coverage for polio, where we thought there were at- 7 risk populations. 8 And again, there's a lot involved in 9 setting that up. Even though, you know, there were 10 samples being collected for SARS-CoV-2 testing, it was 11 very different than what we do for polio globally 12 'cause of course globally, you know, they don't have 13 sewage systems in the places that we're worried about 14 polio transmission. 15 You know, the sewage system is a ditch 16 on the side of the road; and so it's environmental 17 sampling, not, quote, "wastewater testing"; and so 18 it's very different. 19 And when you have very low rates of 20 infection like we had in -- even in New York, even 21 though it was -- the virus was detected for some 22 months, relatively low rates of infection in a large</p>

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<p>1 catchment -- so some big-city catchments' wastewater 2 can be, you know, over a million people. 3 So you're really looking for a needle 4 in a haystack -- in a very nasty haystack in fact 5 because it's sewage, and so it -- it has a lot of 6 practical challenges to doing wastewater surveillance, 7 not that we wouldn't do it in certain cases; but I 8 think it's hard to find the -- the correct use case 9 where that would be useful. 10 DR. ROSENFELD: Can I just follow up 11 with what Steve said? There's a reason why BioFire 12 diagnoses people EV -- entero-positive, rhino- 13 positive. It's because the genomes are also 14 extraordinarily similar. 15 And it's been very difficult to find 16 virus-specific primers so that you would only amplify 17 out, say, EV-71 versus everything else if that's what 18 you think is circulating. 19 So just logistically, you can say: 20 "Yeah. You're EV-positive, rhinovirus-positive." But 21 it takes a lot more than a PCR to really discriminate 22 between the genomes because you're just using a very</p>	<p>1 Dr. Kimberlin? 2 DR. KIMBERLIN: To -- to focus on the 3 bullet under Number 1, two additional things -- well, 4 I guess -- I guess three things come to mind. 5 One, biomarker, if we could have a 6 biomarker that, I guess, could predict who is going to 7 develop severe disease, that would really be ideal 8 'cause then we could get what Kevin Messacar was 9 suggesting earlier built into a protocol where you 10 could -- you could treat earlier for a baby that's at 11 higher risk. 12 I think that could be very important 13 and then also a biomarker for outcome 'cause that 14 could become an endpoint to a study. We'll talk about 15 that later in the afternoon, I would think. 16 Secondly, Mark Abzug mentioned 17 partnerships; and he brought in funding agencies. 18 I -- I am delighted that FDA is -- is taking these two 19 days to -- to take a deep dive into these two diseases 20 that so many of us care so much about. 21 I think FDA, to the extent allowed 22 as -- as the regulatory agency, being part of</p>
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<p>1 small fragment. 2 The -- if you're multiplexing, the 3 primers all have to be at the appropriate annealing 4 temperature; and there's such genetic similarity 5 between the enteros. Plus, there's a huge amount of 6 recombination among enteros, which leads to new 7 enteros arising -- I don't know -- every year. 8 So this is a huge undertaking, as Steve 9 said; but it's also more complicated than, "Let's just 10 throw out some primers." 11 DR. PICA: Okay. That does sound quite 12 challenging. Thank you for that comment. 13 Dr. Hincks, did you want to make a 14 comment? 15 DR. HINCKS: Yeah. I -- I guess there 16 -- there are some models out there. Utah State has a 17 couple different ones for D68, one for polio. They 18 were funded by NIH to set them up. So, I mean, there 19 are other models that are specific for EV infection. 20 So, I mean, there are some out there, not too many, 21 but just to comment on that. 22 DR. PICA: Thank you.</p>	<p>1 conversations early can be really, really helpful 2 to -- to the overall process. 3 And then finally -- and this is broad. 4 This is not just -- it -- it impacts rare diseases, 5 but it impacts everything else too. The -- the OHRP 6 oversight of sights and IRBs, this whole idea of 7 single IRB being a streamlined thing, it is not; and 8 you -- you can ask anybody. 9 All it has done is added additional 10 layers of complexity of review, of everything that 11 goes into having a study approved at a given site or 12 across sites. So there could be -- it would help this 13 and so many other things. There could be some 14 regulatory adjustments that could make the conduct of 15 clinical research much easier. 16 DR. PICA: Thank you for that 17 perspective. 18 Dr. Vogt, I saw your hand come up. 19 DR. VOGT: Sure thing. Actually, this 20 wasn't my initial intent; but I'm just going to second 21 Dr. Kimberlin on that point about central IRBs not 22 necessarily really making things easier. It does feel</p>

<p style="text-align: right;">Page 186</p> <p>1 like it just adds another layer, which is a shame 2 'cause it would be nice if they were easier, as they 3 were intended to be. 4 The point that I was going to make was 5 based more on -- a couple different people have talked 6 about -- and me included -- diagnostics and how nice 7 it would be to have a rapid diagnostic both from the 8 standpoint of, you know, "What is the virus that this 9 child has more specifically than just enteroviruses in 10 general" and also, you know, what seropositivity they 11 may or may not have. 12 I think also the -- the thing is, I 13 don't know that we need that. I would like to have 14 that. So I don't think we should not try to have 15 that. 16 But I think of things like there -- you 17 know, there are certain clinical syndromes where we 18 will just empirically treat for them when we're 19 worried that a child is very sick, and we might need 20 to treat them. 21 So -- so in Dr. Abzug's talk, the 22 example of that was, we often give aciclovir for --</p>	<p style="text-align: right;">Page 188</p> <p>1 may not matter all that much if our drugs and our 2 treatments are relatively innocuous to give, that's 3 something to consider when we're doing our trials -- 4 trial designs as well. 5 DR. BELEW: I had a -- this is Yodit 6 Belew -- a follow-up question to that comment, Dr. 7 Vogt. 8 Would you be concerned -- and, others, 9 please feel free to chime in -- with respect to 10 empiric treatment and the potential for development of 11 resistance if we are using antivirals broadly for any 12 enteroviral-diagnosed -- diagnosed infection and 13 continuing treatment while we're waiting for subtypes 14 and susceptibility testing? 15 DR. VOGT: Sure. I -- I think that's 16 always something we need to think about; and, you 17 know, in some -- when you look at the use of small 18 molecules, for example, there's some small molecules 19 that have worked, you know, for decades and then some 20 small molecules that pretty quickly didn't work that 21 well anymore because the viruses mutated against them. 22 So I think it's hard to predict just</p>
<p style="text-align: right;">Page 187</p> <p>1 you know, to treat for potential herpes simplex 2 infection in scenarios where herpes simplex is maybe 3 not the most likely thing the child has; but of 4 course, we'll do that; and aciclovir is not without 5 its toxicities. 6 I think if we can also, you know, try 7 to make sure that our drugs are within a tolerable 8 level of toxicity one way to potential perform these 9 trials is to have a bit more of an inclusive net and 10 then allow that sort of post hoc analysis, which I 11 know some of the studies that Dr. Abzug cited had, 12 where you sort of break out. 13 "Okay. We -- you know, this was our 14 intention-to-treat group; but then we found out later, 15 you know" -- for example, if we're using a capsid 16 inhibitor, once we type the viruses -- "You know, 17 these were the kids who had viruses that actually have 18 pocket factor that a capsid inhibitor could impair; 19 and these were the kids who didn't have those." 20 We -- just to -- to really try to not 21 limit the potential benefit to a lot of children 22 because we're waiting around on some diagnostics that</p>	<p style="text-align: right;">Page 189</p> <p>1 how that would work, but I -- I think that for 2 enteroviruses -- you know, I think of these as -- a 3 lot of these infections as things that set on pretty 4 quick. They're -- they're kind of a fast burn. 5 Like, they -- they come on pretty 6 quick; and then, you know, the virus -- the damage of 7 the virus may last weeks or months or years; but 8 really, the viral infection, you know, is actually 9 happening over the course of -- of days or at -- at 10 most weeks before the infection is cleared. 11 So you don't have quite the amount of 12 cocirculation of -- of virus and -- and small 13 molecules, and I think the other thing is to -- to 14 think about the epidemiology of these infections, is 15 that, as has been pointed out, this is actually a 16 pretty small group of children who -- certainly who 17 have severe outcomes. 18 But even when you include all the kids 19 without severe outcomes, the amount of children who 20 would receive these empiric drugs is actually pretty 21 small compared to the number of enteroviruses 22 circulating in the world in all adults and children</p>

<p style="text-align: right;">Page 190</p> <p>1 and all-comers.</p> <p>2 So you'd really be applying that</p> <p>3 pressure to a pretty small group of people. So I</p> <p>4 think of this as at least theoretically to me -- so</p> <p>5 I'll -- I'll really emphasize the "theoretically to</p> <p>6 me" part of this -- a lower concern for this group of</p> <p>7 viruses, although I'm sure other people might</p> <p>8 disagree.</p> <p>9 DR. PICA: Yeah. I -- Dr. Rosenfeld,</p> <p>10 I'm not sure if you have your hand up or if that was</p> <p>11 from earlier but --</p> <p>12 DR. ROSENFELD: No. I have my hand up.</p> <p>13 So I have --</p> <p>14 DR. PICA: Okay. Great.</p> <p>15 DR. ROSENFELD: I have several problems</p> <p>16 with -- or several concerns with certain aspects of</p> <p>17 this discussion.</p> <p>18 So for instance, the idea of looking at</p> <p>19 seropositivity for antibodies, there's a lot of cross-</p> <p>20 reactivity against entero -- against enteroviruses,</p> <p>21 and my lab has described the cross-neutralized -- is</p> <p>22 beginning to describe the cross-neutralizing antibody</p>	<p style="text-align: right;">Page 192</p> <p>1 you take virus from children who develop non-severe</p> <p>2 disease and severe disease, the virus' genome is the</p> <p>3 same.</p> <p>4 It has to do with host genetics, and we</p> <p>5 have no understanding of what host genetics -- single</p> <p>6 polymorphism, SNPs, or whatever -- correlate with the</p> <p>7 development of severe disease 'cause severe disease is</p> <p>8 really just a reflection of viral fitness in that</p> <p>9 particular environment, and viral fitness is not</p> <p>10 always defined by the virus.</p> <p>11 And so I think that we -- if we want to</p> <p>12 really address this question appropriately then, we</p> <p>13 need to take into the fact that host genetics really</p> <p>14 does contribute.</p> <p>15 DR. PICA: Thank you, Amy, for that</p> <p>16 perspective -- or, Dr. Rosenfeld, I should say.</p> <p>17 Dr. Kimberlin and Dr. Vogt, I think you</p> <p>18 have direct responses to this; and then we'll hear</p> <p>19 from Dr. Abzug.</p> <p>20 DR. KIMBERLIN: Yeah. I do. I -- I</p> <p>21 don't -- I don't discount what Dr. Rosenfeld was</p> <p>22 saying. I -- I would point out that the neonatal</p>
<p style="text-align: right;">Page 191</p> <p>1 response.</p> <p>2 So just to say you have a neutralizing</p> <p>3 antibody response is not really sufficient to say you</p> <p>4 have a neutralizing antibody response against that</p> <p>5 specific virus, especially when you talk about cross-</p> <p>6 reactivity because we don't really know whether --</p> <p>7 what cross-reactivity means, if it can exacerbate the</p> <p>8 viral infection and the disease or not because this is</p> <p>9 just all done in tissue-culture cells.</p> <p>10 The animal models that were referred to</p> <p>11 are all basically immune compromised. They're</p> <p>12 interferon alpha beta receptor knockout mice, which is</p> <p>13 problematic in the fact that these viruses are</p> <p>14 interferon sensitive.</p> <p>15 So if you look at work that was done by</p> <p>16 the Japanese group for polio, they took out the</p> <p>17 interferon response by removing TLR3; and the virus</p> <p>18 was now all over in all extra-neural tissue,</p> <p>19 suggesting that it is the interferon response that</p> <p>20 constricts the virus to the primary site of infection.</p> <p>21 And we're all talking about this as if</p> <p>22 it's the virus that is the problem. Most likely if</p>	<p style="text-align: right;">Page 193</p> <p>1 population is immunocompromised. I mean, the -- the</p> <p>2 innate immune response is different in a neonate than</p> <p>3 it is in a 2-month-old or a 7-month-old or a 2-year-</p> <p>4 old or whatever it may be.</p> <p>5 So -- so I -- I think that it may be</p> <p>6 more complex than simply saying that: "The virus is</p> <p>7 not the issue. It's the host's response to the</p> <p>8 virus." These -- these people are -- these babies are</p> <p>9 not able to -- to mount the kind of response -- that's</p> <p>10 the reason HSV is -- is devastating in a neonate, and</p> <p>11 if a -- if a 7-week-old gets it, they do fine.</p> <p>12 It's -- it's not the genes that are</p> <p>13 different. It's not the virus that is different.</p> <p>14 It's the innate immune response that has matured over</p> <p>15 those first weeks of life.</p> <p>16 DR. PICA: Dr. Vogt?</p> <p>17 And then, Dr. Abzug?</p> <p>18 DR. VOGT: Sure. I just want to point</p> <p>19 out in response to Dr. Rosenfeld's comments about the</p> <p>20 cross-neutralization of antibodies, you know, I think</p> <p>21 there's an important distinction to make; and that's</p> <p>22 between -- the difference between binding and</p>

<p style="text-align: right;">Page 194</p> <p>1 neutralization, and I think we've kind of been 2 switching back and forth between those two. 3 I think with the -- you know, the 4 therapeutic studies, for example, that Dr. Abzug was 5 talking about, where, for example, they took lots of 6 IVIG and then said: "Okay. Does this lot of IVIG 7 have a 1-to-800 titer against a particular virus," 8 those are neutralization titers. I'm almost certain, 9 although I'm happy to be corrected if I'm wrong. 10 And -- and a lot of these when we're 11 talking about cross-reactivity or when we're talking 12 about -- let's say -- polyclonal sources of antibody 13 usually we are talking about a neutralization readout. 14 And so I'll totally agree to the fact 15 that I couldn't tell you if that antibody was 16 generated in response to a polio vaccine or to an 17 enterovirus infection of any specific type. 18 But in this case, I don't think that's 19 really relevant because if the neutralizing -- if the 20 antibodies neutralize the virus, whether they were 21 elicited by an infection to something or an 22 immunization to another thing, the fact is they</p>	<p style="text-align: right;">Page 196</p> <p>1 the enrolled subjects to reach what we think is a 2 target level that's appropriate. So that's the 3 antiviral piece. 4 But I also think we need to be thinking 5 broadly. We need to be thinking about 6 immunotherapies, be that antibody based or other; and 7 then another whole possibility to think about, 8 which -- which I don't even know if it's in 9 development, are agents that can be either organ 10 protective or organ repairing. 11 So for example, the heart and the 12 liver, as I showed this morning, are two of the major 13 target organs for enterovirus disease. 14 Maybe we don't have the right antiviral 15 to give to a baby; but if we had a medication that 16 could protect that target organ or to help that target 17 -- target organ repair better than natural history 18 would predict, that may be a very important category 19 of therapeutics for us to think about as well. 20 Thanks. 21 DR. PICA: Okay. Thank you all. I'm 22 going to just take one moment now to read one of the</p>
<p style="text-align: right;">Page 195</p> <p>1 neutralized the virus; and so it doesn't really matter 2 what caused the antibody to be generated. 3 It's there; and it's doing its 4 neutralization, you know, activity. So I think that's 5 just a sort of clarification I'd like to point out. 6 DR. PICA: Thanks. 7 And, Dr. Abzug? 8 DR. ABZUG: Thank you. 9 I just want to broaden a little bit in 10 -- in response to the first bullet our thinking. 11 We've been focused on antivirals, as -- as we're -- 12 we're supposed to, and I'm all for that. I just want 13 to make a comment that we also need to think about 14 alternative routes of administration. 15 The fact is that most of the 16 enterovirus antivirals that are in development are 17 being developed by oral routes; and as was mentioned 18 this morning, that's probably not the best route for a 19 very sick newborn. 20 And our study -- I didn't have time to 21 show you the pharmacokinetics data, but it bore that 22 out that it took a while for a significant number of</p>	<p style="text-align: right;">Page 197</p> <p>1 comments that we got in the Q-and-A box from a general 2 attendee. 3 This is from Dr. Park, who is a program 4 officer overseeing the picornavirus at NIH -- at NIH, 5 and Dr. Park notes that: "To address the problem of 6 needing to treat enterovirus infections we are 7 interested to find broad-spectrum antivirals. 8 For that reason, we provide antiviral- 9 screening services against enterovirus using mouse 10 models. Polio, coxsackie, EV-D68, and EV-71 and 11 echovirus model is being developed. 12 Additionally, picornavirus is one of 13 the members of the prototype pathogens for pandemic 14 preparedness; and NIH has programs for developing 15 antivirals against prototype pathogens via the AVIDD 16 program." 17 So thank you, Dr. Park, for sharing 18 that information with us. Unfortunately, the way that 19 our Zoom platform is set up for these meetings, 20 attendees who -- who are not panelists or speakers do 21 not have capabilities of actually commenting verbally 22 during these.</p>

<p style="text-align: right;">Page 198</p> <p>1 So I -- I apologize, but I thought that 2 that was an important point to share with the larger 3 group. 4 So if anyone has follow-up questions, 5 they can -- you know, if -- if you're an attendee, you 6 can ask those questions via the chat; or a panelist 7 can either raise their hand and ask questions if -- if 8 they have additional follow-on questions or comments 9 regarding Dr. Park's information there in the Q and A. 10 I think before we go back -- I see that 11 Dr. Kimberlin has his hand raised again; but before we 12 go to Dr. Kimberlin, I wanted to give -- I know that 13 Ms. Pilon from -- from earlier today had her hand 14 raised. 15 I just wanted to give you the 16 opportunity if you still had comments on your 17 perspectives about these topics for this session. 18 We'd love to hear from you. 19 MS. PILON: Yeah. Just a really quick 20 comment 'cause I was looking at, you know, additional 21 nonclinical discussion. 22 And, you know, earlier there was a</p>	<p style="text-align: right;">Page 200</p> <p>1 see that he's had his hand up for a while, and then we 2 will turn to Dr. Vogt to respond to one of the other 3 questions in our Q-and-A box. 4 But, Dr. Kimberlin, I'll -- I'll go to 5 you next. 6 DR. KIMBERLIN: This -- and this is 7 just circling back to an earlier question about 8 antiviral resistance and -- and antiviral pressure. 9 Yeah. 10 Of course, it depends on the molecule 11 in terms of what -- the likelihood of -- if a drug is, 12 you know, quick to develop antiviral resistance, 13 obviously that's going to be a less attractive drug 14 than if it's more difficult to develop resistance to 15 it. 16 I think Matt's point -- Dr. Vogt's 17 point is a good one that it would be used at least -- 18 is envisioned with this neonatal enteroviral sepsis. 19 It would be used in a really small number of -- of 20 people, even preemptively used in a really small 21 number of people. 22 And so I -- I think my guess is it</p>
<p style="text-align: right;">Page 199</p> <p>1 moment where I thought something relevant to bring up 2 would be, you know, obviously the difficulty in 3 identification of a very heterogeneous cohort but that 4 there are many communities like ours and others whose 5 kids and, you know, infants and neonates also are at 6 higher risk for a severe disease course from 7 enteroviruses and others. 8 And we have that; and we have seen 9 that, you know, time and time again with more severely 10 impacted children. 11 And so just looking at -- you know, 12 when you're looking at the difficulty of -- of that 13 cohort identification and working with a patient- 14 family basis for this in particular 'cause there's not 15 as much of -- in my -- my quick research of -- of 16 patient community behind it, it certainly would be -- 17 there are communities who are more affected by these 18 in general that you could engage in this process as 19 well. 20 DR. PICA: Thank you very much. We 21 appreciate hearing your perspectives on this. 22 I think that Dr. Kimberlin was next. I</p>	<p style="text-align: right;">Page 201</p> <p>1 would be unlikely to -- to lead to much in -- in the 2 way of antiviral resistance. I will say though that 3 if we think about -- let's fast-forward 15 years and 4 say, "We've got two or three drugs on the market." 5 They will be used preemptively just as 6 aciclovir is now when a neonate comes in and there's 7 at least a flash of concern for neonatal HSV. 8 Aciclovir is started along with the antibiotics, and 9 then it's stopped when the diagnostics rule that out, 10 or it's continued. 11 Same kind of approach clinically is how 12 I envision a successful molecule drug being used to 13 treat neonatal enteroviral sepsis. So there will be a 14 broader application utilization than just the smaller 15 population that ultimately rules in for that severe 16 manifestation of enteroviral disease. 17 DR. PICA: Thank you, Dr. Kimberlin. 18 Dr. Vogt, did you want to respond? So 19 let me just quickly read the -- the question that -- 20 that is -- is included in the Q and A here, "So are 21 there any antibodies, even if not neutralizing, that 22 are specific to a particular enterovirus without much</p>

<p style="text-align: right;">Page 202</p> <p>1 cross-reactivity?"</p> <p>2 And Dr. Vogt had volunteered to address</p> <p>3 this question for us.</p> <p>4 DR. VOGT: Sure. And I think one thing</p> <p>5 I'll point out in answering this question is there's</p> <p>6 an important distinction, again, between polyclonal-</p> <p>7 antibody sources -- so that's like the IVIG that Dr.</p> <p>8 Abzug mentioned in some of the clinical trials he</p> <p>9 referenced -- versus monoclonal antibodies, in which</p> <p>10 case if there was a monoclonal-antibody product, you</p> <p>11 know, every single antibody within that product would</p> <p>12 have the sort of same sequence, the same specificity.</p> <p>13 And -- and so for monoclonal</p> <p>14 antibodies, the answer to that is a relatively easy</p> <p>15 answer, which is to say that there are some monoclonal</p> <p>16 antibodies that are indeed specific to certain</p> <p>17 enteroviruses; and then there are other monoclonal</p> <p>18 antibodies that cross-react between different</p> <p>19 enteroviruses.</p> <p>20 So, you know, before using -- oh, yeah.</p> <p>21 So as a potential diagnostic -- so yes. So there are</p> <p>22 definitely, you know, monoclonal antibodies that would</p>	<p style="text-align: right;">Page 204</p> <p>1 out, that might be a combination of different types of</p> <p>2 drugs.</p> <p>3 So there might be small molecules and</p> <p>4 monoclonal antibodies and then maybe something that is</p> <p>5 organ specific to help repair the organ or maybe</p> <p>6 something that is anti-inflammatory, you know, if it's</p> <p>7 a disease process where the immune response is viewed</p> <p>8 as actually potentially causing damage rather than</p> <p>9 helping.</p> <p>10 So hopefully we get to that point where</p> <p>11 we have all those tools.</p> <p>12 DR. PICA: That would -- that would be</p> <p>13 great if we could -- if we could get to that point.</p> <p>14 Dr. Rosenfeld, did you have a comment?</p> <p>15 DR. ROSENFELD: I do.</p> <p>16 So I think that there's a little</p> <p>17 confusion about resistance and how it arises. So</p> <p>18 there's two mechanisms by which it can arise. It can</p> <p>19 arise by point mutations that the polymerase</p> <p>20 introduces, but it can also arise by recombination</p> <p>21 with circulating enteros.</p> <p>22 And we really don't know very much</p>
<p style="text-align: right;">Page 203</p> <p>1 cross-react between different enteroviruses; and, you</p> <p>2 know, right now you can, you know, buy those as</p> <p>3 laboratory reagents, for example, from, like, big</p> <p>4 companies like Thermo Fisher.</p> <p>5 And, you know, we're working on</p> <p>6 identifying some that come from humans; and they're --</p> <p>7 so -- so I think the answer is "yes."</p> <p>8 And actually, in such a diagnostic,</p> <p>9 especially if you put a few, you know -- let's say</p> <p>10 even two or three -- monoclonal antibodies you might</p> <p>11 really be able to make sure you've got that cross-</p> <p>12 reactivity you're looking for in a diagnostic.</p> <p>13 And then also, I just wanted to support</p> <p>14 what Dr. Kimberlin said, which is that -- I agree. I</p> <p>15 mean, my hope would be long term if we can have</p> <p>16 multiple options in our toolbox, if we get that lucky.</p> <p>17 You know, we would give this to any</p> <p>18 child that we were worried about enteroviral sepsis</p> <p>19 before we even eventually hopefully figured that out,</p> <p>20 you know, one way or the other, exactly the way we</p> <p>21 treat HSV.</p> <p>22 And, you know, as Dr. Abzug pointed</p>	<p style="text-align: right;">Page 205</p> <p>1 about recombination partners. So we know something</p> <p>2 about recombination partners for polio; and we know</p> <p>3 something about the polymerase and reversion rates;</p> <p>4 and in fact, actually the reversion rate for certain</p> <p>5 alterations in the genome is very quick.</p> <p>6 So work done -- if you look at the</p> <p>7 reversion of the Stem Loop 5 alteration in the Sabin</p> <p>8 variant of polio, that reversion occurs from the gut</p> <p>9 selective pressure without 48 hours -- 24 hours of</p> <p>10 giving the vaccine to the child, and that's work that</p> <p>11 was done by David Evans and Phil Minor in the 1980s.</p> <p>12 And then the majority of viruses that</p> <p>13 we see circulating that cause -- let's say -- cVDPV2</p> <p>14 outbreaks, they're all recombinants in which the</p> <p>15 three-prime end of the virus has been changed and</p> <p>16 recombined with an entero that is circulating.</p> <p>17 So to say that we wouldn't get</p> <p>18 resistance against some kind of small molecule may not</p> <p>19 -- may be ideal, but it's probably not realistic, and</p> <p>20 we probably also need to sample what is circulating in</p> <p>21 the environment to understand if there are</p> <p>22 recombination partners available.</p>

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<p>1 And that's one reason why you develop 2 combination therapies also, is to prevent that. 3 And that has been one of the concerns 4 about the development of the antiviral program for 5 polio, is whether or not you really need combination 6 therapy or you can just combine -- let's say -- 2C 7 protease inhibitor with a monoclonal antibody, which 8 has been proposed.</p>	<p>1 of reference when we're thinking about the likelihood 2 of -- of that 'cause I agree that -- can viruses 3 develop resistance? Yeah. These are small -- 4 these -- these are small RNA viruses. 5 And one of the main features that we 6 all learn about in, like, Viruses 101 in -- in even 7 high school or, if not, college is that those bad boys 8 -- they like to mutate, and that's kind of how they -- 9 how they, you know, succeed.</p>
<p>9 DR. PICA: So I think Dr. Abzug has a 10 response and then Dr. Vogt.</p>	<p>10 And so we know they're going to mutate.</p>
<p>11 DR. ABZUG: Yeah. A couple of comments 12 to what -- what Amy just said, you know, resistance is 13 always a concern any time you have an anti-infective. 14 We've learned that by history.</p>	<p>11 The question is: Is that mutation that's going to 12 arise be fit enough to actually become a dominant 13 mutation and then also transmit not just from that one 14 infant but to other people and then actually continue 15 to circulate successfully?</p>
<p>15 I think one feature that is in our 16 favor here is we're talking about a newborn, and 17 newborns unfortunately haven't had much exposure to 18 the environment, particularly in that first week or 19 two of life when -- when the ones we're -- we're most 20 worried about are getting sick.</p>	<p>16 And I think that that likelihood is a 17 very different likelihood when you're talking about an 18 infant with neonatal sepsis from an enterovirus versus 19 populations where every single person has received, 20 you know, a vaccine, for example.</p>
<p>21 So it is not impossible but unlikely 22 that that host will be having multiple enteroviruses</p>	<p>21 DR. PICA: Thank you, Dr. Vogt. 22 We'll -- we'll let Dr. Oberste make a</p>
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<p>1 onboard that have the chance for recombination in that 2 narrow population. 3 Ultimately though, I -- I think the 4 goal will be to have multiple agents that can be used 5 in combination, particularly agents of different 6 mechanisms; and that will further reduce the chance of 7 resistance developing. Thanks.</p>	<p>1 comment, and then we'll read a question that we got in 2 the chat. 3 DR. OBERSTE: Yeah. I'd like to 4 address a couple things having to do with 5 recombination. First, with the circulating vaccine- 6 derived polioviruses, I'm not sure there's any 7 evidence that recombination actually plays a role in 8 their emergence per se and certainly not in their -- 9 their pathogenesis or pathology.</p>
<p>8 DR. PICA: And, Dr. Vogt?</p>	
<p>9 DR. VOGT: And I think just to try 10 to -- to put further context on that, similar to what 11 Dr. Abzug was just doing, is -- you know, as he 12 pointed out -- right -- there's, you know, one baby 13 and one hospital and not a lot of exposure to the 14 enteroviruses.</p>	<p>10 As Amy pointed out, the -- the 11 attenuation site and the five-prime NTR of -- of 12 entero -- of the Sabin virus reverts extremely 13 quickly, and that in itself is sufficient to confer 14 neurovirulence on what used to be the vaccine.</p>
<p>15 And so while -- when we think about the 16 circulating vaccine-derived polioviruses that, you 17 know, have arisen from recombination, those have 18 arisen in populations where, like, every child has 19 received that vaccine. So you're talking, you know, 20 hundreds of thousands or even millions of people 21 interacting and sharing these things.</p>	<p>15 My other point is that recombination in 16 the context of drugs and drug treatment really only 17 becomes relevant -- it -- it's really dependent on the 18 target. So for example, if you have a capsid-binding 19 drug, you know, the capsid is what defines an 20 enterovirus type. 21 And while there is going to be some 22 variability or could be some variability within type,</p>
<p>22 So just kind of another sort of point</p>	

<p style="text-align: right;">Page 210</p> <p>1 that doesn't recombine out because that's what tells 2 you which type it is. 3 Now, if you have a drug that targets 4 another part of a genome that can recombine with -- 5 with other circulating enteroviruses, that could cause 6 some issues. However, the key would be to find broad- 7 specificity drugs -- for example, to target the -- the 8 protease. 9 And there are some drugs that have been 10 developed over the years or at least taken to certain 11 stages of development over the years that have much 12 broader specificity, and so then you wouldn't worry as 13 much about recombination because it may -- may 14 recombine out one version, and the new one comes -- 15 that comes in is just as susceptible. 16 So just kind of thinking of that, 17 recombination to me is maybe not a huge concern. I 18 think it's -- it's some of the point mutations that 19 can confer resistance to, you know, all kind of drugs. 20 And it's -- and it's very similar to 21 the HIV situation -- let's say. They of course -- 22 they've had drugs for decades, and you don't give a</p>	<p style="text-align: right;">Page 212</p> <p>1 broadly effective therapeutics, we've heard a common 2 theme that it's important to really identify the 3 target. 4 And we do have someone who's typed into 5 the question -- into the Q-and-A box: "How accurate 6 could viral typing be in identifying which virus might 7 respond to a specific drug? Is that something that we 8 think is possible in the context of enterovirus 9 diversity?" 10 DR. OBERSTE: I can tackle that one, 11 and maybe others want to comment as well. I think in 12 cases where it's well known how the -- the mechanism 13 of action of the drug -- so for example, the capsid- 14 binding drugs, it's pretty well known where they 15 interact. 16 And there have been efforts to generate 17 -- either generate resistant viruses in the lab or to 18 characterize viruses from, for example, clinical 19 trials; and so it's pretty well-known which parts of 20 the capsid conferred that resistance; and so by -- 21 again, it would be by sequencing, which is not rapid. 22 But it would be at least accurate if</p>
<p style="text-align: right;">Page 211</p> <p>1 single drug if you don't have to. 2 You know, we would expect resistance to 3 occur at some frequency; and that's the way we -- I 4 think we would want to have a combination, you know, 5 down -- down the road when we -- when we do have 6 treatments. 7 And finally, I'd just like to mention I 8 -- I would second all the calls for having the ability 9 to use some of these drugs empirically. I think it 10 will depend largely on the safety profile of the 11 drugs, especially since we have been discussing how 12 difficult it is to do the studies. 13 But if you have a drug that's shown to 14 be extremely safe by, you know, every possible test 15 you can run, then I think that you could make an 16 argument that it's -- it's at least reasonable to try. 17 Obviously, there's lots of caveats that 18 go with that; but I -- I think that -- that would be 19 the first hurdle; and if you have a very safe drug, 20 that maybe lowers the bar just a little bit. 21 DR. PICA: Thank you. 22 Just in the absence of, you know,</p>	<p style="text-align: right;">Page 213</p> <p>1 you can identify parts of the capsid that have -- have 2 characteristic amino acids that -- that are known to 3 confer resistance. 4 And presumably, you could do the same 5 thing with things like a protease inhibitor or others, 6 where the mechanism is known; and you could try -- you 7 could look at the active site of the enzyme. 8 DR. PICA: Thank you so much. This has 9 certainly been a very spirited discussion. In the 10 interest of time, I just want to introduce our second 11 topic for the panelists. 12 I'm hoping that we can now talk about 13 potential strategies that could be considered to 14 improve collaboration between industry, academia, 15 parents -- and parents and caregivers to facilitate 16 antiviral therapeutic development for the treatment of 17 enterovirus infection in infants and neonates. 18 I know Dr. Abzug touched upon this 19 briefly earlier in -- in the afternoon, talking about 20 the importance of network studies. 21 I don't -- Dr. Abzug, do you want to 22 talk more about that?</p>

<p style="text-align: right;">Page 214</p> <p>1 Or does anyone else have any other 2 ideas or comments? 3 DR. ABZUG: I'm going to take your 4 question and change it a little bit because before we 5 can get to network studies we need agents to -- to 6 study in those networks. 7 So I think it might be useful to hear a 8 little bit more about the industry-academia 9 partnership, and -- and I -- and I include funding 10 agencies as the third partner in that collaboration to 11 even to the point of having agents to bring to a 12 clinical trial's networks. 13 So I -- I -- I'd -- I'd like -- like to 14 hear from our industry partners as to what they see as 15 what's necessary to move the field along. 16 DR. PICA: Yeah. I think that would -- 17 it would be great. 18 Dr. Hincks, do you have any comments or 19 just -- 20 DR. HINCKS: Sure. It is tough to get 21 funding. That's for sure. I mean, we're advancing 22 two drugs, two different molecular mechanisms of</p>	<p style="text-align: right;">Page 216</p> <p>1 is always an issue; and the duration of time it takes 2 to do studies on these rare diseases makes not only 3 funding an issue. 4 But -- but also for the sponsor, they 5 have to realize that the time -- the time that they 6 will be spending studying sufficient sample sizes is 7 going to be measured not in months or what we would 8 typically do in the industry in terms of months to 9 perhaps years but a limited number of years. 10 But if the number of years becomes very 11 long because the number of subjects needed to get an 12 adequate sample size requires, as Mark -- as Dr. Abzug 13 had mentioned, requires a significant number of -- of 14 sites -- sites, and each site sometimes only enrolls 15 one to two subjects in a year or less. 16 It just -- it -- it adds to the 17 complication from an industrial perspective to want to 18 get behind that support because the end is so far away 19 from the current time. So it's -- it's another 20 complication of studying these in -- you know, 21 whatever you might characterize as ultra-rare 22 diseases.</p>
<p style="text-align: right;">Page 215</p> <p>1 action; and we're working hard to try to get funding 2 to -- to do a study, a Phase 2 -- well, Phase 2, 3; 3 and it's -- it's been difficult. I guess that's all I 4 can say about that. 5 DR. PICA: Thank you. 6 And, Mr. Byron, do you have anything to 7 mention? We're -- we're not able to hear you, if 8 you're -- if you're providing a response. 9 Well, it -- it does sound like there 10 are substantial challenges for sure beyond -- beyond 11 even getting to a target in which to study. Are there 12 any other -- other comments related to this question? 13 DR. ABZUG: I was just going to ask 14 whether any of our government partners on -- on the 15 phone or online have any thoughts on the issue. 16 MR. BYRON: Can you hear me now? 17 Can -- can anybody hear me? This is Dave Byron. 18 DR. PICA: Oh, yes. Yes. We can hear 19 you now. Thank you. 20 MR. BYRON: Okay. So sorry for that. 21 It -- I got a technical glitch, I guess. I mean, I'll 22 follow up on Mark's comment; and funding is always --</p>	<p style="text-align: right;">Page 217</p> <p>1 DR. PICA: Yeah. Excellent points. 2 And just as a follow-up, Mr. Byron -- 3 and, Dr. Hincks, you may want to chime in here as 4 well. 5 Do you think there are things that we 6 could do or things that the broader community could do 7 to encourage more industry partners who would be 8 interested in developing treatments for enterovirus? 9 MR. BYRON: Well, I mean, I'll -- I'll 10 just finish up. I mean, I think -- I think the 11 community -- the medical community and certain -- and 12 certainly Dr. -- Dr. Abzug and Dr. Kimberlin have done 13 quite a bit to -- to, I think, encourage interactions 14 with -- with the industry. 15 But one of the pieces that is missing 16 is kind of the early-on FDA interactions to -- to be 17 sure that no studies are started for which there will 18 be questions asked later or that the studies started 19 are -- are kind of previewed so -- so that there isn't 20 -- there isn't time spent or money spent or effort 21 spent that will end up with -- with questions asked 22 that -- that then add more time to the process.</p>

<p style="text-align: right;">Page 218</p> <p>1 So I guess I'm not saying that maybe 2 it's not just the academic -- the academic 3 institutions, but it's also perhaps the agency in -- 4 in fostering a clearer view of what will be expected 5 that can always not change but would at least give 6 some comfort. 7 DR. PICA: I think it's -- and point 8 taken. I just want to make the comment that the FDA 9 has a few mechanisms for interaction with the 10 industry, one of which is through the Pre-IND Program, 11 where some of these questions that you're alluding to 12 could -- could potential be answered. 13 MR. BYRON: Yeah. Thank you. I -- I 14 do know that -- that there are -- there are mechanisms 15 out there. 16 But again, from an industry 17 perspective, sometimes as we go through the process or 18 as new -- let's say -- new reviewers come onboard 19 during these long programs, new questions come up that 20 were -- that were perhaps -- you know, that were 21 not -- we were not aware of at the beginning because a 22 new -- a new reviewer has new input.</p>	<p style="text-align: right;">Page 220</p> <p>1 make one more comment before we take another break. 2 DR. KIMBERLIN: And this may be a 3 foretaste of the post-break conversation. 4 In -- in thinking about -- as an 5 outsider looking into what FDA does, it -- it -- I 6 would encourage to the -- encourage all of us to think 7 about what we could be doing to -- to improve our 8 situation with respect to antiviral drug development 9 in -- in these two diseases that we'll be talking 10 about today and tomorrow. 11 Looking at the data from an -- from an 12 academic standpoint, at least in clinical care, the 13 way I -- the way I approach it is, I kind of look for 14 the trends. I look for the threads. I look for the 15 truth across studies, and -- and sometimes that's with 16 a primary endpoint that hits. 17 Sometimes it's that another study did 18 not hit the primary endpoint, but there's some 19 secondary endpoints or some other very useful data in 20 -- in the manuscript that I'm -- that I'm reading to 21 make a clinical decision. 22 And for these rare diseases, that kind</p>
<p style="text-align: right;">Page 219</p> <p>1 So it just -- that's not a -- I'm not 2 trying to be -- to express a frustration. I'm trying 3 to just say, you know, "What can we do?" Well, we're 4 not going to change that; and new reviewers are going 5 to be added all the time. It just -- those are the 6 things that -- that cause starts and stops to 7 programs. 8 MS. HODOWANEC: Thank you, Mr. Byron. 9 No. We -- we certainly appreciate your -- your 10 concerns, and -- and, you know, I think we -- we don't 11 have all of the answers at this point in terms of what 12 is the path to development for products for neonatal 13 enteroviral infections. 14 And that is why we are, you know, 15 putting the -- the time and energy into this workshop 16 here today, is to help us get a better understanding 17 of -- of what that path might look like; and 18 ultimately, we would love to be able to put out a 19 guidance document and to provide, you know, some of 20 these answers that you're seeking. 21 MR. BYRON: Thank you. 22 DR. PICA: Dr. Kimberlin, I'll let you</p>	<p style="text-align: right;">Page 221</p> <p>1 of -- where is truth? Where is -- across studies, you 2 know, retrospective studies, prospective studies, 3 randomized studies, where is the trend of -- of 4 evidence that a particular molecule might be helping 5 with the outcome? 6 And I think -- I think greater 7 flexibility for rare diseases where it is so 8 difficult, as -- as Mr. Byron was saying, to do these 9 studies, they just take a decade to do sometimes. 10 And -- and being willing to have a 11 little bit more flexibility, I think, for these rare 12 diseases is something that -- that I think could move 13 the needle somewhat. 14 DR. VISWANATHAN: Thank you, Dr. 15 Kimberlin; and I would say that personally the -- I 16 completely agree with you, and I would say that the 17 agency has taken numerous steps specifically for rare 18 diseases. 19 And so, as mentioned during the morning 20 presentations, this evidentiary standard in terms of 21 substantial evidence of effectiveness is applicable 22 both to rare diseases as well as diseases that are</p>

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<p>1 more common. So that evidentiary standard does not 2 change between the two types of diseases. 3 But where the agency has made it clear 4 is that -- and -- and there have been a number of 5 guidances that have been put forth to, again, as you 6 stated, consider some additional flexibility in 7 getting clinical trials up and running for these rare 8 diseases, which, as we have been talking about today, 9 can be quite challenging. 10 And just echoing Dr. Aimee Hodowanec's 11 point earlier, you know, we all recognize the 12 challenges of drug development in these two disease 13 areas; and that is one of the reasons that, you know, 14 this -- this workshop was organized. 15 And we are hoping that all the 16 discussions that are happening today will help us inch 17 a little bit forward, you know, both in terms of 18 potential in the future putting out guidances and/or 19 collectively for the community to understand some of 20 the nuances of what it means to -- to have evidence of 21 effectiveness for consideration, what additional 22 nonclinical or scientific work that needs to be</p>	<p>1 first? 2 DR. KIMBERLIN: Yes. Thank you. 3 Dr. Abzug mentioned this during his 4 talk, I believe. One of the studies that the 5 Congenital and Perinatal -- and Perinatal Infections 6 Consortium or CPIC, the -- the successor to the CASG, 7 is undertaking now is a natural-history study of 8 neonatal enteroviral sepsis. 9 And we liberalized the enrollment 10 criteria relative to what was used in the prior CASG 11 pleconaril treatment -- Phase 2 treatment study. So 12 we're -- we're -- we are catching -- catching a 13 broader net of -- of babies with -- with potential 14 enterovirus infection. They don't have to have it to 15 -- to enroll in the study. 16 But -- but of the subset that will test 17 positive for enterovirus, once we're doing those 18 analyses in our research lab, of those, we -- we 19 should have a broader grouping, compared with that -- 20 that tighter more sick patient that we enrolled in the 21 pleconaril study. 22 Part of the reason of doing this study</p>
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<p>1 considered so that the overall evidence in terms of a 2 disease, endpoints, trial designs, et cetera, could be 3 refined and moved forward. 4 Thank you. 5 DR. PICA: Thank you. Thank you so 6 much to all the panelists for this excellent 7 discussion. I think it's given us some food for 8 thought, and we'll have a lot more to talk about when 9 we come back from a short break and reconvene at 2:15. 10 Thanks so much. 11 (Off the record.) 12 DR. PICA: Hello, everyone. Welcome 13 back from the break. We will now continue our panel 14 discussion, this time turning our focus specifically 15 to clinical-trial design considerations. 16 I'm hoping during the next hour and 15 17 minutes we can discuss ideal study populations for 18 enrollment into clinical trials, appropriate clinical- 19 trial endpoints, and comparator-treatment groups. I 20 now open the floor to anyone who would like to make 21 comments. 22 Dr. Kimberlin, would you like to go</p>	<p>1 and being a little bit more forgiving with respect to 2 enrollment, these babies still have, you know, 3 elevated transaminases, myocarditis, things like that, 4 just not as -- quite as strict of criteria of how bad 5 it had to be. 6 Part of the reason of doing that is to 7 try to inform endpoints to -- to help people who are 8 listening on this call as they think about developing 9 a drug. What would that look like? 10 And -- and perhaps if they were working 11 within a network such as ours, you know, helping us 12 also design what those future treatment studies would 13 look like, Phase 2 or Phase 3 studies would look like. 14 So -- so only to make the point that 15 there are some data being generated, being gathered 16 now that hopefully will be informative for the future. 17 DR. PICA: Yes. Thank you. Thank you 18 for that. 19 We'll hear from Dr. Vogt and then Dr. 20 Abzug. 21 DR. VOGT: So a question, David, to you 22 about that. For a clinical study like yours where</p>

<p style="text-align: right;">Page 226</p> <p>1 you're more information gathering -- right -- this 2 isn't an interventional study. You're trying to 3 define the natural history. 4 Is there -- I know the answer as the 5 study is constructed now, but is there any room in 6 study design to sort of include patients who aren't at 7 one of the actual study sites? 8 So, you know, and -- and we talked 9 about this with a particular patient once before. So 10 that's why I know the answer as the study is designed 11 today. 12 But for something like natural history, 13 it would seem like it's an easier ask to go outside 14 the network to say: "All right. Invest -- you know, 15 you have to identify an investigator at this other 16 hospital or this institution. 17 So if you can fill out our form, we can 18 include your patient in the study," as opposed to an 19 intervention obviously, which is a far different type 20 of -- of out-of-network question and -- and seems 21 incredibly unlikely. 22 DR. KIMBERLIN: Hey, your -- your -- I</p>	<p style="text-align: right;">Page 228</p> <p>1 DR. VOGT: And is that limitation due 2 to the funders, Dr. Kimberlin; and who is that funding 3 source; or, like, where -- where does the limitation 4 come from just to try to identify places where maybe 5 we can try to liberal -- liberalize the -- the way we 6 do these trials a little bit? 7 DR. KIMBERLIN: Yeah. It's the 8 regulatory oversight of studies. So it's -- it's not 9 really so much the -- the funding source, although 10 they -- they're going to be -- they obviously will be 11 compliant with what -- with the regulatory environment 12 that we work under. 13 But it's -- it's everything else, and 14 it also involves subcontracting and -- and getting a 15 legal agreement so there is a mechanism by which data 16 can leave one place to go to a -- 17 DR. VOGT: Yeah. 18 DR. KIMBERLIN: -- centralized 19 database. 20 DR. VOGT: Sure. 21 DR. KIMBERLIN: And you add all those 22 things together, things that -- you know, if you and I</p>
<p style="text-align: right;">Page 227</p> <p>1 love the tenor of your question. The way the regs 2 are, unless I'm totally missing it, we can't do it. I 3 mean, we've got to have everybody at -- 4 DR. VOGT: Okay. It's just a hard 5 "no"? 6 DR. KIMBERLIN: The number of hoops 7 that you've got to jump through to get a -- to get a 8 site activated, it takes months and -- and all the 9 different documentation, and they've had their -- 10 their training and so on and so forth, and I 11 understand why we do that. 12 But as we talk about it -- and I sort 13 of finished prebreak, you know, advocating for 14 flexibility. I would love to have that degree of 15 flexibility. I don't see it happening right now. 16 We had -- we had a little bit more -- 17 David Boulware up in Minnesota did some interesting 18 work during the pandemic, and -- and -- but it -- 19 it -- it's not one that -- that I'm aware of, of a way 20 -- path forward with it. I'm -- I'm -- I'd love to 21 hear more from people that might be smarter with -- 22 than I am with that.</p>	<p style="text-align: right;">Page 229</p> <p>1 were taking care of a patient, we'd call each other. 2 We'd work through it, and we'd have something taken 3 care of in 15 or 20 minutes. 4 It -- it would take -- it -- it'd take 5 substantially longer, months to -- to do the same sort 6 of thing within the confines of the research realm. 7 DR. VOGT: Sure. Thanks for that 8 answer. 9 DR. KIMBERLIN: And -- and again, if 10 other people have a different way of doing it, I will 11 be taking notes. I would love to hear it, but that's 12 been -- that's been my experience. 13 DR. PICA: Thank you for those 14 perspectives. 15 Dr. Abzug, do you have a comment? 16 DR. ABZUG: Thank you. Yes. 17 I'd like to make two comments, one in 18 response to Dr. Kimberlin's description of the 19 natural-history study just to add that, as he 20 mentioned, that study will hopefully identify 21 appropriate endpoints for the next treatment trial. 22 It will also help to, as he implied -- help to -- us</p>

<p style="text-align: right;">Page 230</p> <p>1 to know more about the appropriate inclusion.</p> <p>2 In the pleconaril-treatment study, we</p> <p>3 picked the sickest of the sick deliberately to try to</p> <p>4 get meaningful endpoints.</p> <p>5 This natural-history study will tell us</p> <p>6 whether we can be more liberal and have a sick but not</p> <p>7 the sickest of the sick study population, which will</p> <p>8 make the study -- the next study a little bit easier</p> <p>9 to do, or whether we really need to focus on the most</p> <p>10 sick infants to -- to get to meaningful endpoints.</p> <p>11 And then I want to just make an</p> <p>12 anecdote because we -- we talked this morning about</p> <p>13 the challenges of enrolling families of -- of very</p> <p>14 sick newborns into studies.</p> <p>15 My anecdotal experience is that for a</p> <p>16 treatment study like the pleconaril-treatment study,</p> <p>17 where there's either a 2-to-1 or 2-out-of-3 or 1-out-</p> <p>18 of-2 chance at a baby who's going to receive what we</p> <p>19 think is an active drug, it was much easier to</p> <p>20 convince parents, even those who are really dealing</p> <p>21 with a dreadful situation in front of them, to</p> <p>22 participate in that sort of study than it has been to</p>	<p style="text-align: right;">Page 232</p> <p>1 some efficacy.</p> <p>2 But at the same point then, the</p> <p>3 challenge with the rare outcomes is of course -- how</p> <p>4 do you know -- how do you select the kids enough in</p> <p>5 advance that your end could be high enough to actually</p> <p>6 point out that there were some kids who never actually</p> <p>7 got that sick at all but otherwise would have gotten</p> <p>8 that sick?</p> <p>9 I think most folks on this call with at</p> <p>10 the FDA have probably had to think about that a</p> <p>11 million times. So maybe I'm just sort of speaking</p> <p>12 into an echo chamber here, but I think that for a lot</p> <p>13 of these antiviral drugs definitely earlier is the</p> <p>14 better.</p> <p>15 And we -- we've seen this in animal</p> <p>16 models; but, you know, animal models are one thing;</p> <p>17 and -- and humans are another with -- with all the</p> <p>18 different challenges that have been mentioned before.</p> <p>19 DR. PICA: Dr. Abzug?</p> <p>20 DR. ABZUG: Thanks. And I can comment</p> <p>21 on a couple of the bullets that -- that you -- you</p> <p>22 have up there -- virtual connectivity interruption --</p>
<p style="text-align: right;">Page 231</p> <p>1 convince them to start participation in a natural-</p> <p>2 history study, where the only potential benefit is</p> <p>3 future knowledge that hopefully will -- will help</p> <p>4 other babies but will not help their own because for</p> <p>5 those, you know, families with a very sick child one</p> <p>6 more blood draw is one more blood draw too much</p> <p>7 sometimes.</p> <p>8 Thanks.</p> <p>9 DR. PICA: Absolutely, well put.</p> <p>10 Dr. Vogt?</p> <p>11 DR. VOGT: I think I'll try to build</p> <p>12 off what Dr. Abzug was just saying in the -- you know,</p> <p>13 how do we pick what children to target; right? The</p> <p>14 sickest of the sick versus, you know, intervening a</p> <p>15 little bit early, I think when you think about it from</p> <p>16 a virologic standpoint, the earlier we give these</p> <p>17 drugs, the better.</p> <p>18 I mean, you know, if we give the</p> <p>19 drug -- if we give the virus more time to infect more</p> <p>20 cells or to maybe get father in a life cycle within a</p> <p>21 cell, it makes sense to me at least to think that that</p> <p>22 -- that drug now has a harder hill to climb to show</p>	<p style="text-align: right;">Page 233</p> <p>1 study looking at pleconaril for infants with</p> <p>2 meningitis. So these were outside the newborn grade,</p> <p>3 and they were not as sick as the kind of sick newborns</p> <p>4 we're talking about.</p> <p>5 And the challenge there is that</p> <p>6 fortunately those babies -- those children are just</p> <p>7 not as ill, and they generally do quite well.</p> <p>8 And we actually aborted the study</p> <p>9 because it was clear that we were not going to have</p> <p>10 enough meaningful endpoints to get to say whether the</p> <p>11 treatment was beneficial or not because most of the</p> <p>12 children in the study had short hospitalizations and</p> <p>13 really did not suffer at least in the near term</p> <p>14 significant morbidity and mortality.</p> <p>15 So that's why we have chosen to start</p> <p>16 really focusing on the sickest babies, those being the</p> <p>17 newborns.</p> <p>18 DR. PICA: Dr. Massaro?</p> <p>19 DR. MASSARO: Thanks. I just wanted to</p> <p>20 piggyback on some of the comments that have been made</p> <p>21 from the neonatology perspective. You know, I -- I</p> <p>22 think everybody is homing in on this point that the</p>

<p style="text-align: right;">Page 234</p> <p>1 studies -- and I mentioned also during my introductory</p> <p>2 comments these studies -- studies are so incredibly</p> <p>3 challenging.</p> <p>4 And I -- I hope after I speak that</p> <p>5 if -- if Betsy is still on she can speak to this as</p> <p>6 well.</p> <p>7 But we do have a lot of experience in</p> <p>8 the NICU and in the neonatal space and in trials that</p> <p>9 -- that really do have some of the same issues that</p> <p>10 have all been mentioned, you know, time sensitivity,</p> <p>11 critical illness, the HIE population, which Betsy</p> <p>12 talked about her experience there as a prime example</p> <p>13 of that where, you know, we enrolled in -- in acute</p> <p>14 trials with a therapeutic window of six hours in a</p> <p>15 really, really, really sick population as well.</p> <p>16 So I think the keys that we've learned</p> <p>17 from those experiences, the leveraging of networks,</p> <p>18 that's been mentioned. Involvement of parents really</p> <p>19 early in the process -- and we've even learned from,</p> <p>20 you know, our early successes in that hypothermia for</p> <p>21 hypoxic ischemic encephalopathy space is -- we're --</p> <p>22 we're still learning, and we're still improving.</p>	<p style="text-align: right;">Page 236</p> <p>1 who really have complex illnesses.</p> <p>2 So there's, you know, the ethical</p> <p>3 issues of -- of therapeutic misconception and making</p> <p>4 sure that if it's a treating physician or a clinician</p> <p>5 that can answer questions for families.</p> <p>6 But -- but, you know, the -- the</p> <p>7 families just really -- I think we have pretty high</p> <p>8 consent rates in some of our trials where, you know,</p> <p>9 one of the investigators was really somebody who could</p> <p>10 answer questions for the family about the disease</p> <p>11 process and -- and answer questions about the study.</p> <p>12 So there's some benefit or -- or -- you</p> <p>13 know, to the consent process, as we've discussed, in</p> <p>14 the information that's conveyed to families through</p> <p>15 that process. So I think that -- and there's, you</p> <p>16 know, tools and -- and things that are being developed</p> <p>17 that help with that consent -- that consent process.</p> <p>18 So I'll -- I'll just put a plug in to</p> <p>19 kind of look at some of those resources and some of</p> <p>20 those trials in other spaces in neonatology that may</p> <p>21 be helpful for the discussion here; and I see Betsy's</p> <p>22 hand up, which I'm glad about 'cause I'm sure she has</p>
<p style="text-align: right;">Page 235</p> <p>1 So we had mentioned the International</p> <p>2 Neonatal Consortium; and Lily mentioned the, you know,</p> <p>3 development of -- of seizure-trial guidelines through</p> <p>4 that group; and even still, we've struggled with some</p> <p>5 neonatal-seizure trials, which is another area where,</p> <p>6 you know, this -- that faces some of these similar</p> <p>7 challenges.</p> <p>8 And we've worked on -- in meeting with</p> <p>9 parent groups, and -- and there have been</p> <p>10 publications, as Betsy mentioned, from the</p> <p>11 erythropoietin and -- and HIE trial from family and</p> <p>12 patient experiences to try to kind of identify some of</p> <p>13 those best practices.</p> <p>14 So that may be an area to kind of look</p> <p>15 at some of those publications and resources that may</p> <p>16 help in this space as well.</p> <p>17 So, you know, one of the things we</p> <p>18 identified in the seizure-trial network is -- is, you</p> <p>19 know, the use of -- of, you know, the investigators,</p> <p>20 who are consenting and -- and not having the -- using,</p> <p>21 you know, even the well-trained clinical research</p> <p>22 assistant to come and talk to some of these families,</p>	<p style="text-align: right;">Page 237</p> <p>1 things to add here as well.</p> <p>2 DR. PICA: Yes.</p> <p>3 Betsy, please?</p> <p>4 MS. PILON: Yeah. So I just wanted to,</p> <p>5 you know, dovetail off of that a little bit; and</p> <p>6 obviously, there's a lot of work that's been -- that's</p> <p>7 been going on, as An mentioned, and lots of resources</p> <p>8 out there.</p> <p>9 You know, some of the things that we</p> <p>10 found partnering on -- on these trials as they're</p> <p>11 underway now is the real-time problem-solving of</p> <p>12 looking at, you know, if there's consenting issues or</p> <p>13 even bias and things that -- that we're, you know,</p> <p>14 observing or, you know, questioned.</p> <p>15 As patient families involved, we've</p> <p>16 done a lot of PCORI work; and there's a lot of great</p> <p>17 PCORI work out there as well, especially the neonatal</p> <p>18 seizure research network; and there's a lot of</p> <p>19 resources that have come out of that as well.</p> <p>20 So just, you know, some things to</p> <p>21 consider because, you know, there are lots of cohorts</p> <p>22 like ours and -- and the -- the -- you know, the</p>

<p style="text-align: right;">Page 238</p> <p>1 relevance here, just looking at what that is and -- 2 and that consenting process, again, to An's point, you 3 know, what they tell you, it is very short. 4 But that doesn't necessarily mean that 5 -- you know, that this can't be done; but it certainly 6 -- you know, there's -- there's things that are 7 learning -- that we're learning and -- and can bring 8 those perspectives and other patient-family 9 involvement that I think, you know, kind of allows for 10 these -- these challenges that -- that are brought up. 11 You know, and -- and I hear this again 12 from the patient-family perspective of -- I -- you 13 know, these are very sick babies we're talking about; 14 and there's a perception of not wanting to overburden 15 families. 16 But also, if you're not bringing things 17 to the bedside that their babies and kids can benefit 18 from and you're, you know, making that decision for 19 them of not even approaching families, that also, you 20 know, can be problematic, especially for a lot of, you 21 know, therapeutic interventions and potential, you 22 know, that needs the good enrollment data and</p>	<p style="text-align: right;">Page 240</p> <p>1 being more severely sick, and these babies are still - 2 - are so few and far between that if we -- if we blend 3 populations too much we won't have the power to be 4 able to see those differences 'cause there just aren't 5 enough to enroll. 6 So I think it's good and -- and 7 maybe -- I hope anyway the natural-history study that 8 we're conducting now can be informative for the sub -- 9 well, across the spectrum but including the subsets 10 that are -- that are most severely ill in terms of 11 what their outcomes are with their mortality, for 12 example, at 1 month or at 3 months. 13 But maybe as well, it might, since it's 14 a noninterventional study, allow us to identify those 15 predictors of which ones start out more mild and stay 16 mild versus those that start out more mild and get 17 more severe. 18 If we could find that, then I would 19 liberalize and go with an -- enroll across the 20 spectrum. If we don't know that, I think I would stay 21 focused on the sickest of the sick. 22 DR. PICA: Thank --</p>
<p style="text-align: right;">Page 239</p> <p>1 longitudinal follow-up, you know, to get -- get an 2 actual sizable amount of data for these. 3 Thank you. 4 DR. PICA: Excellent point. Thank you 5 so much. 6 So I -- I think we could just maybe 7 tackle some of these questions a little bit more 8 directly. I'm -- I'm interested in this concept of 9 infection severity. You know, what -- what do we 10 gain, or what do we lose by focusing on severe 11 infection or disease versus mild symptomatic 12 infection, for example? 13 Dr. Kimberlin? 14 And then, Dr. Vogt? 15 DR. KIMBERLIN: Yeah. 16 In conversations over -- over the 17 years, Dr. Abzug, I think, has shifted my opinion on 18 this to some degree and -- and convinced me that it's 19 really -- it is the sickest ones that -- that are 20 probably most appropriate to study because some of 21 those that are less sick are never, as Dr. Vogt said 22 just a moment ago -- are never going to progress to</p>	<p style="text-align: right;">Page 241</p> <p>1 DR. VOGT: So, Dr. Kimberlin, I think 2 you -- you teed up my question well and maybe even 3 partially answered it. Unfortunately, I don't have 4 the benefit of the years of discussion between -- 5 between you guys to frame my thinking on this. 6 But, you know, I was thinking -- so 7 whoever -- I forget whose slide it was; but someone 8 had their unicorn slide about, you know, what's the 9 ideal clinical study; and -- and, you know, they 10 presented it as a unicorn 'cause obviously it's hard, 11 if not impossible, to get your ideal study. 12 But if I were to dream up an ideal 13 study, you know, I -- I was told when we were planning 14 for this, this isn't a meeting about prevention. This 15 is a meeting about treatment, but that also kind of 16 exists on a spectrum, and I think that's what this 17 bullet point about infection severity is pointing out. 18 You know, infection just means you have 19 virus in you; and then disease, as Dr. Abzug pointed 20 out in his talk, there's a -- there's a wide range of 21 disease. 22 So at what point, you know, does</p>

<p style="text-align: right;">Page 242</p> <p>1 something become prevention of maybe not infection so 2 much 'cause the infection has already happened but 3 prevention of progression to severe illness versus 4 treatment of a mild illness; and -- and is it even -- 5 is it important that we distinguish that? 6 It seems the FDA thinks it's important 7 because there's a bullet point right there about it. 8 So to get back to that unicorn study, I would love to 9 see no kids get any severe disease. 10 And so, you know, I think we lose a 11 little something by only focusing on the children with 12 the most severe disease because the cat is already out 13 of the bag. The horse is out of the barn, whatever 14 you want to use. 15 So my question -- maybe to frame it as 16 a real question to either Dr. Kimberlin or Dr. Abzug, 17 who've probably thought about this much more than me, 18 would your end needed to find that -- you know, that 19 actual statistical endpoint change if you could 20 prevent every instance of severe disease, every 21 instance? 22 So we had a drug that's very safe. In</p>	<p style="text-align: right;">Page 244</p> <p>1 response, and Dr. Kimberlin can give the second. I'm 2 -- you know, first of all -- virtual connectivity 3 interruption -- actually, I'm sorry. Are you hearing 4 me? Can you hear better as I lean closer to my 5 laptop? 6 THE REPORTER: Yes. 7 DR. PICA: I think it might be 8 something with your connectivity, but it is better 9 when you lean a little bit closer. 10 DR. ABZUG: Okay. I will try to speak 11 up and lean into my laptop. I think in the real world 12 medications aren't available to be used in the way Dr. 13 Vogt is describing. Could one do a clinical trial in 14 that way? I think that depends on resources. It 15 would have to be quite a large study with quite a 16 large budget. 17 And that hasn't been the situation to 18 date, which is why we have focused on a sicker 19 population likely to give clinically meaningful 20 endpoints more -- more quickly. 21 DR. PICA: So, you know, I think just 22 thinking a little bit more about what Dr. Vogt had</p>
<p style="text-align: right;">Page 243</p> <p>1 my unicorn world, this drug is very safe. So we don't 2 feel bad about giving it to basically -- let's say -- 3 any child who is either born to a mother who tests 4 positive for enterovirus or tests positive themselves 5 for enterovirus. So you're just screening kids and 6 screening moms as they come in and give birth. 7 So now you've identified your sort of 8 overall cohort as just enterovirus-positive, you know, 9 mother-infant dyad. We give all those babies drug, 10 and yeah. Probably only a very, very, very small part 11 of that population was going to progress to any sort 12 of illness. 13 But if you see a flat line, you don't 14 really need a ton of severe disease -- right -- to get 15 statistical significance when one of your lines is 16 flat. Is that -- let's say again that dollars are not 17 an issue in our unicorn world. Could you do a study 18 like that, Dr. Kimberlin or Abzug; or is that, like, 19 completely impossible to -- to dream of? 20 DR. PICA: Feel free, Dr. Abzug, to 21 respond. 22 DR. ABZUG: I -- I can give the first</p>	<p style="text-align: right;">Page 245</p> <p>1 said, you are enrolling mild symptomatic population 2 and want to prevent severe disease; or you're -- 3 you're enrolling individuals who already have severe 4 disease. 5 You know, what do you think the 6 appropriate trial endpoints would be? Would it be 7 mortality? Would it be time to hospital discharge? 8 What are kind of the key things? And -- and maybe 9 this is informed by your clinical practice, but -- but 10 what would be the -- the endpoints that you think 11 would be the most important to focus on? 12 And -- and I -- I also want to give Dr. 13 Hincks the -- the opportunity to address some of these 14 comments as well. 15 DR. VOGT: Yeah. Was that -- 16 DR. ABZUG: I'll just -- 17 DR. VOGT: Yeah. Go ahead. 18 DR. ABZUG: Go ahead, Matt. 19 DR. VOGT: Yeah. I don't know if that 20 was directed at anyone specifically. 21 DR. PICA: Dr. Vogt, I was thinking in 22 the context of your unicorn study and -- and also what</p>

<p style="text-align: right;">Page 246</p> <p>1 Dr. Kimberlin had mentioned before. So if you -- if 2 you want to, respond; but then -- then we can turn it 3 over to Dr. Hincks. 4 DR. VOGT: And it sounds like Dr. Abzug 5 probably has an idea there. I mean, to me, it would 6 just be progression to, you know, severe disease with 7 a broad definition of that 'cause I think that gets 8 back to the one slide that Dr. Abzug had, which was, 9 like, myocarditis, hepatitis, coagulopathy. 10 These are all bad things, mortality 11 certainly; but -- but all of those are bad things; and 12 I think if we intervene early we actually have a 13 chance to prevent all of those things if we have drugs 14 that are broadly enough acting. 15 And I do think you'd probably want to 16 have some kind of, you know, post hoc analysis where 17 you have -- again, if, it's, like, a capsid-inhibiting 18 drug, you know, you identify the -- the -- you know, 19 eventually you get to the point where you can identify 20 the specific virus the child; and you can see if there 21 was a match to be made or not. 22 Or for me, you know, I -- I think about</p>	<p style="text-align: right;">Page 248</p> <p>1 be best to take all severe and minor effects of the 2 disease and then look at the data they generate. 3 DR. PICA: Dr. Kimberlin? 4 DR. KIMBERLIN: I really like what Dr. 5 Hincks just said at the very end, "Look at the data 6 that you generate." 7 If we set mortality as the primary 8 endpoint and we have a number of different things, 9 hospital discharge, including virologic endpoints as 10 secondary or tertiary, and then we don't hit mortality 11 and so it's just tossed out because the primary 12 endpoint wasn't achieved, that would be a real shame. 13 I think we've got to -- this is a point 14 I was advocating for earlier as well. 15 I think you've got to look at the 16 totality of the data, whatever the population, whether 17 it's just the sickest of the sick or whether it's, you 18 know, a more broad spectrum, and -- and really look 19 and see what the story that is -- is there that's 20 being told and -- and being -- being willing to -- to 21 think more about the art of it than the science of it, 22 at least as a component, as you would if you're</p>
<p style="text-align: right;">Page 247</p> <p>1 antibodies; and so, you know, we know the antibody is 2 only going to react to certain viruses. Did we 3 actually have one of those viruses or not? Hopefully 4 that maybe gets a little bit at your question, and 5 maybe Dr. Abzug has some more thoughts to add. 6 DR. ABZUG: I agree. 7 DR. PICA: And -- and, Dr. Hincks, your 8 perspective? 9 DR. HINCKS: I think doing a trial on 10 everybody that comes in, if they have enteroviral or 11 not, is difficult 'cause we would be treating babies 12 that may not need treatment at all. 13 So I -- I think there has to be some 14 endpoint that's already detected, whether it's 15 myocarditis, hepatitis, encephalitis; but something is 16 going on that would warrant treatment in the baby. 17 And I -- I think taking all-comers -- 18 again, it might -- might impact the end; but I think 19 going after the severe disease, you're asking a lot of 20 the antiviral because, again, once the organ is 21 damaged far enough it's not going to recover. 22 So I don't know. I -- I think it would</p>	<p style="text-align: right;">Page 249</p> <p>1 reading a book. 2 What is the storyline that we're 3 seeing, and is it strong enough to -- to get a product 4 to the finish line in terms of the licensure kind of a 5 result for the NDA? 6 DR. PICA: Dr. Rosenfeld? 7 And then, Dr. Hincks, again? 8 DR. ROSENFELD: Yeah. I'm a little 9 confused if -- if we absolutely know that severe 10 disease and replicating virus are concordant. Like, 11 that -- when you see severe disease, you can detect 12 replicating virus rather than the severe disease is 13 due to the body responding to the viral infection; and 14 the virus has already been cleared. 15 So if you're targeting the virus only 16 and there's no virus, then I'm not clear what we're -- 17 what we're looking at. I understand about, like, IVIG 18 working because it can dampen the viruses that are 19 surrounding and stuff that may contribute to the 20 development of severe disease. 21 But if you're -- if the actual -- if 22 the actual virus that you think is causing the disease</p>

<p style="text-align: right;">Page 250</p> <p>1 is gone, then I don't know what we're -- we're 2 targeting. So I think we need to understand whether 3 or not virus is really replicating in present at that 4 time that severe -- we detect severe disease, and I 5 don't think we have that data. 6 DR. PICA: Yeah. I think that's an 7 excellent point, Dr. Rosenfeld. 8 Dr. Hincks? 9 Then, Dr. Abzug? 10 Then, Dr. Kimberlin? 11 DR. HINCKS: Yeah. I mean, we have 12 quite a bit of data from our Capacity Use Program; 13 and, I mean, the -- the way they approach us, PIs will 14 approach us and say, "We have this check -- this 15 neonate, and they're PCR-positive," which -- no -- 16 that might not be culturable or -- or replicating 17 virus. 18 But they're PCR-positive for 19 enterovirus and typically rhino, entero; and they're 20 presenting with these diagnoses or these effects: 21 myocarditis, hepatitis, things like that; and you put 22 the two together, and you think they have -- have a</p>	<p style="text-align: right;">Page 252</p> <p>1 babies are viremic at the time that they're presenting 2 and showing organ disease. So I don't think there's 3 doubt that there's a component of active viral 4 infection. 5 But I -- I will add that pathology 6 studies of babies who've died suggest there's both a 7 component of cytolysis, cell breakdown due to direct 8 viral infection, as well as an inflammatory response 9 of the host, the baby, that may be contributing to the 10 ultimate pathology. 11 DR. BELEW: Thank you, Dr. Abzug. 12 This is Yodit Belew. Before we go to 13 Dr. Kimberlin, I just had a follow-up question to both 14 Dr. Kimberlin and Dr. Abzug, considering your long 15 history of -- of taking care of these babies with 16 enteroviral infection and sepsis. 17 So considering other viral diseases and 18 the effectiveness of antivirals having been 19 established to be generally the earlier you give it, 20 the better they're effective, I wanted to go back to 21 Dr. Kimberlin's earlier point about the natural 22 history and identifying potential baseline</p>
<p style="text-align: right;">Page 251</p> <p>1 condition of, you know, enteroviral infection with 2 severe disease. So then we treat with pocapavir. 3 So I don't think it's just one or the 4 other, and -- and I think in -- in a trial you'd be 5 doing the same thing; right? You -- you'd get a 6 patient that would come in. They're positive for PCR 7 entero, and you go ahead and have other conditions 8 that would predict its enteroviral infection with 9 severe disease. 10 That severity depends on how far the 11 organ has been damaged; right? So you -- you don't go 12 in with one or the other. You kind of -- you need 13 both pieces of information. 14 DR. PICA: Okay. And even the 15 information is somewhat incomplete because you may be 16 PCR-positive for enterovirus or rhino, entero for that 17 matter; and you don't know, you know, in fact what is 18 -- what is the infecting agent. 19 Dr. Abzug? 20 And then, Dr. Kimberlin? 21 DR. ABZUG: We do have data from the 22 pre-PCR era that shows that -- that these very sick</p>	<p style="text-align: right;">Page 253</p> <p>1 characteristics and/or biomarkers. 2 So from the preexisting literature, are 3 there reasonable characteristics that we could rely on 4 if we were to consider therapeutics where you're 5 treating to prevent severe disease, including death? 6 Thank you. 7 Yes. Dr. Kimberlin, please? 8 DR. KIMBERLIN: I was hoping that Mark 9 would jump in on that one. I don't know the answer to 10 that. To my -- to my knowledge, we don't have that 11 well defined a biomarker yet. Either -- either that, 12 or I'm -- or I'm flat on my feet in terms of thinking 13 about it. 14 I -- I would -- my hand up was -- was 15 up in response to the -- the conversation just before 16 that, which might actually be informative to this too 17 about whether it's replicating virus or -- or not. 18 And the -- and the -- the graphic that 19 popped in my head was what Dr. Abzug showed from our 20 pleconaril study, where there was more rapid clearance 21 of virus among the -- or at least a trend toward that, 22 a P-value, I think, of 0.08, with -- with respect to</p>

<p style="text-align: right;">Page 254</p> <p>1 the group getting active drug versus the group getting 2 placebo, which, you know, either was erroneous. 3 Or it's because there's actively 4 replicating virus; and the antiviral drug is slowing 5 that down. Now, whether we have enough to -- to call 6 viral load the kind of biomarker that -- that your 7 question is getting at, I -- I don't know. 8 Or is this a rare enough and unusual 9 enough disease, and we want enough flexibility to -- 10 to simply accept virologic endpoints and say that -- 11 that that's good enough for where we are right now? 12 And maybe post licensure, we could do 13 some of the additional work because then it is -- you 14 don't have to jump through all the different 15 complexities of having a site and being positioned 16 right in the hospital where that particular woman 17 delivers the baby or brings the baby back when the 18 baby gets sick. 19 Instead, you could do more real-world, 20 to use the -- the catchy phrase, follow-up and -- and 21 learn more about the use of the drug that in -- in 22 this hypothetical is -- has been licensed based upon</p>	<p style="text-align: right;">Page 256</p> <p>1 useful is a positive serum viral culture at the time 2 the child presents, but nobody does viral cultures, 3 and nor are they rapid. 4 So I don't think that's particularly 5 useful to pick out that child from the start who's 6 going to have a higher likelihood of an adverse 7 outcome. 8 And I also just want to clarify in case 9 there's a misconception. It's not like these babies 10 who are the sickest -- it's not like they sit around 11 for three, four, five days with a mild infection and 12 then deteriorate five, six, seven days later. 13 These sickest babies present and within 14 either -- either on presentation or within 24 to 48 15 hours are -- are really telling you, "I'm one of the 16 sick ones." So it's not like anyone is sitting around 17 for days thinking, "Hmm, antiviral or not?" That -- 18 that really isn't the clinical reality. 19 DR. BELEW: Thank you, Dr. Abzug. 20 Dr. Hincks? 21 DR. HINCKS: You're -- you're asking me 22 for a comment?</p>
<p style="text-align: right;">Page 255</p> <p>1 virologic endpoints. 2 DR. BELEW: Thank you, Dr. Abzug. I 3 was -- I was thinking more along the lines of elevated 4 white count; anemia; maternal status; young age, I 5 think, in Dr. Abzug's presentation being less than 7 6 years of age, so using those, I guess, characteristics 7 that have been described for a number of years as a 8 way of identifying infants who are likely to have a 9 higher risk of progressing to severe disease to allow 10 identifying an enrollment of these neonates into a 11 potential clinical trial. 12 Dr. Abzug, please? 13 DR. ABZUG: Thank you. And I'm leaving 14 my video off just so hopefully you can hear me better. 15 For the demographic predictors like illness within the 16 first seven days of life, I think we need still to 17 learn how predictive that is. I mean, it -- it's 18 clearly a predictor; but what it's positive predictive 19 value is, I think, still needs to -- to be defined. 20 Things like white count and hematocrit 21 and that sort of thing haven't really been shown to be 22 terrific predictors, but one lab predictor that can be</p>	<p style="text-align: right;">Page 257</p> <p>1 DR. PICA: Your hand is up. So we just 2 want to -- 3 DR. HINCKS: Oh, thank you. Okay. 4 That was a while ago, but just commenting on what -- 5 what Mark just said, I -- I agree. Some of these 6 cases present very quickly; or they've been seen at 7 one hospital; and they're transferred to another; and 8 within a couple days after that, they become very ill. 9 So it -- it -- again, it depends on 10 each individual, I would have to say. So I agree with 11 what Mark said. 12 DR. PICA: Dr. Kimberlin, we'll give 13 you an opportunity to respond; and then we have a 14 different question. 15 DR. KIMBERLIN: Well, it -- it's -- 16 it's really kind of a question for Dr. Abzug to see if 17 my memory is accurate. Way back in the '90s when the 18 pleconaril study -- when we developed it and we had to 19 define what severe hepatitis was, what severe DIC was, 20 what severe myocarditis was, my recollection is that 21 we kind of made it up. 22 I mean, we kind of -- we kind of used a</p>

<p style="text-align: right;">Page 258</p> <p>1 threshold that we thought would define a severe -- a 2 severe baby; but it wasn't based upon a prior study 3 that showed that, you know, 3.5 fold over baseline is 4 -- is really bad versus 3.4 over baseline being not so 5 bad.</p> <p>6 So there was -- as we look at what has 7 been in the literature, I think we have to have some 8 grace with respect to -- there -- there could be some 9 variability. It's not written in stone simply because 10 that's the way it was defined once that that's the way 11 severe disease has to be defined going forward.</p> <p>12 Mark, do I -- do I have a faulty memory 13 on that?</p> <p>14 DR. ABZUG: No, 'cause your memory is 15 better than mine. But -- but I'll -- I'll add that 16 there's -- there were some preexisting data. We and 17 others have written case -- had written case series 18 where we described our sick population, and these were 19 the kinds of lab findings or parameters that -- that 20 describe them.</p> <p>21 But -- but there isn't in the 22 literature that finer gradation to say that 2X normal</p>	<p style="text-align: right;">Page 260</p> <p>1 DR. ABZUG: This is Mark. I'll start. 2 Well, if -- if you believe the study from the -- the 3 pleconaril study that we talked about earlier this 4 morning, I believe we showed a mortality benefit. It 5 didn't meet all of the rigor that we would have liked 6 and that the FDA would have liked.</p> <p>7 But I think at least as proof of 8 concept it did show that treating those sickest babies 9 was beneficial, and I -- as far as I know, 10 pleconaril's activity is purely as an antiviral. So 11 that suggests to me that antiviral therapy at that 12 stage of illness can be effective.</p> <p>13 DR. BELEW: Thank you for that -- 14 DR. ABZUG: I welcome other opinions. 15 DR. BELEW: It sounds like you have the 16 final word on the -- on the question, Dr. Abzug. 17 DR. PICA: Just as a follow-up, maybe 18 looping back to the comment that Dr. Kimberlin had 19 made earlier, what -- what questions do you think 20 could be answered from larger natural-history studies 21 with -- in regard to understanding appropriate 22 populations and trial endpoints?</p>
<p style="text-align: right;">Page 259</p> <p>1 LFT is different from 3X normal LFT. We just picked 2 the ones that had been described, but -- but not -- 3 but there had not been a full analysis of different 4 gradations of those abnormalities, if that makes 5 sense.</p> <p>6 DR. VISWANATHAN: This is Prabha 7 Viswanathan. I have a question to our clinical 8 experts in the room, and this is tying together 9 comments from -- from many people. One question for 10 Amy Rosenfeld though is -- is: What can we ask of an 11 antiviral?</p> <p>12 So it is clear that the disease course 13 is heterogeneous. The rate of clinical deterioration 14 is heterogeneous, but is there a point that we reach 15 where we think that an antiviral really is not likely 16 to help a child?</p> <p>17 So if we have a child who has 18 myocarditis with heart failure, a child with liver -- 19 like, full liver failure, are these groups of patients 20 that you feel like are -- are too severe to include in 21 your clinical trial and may impact your ability to 22 have a successful primary endpoint?</p>	<p style="text-align: right;">Page 261</p> <p>1 Do you think that the disease is so 2 heterogeneous that the data will be hard to interpret, 3 or -- or are there goals for these natural-history 4 studies in the context of -- of designing clinical 5 trials?</p> <p>6 DR. ABZUG: Dr. Kimberlin, do you want 7 to start with that one?</p> <p>8 DR. KIMBERLIN: Yeah. I'd be happy to. 9 I -- I think we can always learn more, and I think 10 more information, more data are better than -- than 11 less. I -- I think that we -- that -- that many of 12 the good points raised about, you know, is -- is a 13 particular, you know, coxsackievirus worse in neonates 14 than another, you know, echovirus is?</p> <p>15 To -- to some extent, I -- I appreciate 16 it, but if we -- if we stay in that rabbit hole, we 17 don't ever have the opportunity to move into a 18 clinical trial to see if an antiviral works.</p> <p>19 And I remember with the pleconaril 20 trial design back in the '90s there -- there was one 21 very smart person who was advocating strongly that, 22 "100 different enteroviruses, we can't do this --</p>

<p style="text-align: right;">Page 262</p> <p>1 can't do it." 2 And -- and maybe that's the right 3 answer; but ultimately, I -- I kind of agree with Mark 4 that we did show a benefit, albeit in a Phase 2 study 5 that was never in -- you know, intended to be a 6 licensure trial. 7 Nevertheless, the data -- I think the 8 story told would, to me anyway, suggest that -- that 9 it works for that particular drug in -- in that 10 population. 11 So -- so I -- I think that we -- we 12 don't have to -- what is the phrase? You know, you 13 don't -- don't let the -- the good be the enemy, the 14 perfect -- or whatever it is. You know what? Let -- 15 let's -- let's kind of get our -- roll up our sleeves 16 and -- and move forward with what we have. 17 And if -- if additional information 18 comes out through natural-history studies and others 19 down the road, that's fine; and we can make 20 modifications as needed; but let's not just sit back 21 and wait for it if we have a drug that has the 22 potential that really could move forward and move the</p>	<p style="text-align: right;">Page 264</p> <p>1 comment? 2 DR. HINCKS: Yeah. I guess it comes to 3 the next point that we might be talking about, but 4 what about using the natural-history study as the 5 comparator arm to an active trial? 6 That was for Mark, David. 7 DR. PICA: If no one has anything to 8 add right at the moment, you know, I think that your 9 question will be a great segue into our final question 10 for this panel discussion; but we did have a couple Q- 11 and-As from online that we wanted to get to regarding 12 the -- the topic that -- that we've already covered. 13 So maybe I'll go to those first, and 14 then we can -- can move on altogether then and -- and 15 go into that last discussion topic. So we -- I 16 promise we will come back to you, Dr. Hincks. 17 But going to the -- the Q-and-A briefly 18 here, so we had several comments in here -- and 19 apologies. We will not be able to address all of -- 20 of the comments, but I wanted to -- I wanted to read 21 out one comment, not really a question but, I think, 22 an -- an important comment to share with the group.</p>
<p style="text-align: right;">Page 263</p> <p>1 field. 2 DR. ABZUG: And I'll add that -- that 3 I'm -- I'm really very hopeful, 'cause I'm an 4 optimist, that the current natural-history study will 5 tell us something about the value of quantitative PCR 6 in this disease. I come from a background of treating 7 children with HIV; and as we all know, that marker has 8 proved incredibly useful. 9 So whether it's as -- useful as a 10 predictor of babies who are destined to have worse 11 outcomes, which then helps us identify who should be 12 treated and who shouldn't be treated, or whether it's 13 value as an endpoint of -- of treatment because it has 14 predictive value of outcome, I don't know; and 15 maybe -- maybe it'll help with both. 16 But if we can identify something like 17 that through natural-history studies that then make 18 mortality -- while obviously an important endpoint, 19 not the only endpoint that we need to strive for 20 and -- and hopefully an -- an easier-to-achieve 21 endpoint, then I think that will be a major gain. 22 DR. PICA: Dr. Hincks, did you have a</p>	<p style="text-align: right;">Page 265</p> <p>1 So we had an attendee who says: "I 2 think it is important to separate the idea of trials 3 to license a drug from trials to optimize treatment. 4 A company wants one thing from a trial for licensure, 5 which is a license within a reasonable time. 6 It is utterly unrealistic to expect an 7 industry-supported trial to look more -- to look at 8 more complex endpoints that will take more patients, 9 read higher costs, and take more time to license a 10 drug." 11 And I think these are all very fair 12 points; and, you know, the focus of today is really to 13 talk about that licensure issue; but -- but you're 14 right. There are two different objectives there. 15 And then another question that came in 16 that we've somewhat touched on here but just wanted to 17 -- to close the loop on, so we have a question: "Have 18 any studies looked into risk-based scoring models to 19 predict severe illness? Perhaps a composite of 20 different risk factors?" 21 I know we've been talking about how 22 this would be really advantageous if we had such</p>

<p style="text-align: right;">Page 266</p> <p>1 predictors to identify those at risk for more severe 2 illness, but does anybody have anything else to add on 3 that line of -- of thinking? 4 Anything from the real world or from 5 the natural-history studies that are -- that are 6 ongoing that could be used to further look into this? 7 And I will stop there. 8 DR. ABZUG: You know, as I showed 9 earlier in my -- my talk, people have identified some 10 predictors; but I have not seen a composite-scoring 11 model to specifically look at the risk of severe 12 neonatal enterovirus disease. 13 That is a potential outcome from the -- 14 from the ongoing natural-history study. We're 15 collecting a lot of clinical and laboratory data. So 16 we certainly can look to see if something like that is 17 able to be derived from the dataset. 18 DR. PICA: Thank you. Does anyone have 19 any other comments on the population discussion before 20 we move on? 21 DR. VOGT: I mean, I guess just so that 22 my silence isn't, you know, seen as opposition, I</p>	<p style="text-align: right;">Page 268</p> <p>1 But it's a -- it's a lot easier to sit 2 down and say, "Your baby will get the drug either 3 because everybody is getting treated at the same 4 dose"; and -- and maybe there's natural history or 5 comparators, as -- as Dr. Hincks was suggesting. 6 Maybe the natural-history study could provide -- or I 7 -- I come back to what I said before. 8 If a drug has not been studied in 9 babies and we have modeling data and we -- you know, 10 we think we know what dose to use but it hasn't been 11 studied, that's the reason we're doing the trial. 12 Maybe something -- this is a new concept to me, and 13 I'm -- I'm developing it as I'm saying it out loud. 14 But multiple doses of the active drug, 15 some of which are the sweet spot, based upon -- that 16 we anticipate based upon the modeling data, but also a 17 little bit above and some below that too, some of 18 which may be based upon modeling data, are -- are 19 anticipated to be subtherapeutic. 20 If they're subtherapeutic, they're not 21 going to work. That's your placebo. That's your 22 comparator, or you look across the spectrum of the</p>
<p style="text-align: right;">Page 267</p> <p>1 mean, I think that makes a lot of sense. We have a 2 rare disease. It's really hard to get that comparator 3 population. 4 And maybe Dr. Kimberlin is working on 5 that comparator population right now. I think it 6 seems pretty reasonable, just to support what Dr. 7 Hincks had said. 8 DR. PICA: Great. So I think in the 9 remaining minutes we could maybe try to discuss the 10 most appropriate comparator-treatment groups, and I -- 11 I open the floor to either Dr. Hincks or Dr. Kimberlin 12 to start us off. 13 DR. KIMBERLIN: I'd be happy to, and -- 14 and I -- I guess the -- the theme I would -- I would 15 advocate for, if possible, is to find a creative study 16 design that would not require a placebo. 17 Enrolling even a 2-to-1 randomization 18 or a 3-to-1 randomization on a placebo-controlled 19 trial when a family's 7- or 8-day-old baby is 20 critically ill is -- it -- it can be done, especially 21 if the drug is not available otherwise, through 22 compassionate use or something along those lines.</p>	<p style="text-align: right;">Page 269</p> <p>1 amount of drug exposure you're achieving and correlate 2 that with viral load, or you correlate that with 3 outcome of some kind or a series of outcomes. 4 Something creative like that would -- 5 would help, I think, with getting a study that not 6 only reads well but actually implements well and has a 7 chance of enrolling. 8 DR. HINCKS: I -- I definitely agree 9 that designing a study without a true placebo control 10 would enroll a lot faster, and I just think -- I mean, 11 I hate using that "unethical" word; but it -- it seems 12 unethical, similar to oncology studies where all -- 13 all, you know, patients get treated. 14 But again, it's -- it's -- what is that 15 comparator arm, is the key; and would FDA accept a 16 non-placebo comparator? 17 DR. PICA: Dr. Vogt? 18 DR. VOGT: I mean, I think we're 19 already doing this -- right -- this non-placebo 20 controlled trial with pocapavir; and we just call it 21 expanded access or, you know, compassionate use; and I 22 don't say that to be inflammatory or anything like</p>

<p style="text-align: right;">Page 270</p> <p>1 that; but that's kind of how it's done; right?</p> <p>2 So, you know, Dr. Kimberlin or I have a</p> <p>3 baby in front of us that we're very concerned about</p> <p>4 and enterovirus-positive and that sort of thing; and,</p> <p>5 you know, we call them up and say, "Hey, man, let's --</p> <p>6 let's give them this drug, please"; and so we do it.</p> <p>7 There's no placebo in that, but there's</p> <p>8 also no -- there's no real rigorous trial design to</p> <p>9 that either; right? It's just the whim of particular</p> <p>10 investigators who take it upon themselves to, you</p> <p>11 know, call up the company and say, "Hey, Dr. Hincks,</p> <p>12 can we have your drug?"</p> <p>13 So I think we're already doing it. It</p> <p>14 makes a lot of sense to me to try to do it a little</p> <p>15 bit more prospectively with a little bit more design</p> <p>16 behind it. I think when we think of it that way --</p> <p>17 again, I'm kind of thinking this out loud just the way</p> <p>18 that Dr. Kimberlin was -- was thinking out loud</p> <p>19 earlier.</p> <p>20 But it sure makes sense to me that I</p> <p>21 would rather see a non-placebo-controlled trial that</p> <p>22 has been prospectively designed and implemented rather</p>	<p style="text-align: right;">Page 272</p> <p>1 apologies for that. This is Prabha Viswanathan again</p> <p>2 from FDA. There's a lot to unpack here; but clearly,</p> <p>3 there are hesitations about placebo control.</p> <p>4 And I would like to hear more about</p> <p>5 what -- whether the hesitation is -- is parental --</p> <p>6 it's a concern of parental refusal for enrollment,</p> <p>7 whether this is really on the provider side, feeling</p> <p>8 that it's infeasible or unacceptable from a scientific</p> <p>9 perspective.</p> <p>10 And then I want to remind everyone that</p> <p>11 we -- we have an obligation to the patients and the</p> <p>12 families who enroll in these clinical trials to</p> <p>13 conduct trials that are -- that are interpretable,</p> <p>14 that in the end when we enroll children and expose</p> <p>15 them to investigational product there needs to be a</p> <p>16 real end there that we can -- we know what to do with</p> <p>17 the data that we have.</p> <p>18 And without a comparator, it's very</p> <p>19 hard to know whether these drugs really work. So we</p> <p>20 certainly want to dialogue with you about -- about</p> <p>21 different solutions for how we get interpretable data;</p> <p>22 and I think part of that is, it's important to</p>
<p style="text-align: right;">Page 271</p> <p>1 than compassionate use, which is kind of the same</p> <p>2 thing but just way more willy-nilly 'cause I do worry</p> <p>3 that when we do that compassionate-use stuff that, as</p> <p>4 has been raised before, just the -- the organ damage</p> <p>5 is just so far gone by the time we give the drug.</p> <p>6 I worry that we're going to miss --</p> <p>7 that we're going to miss potential benefits that we</p> <p>8 otherwise might see if we weren't just, you know --</p> <p>9 'cause it takes -- it's -- it's not an instant thing.</p> <p>10 We don't just call the drug company, and they send the</p> <p>11 drug that day.</p> <p>12 I mean, it's -- I will give them</p> <p>13 credit. I've had colleagues who've done this, and it</p> <p>14 seems pretty well streamlined compared to maybe some</p> <p>15 other expanded-access stuff I've been exposed to. So</p> <p>16 that's not a knock. It's just the way it is. It's --</p> <p>17 it's a very hard thing to do, a lot of paperwork and</p> <p>18 stuff.</p> <p>19 And -- and I'd love to hear from</p> <p>20 anyone, especially Dr. Hincks on the company side, his</p> <p>21 perspective on that.</p> <p>22 DR. VISWANATHAN: Hi, this is --</p>	<p style="text-align: right;">Page 273</p> <p>1 understand what are the real factors limiting</p> <p>2 enrollment.</p> <p>3 Is it the concern that my child is not</p> <p>4 going to get something that works? We -- we only do</p> <p>5 trials when there is clinical equipoise about whether</p> <p>6 the trial -- whether the drug really will impact the</p> <p>7 endpoint that we're studying. Otherwise, we wouldn't</p> <p>8 do the trial. We would already know the answer; and</p> <p>9 in this case, we don't.</p> <p>10 So for anybody who cares to respond,</p> <p>11 I'd like to go back to that a little bit and talk</p> <p>12 about what are the factors that are -- that are</p> <p>13 keeping us from doing placebo-controlled trials.</p> <p>14 DR. KIMBERLIN: Well, I might -- I</p> <p>15 might start with that. My impression or experience is</p> <p>16 that the bigger barrier is -- is with the parents.</p> <p>17 Think about it.</p> <p>18 If, you know, your 10-day-old is -- is</p> <p>19 critically ill and somebody comes to you and says: "I</p> <p>20 can -- you can enroll on this study that's placebo</p> <p>21 controlled. There's a three-to-one chance you're</p> <p>22 going to get active drug. We're going to take all</p>

<p style="text-align: right;">Page 274</p> <p>1 this blood. We're going to do all these things, or I 2 could call Company X and get it compassionate use, and 3 -- and we'll get it tomorrow. What do you want to 4 do," a different drug probably, although sometimes 5 this is -- if there is a compassionate-use program, 6 that can -- with -- with the same drug, that can be -- 7 that can be a disincentive as well. 8 And they're going to generally -- not 9 generally, but a lot of times they will take the -- 10 the path of: "I want the real thing. I want what has 11 a chance of working." 12 I do fully appreciate what you're 13 saying about the ethics of -- of the -- of -- of 14 enrolling and exposing -- enrolling babies, exposing 15 them to a -- to an investigational product when 16 there's -- when there's a chance that we won't know 17 how to interpret the data. 18 But again, I come back to this idea 19 that -- what if we do a range of exposure, and you see 20 a range of response so that the worst outcomes are 21 when there's very little or subtherapeutic exposure? 22 Best outcomes is when you get really good drug</p>	<p style="text-align: right;">Page 276</p> <p>1 And so, you know, it's possible that 2 100 milligrams of the drug and 20 milligrams of the 3 drug in a baby, because of the difference in the way 4 it's metabolized, the 20 milligrams is as good as 100 5 milligrams. We don't know that. 6 And if we only come in with 100 versus 7 placebo, we'll never know that; but if we give a range 8 of exposure, including some that's on the very low 9 side, I think it's -- it's an ethically sound thing to 10 do, as I'm just kind of developing the concept or -- 11 you know, in -- in midstream here, and I -- I think it 12 definitely is easier for the family. 13 I mean, if the family says: "Yeah. 14 You're going to be getting the drug" -- or you say to 15 the family: "You're going to be getting the drug. We 16 don't know the dose you're going to be getting, but 17 you will be getting the drug," that is a much easier 18 thing to -- a much easier discussion to have. 19 DR. VISWANATHAN: I'll just add -- 20 we -- we definitely endorse dose-ranging trials, and 21 it is possible that we -- we end up with doses that 22 have enough similar activity, or you can cap out at</p>
<p style="text-align: right;">Page 275</p> <p>1 exposure. 2 That in and of itself within one single 3 treatment study could provide its own comparator that 4 would be placebo-ish, if you will. 5 DR. VISWANATHAN: I'd like to just 6 briefly respond to that, and then I'll hand it over to 7 Dr. Vogt. I -- I just am not sure what the difference 8 is practically from having a micro subtherapeutic dose 9 versus a placebo. Is it just telling the -- the 10 family that you're getting something? 11 But if it's something that you don't 12 think is actually going to work, isn't that just a 13 placebo that also exposes a baby to potential 14 toxicity? 15 MR. KIRSCH: That -- that's certainly 16 an argument; but the point is, we don't know the dose. 17 If we did -- if we knew the dose and we knew that it 18 worked, then yes. That would be -- that -- that would 19 be a problem, but we don't know that. 20 There is a -- at -- at least with -- 21 with the kind of point in drug development that I'm -- 22 that I'm envisioning as I make this argument.</p>	<p style="text-align: right;">Page 277</p> <p>1 your -- at your therapeutic dose. 2 But you may not be able to appreciate 3 the difference between treatment arms, but we 4 certainly do endorse trials that investigate multiple 5 doses for potentially multiple durations so that we 6 arrive at that -- at that correct dose. 7 I know that there are a number of 8 people who are waiting to speak, and I believe Dr. 9 Vogt is next. 10 DR. VOGT: I think I'm -- I'm in 11 agreement. I -- I don't know the difference between 12 the homeopathic dose and just a straight-on placebo 13 dose other than to be able to say something to the 14 family that, you know, there's medicine in here. 15 And personally, I actually kind of find 16 that a bit troubling to try to, you know, convince 17 them there might be some -- some benefit when you 18 actually kind of know that it's -- it's more or less a 19 homeopathic dose. 20 But I -- I see where you're going, 21 David. Like, you know, again, this is -- this is -- 22 it's an awkward forum because it's online, and we're</p>

<p style="text-align: right;">Page 278</p> <p>1 sort of taking turns on our camera. 2 I'd like to think in real life we'd 3 probably be, like, you know, chatting this out, you 4 know, one -- going -- going around the table pretty 5 quickly, working through these ideas because I -- I do 6 like the idea that -- I guess to clarify what I had 7 said earlier about, you know, wanting to have a not- 8 placebo-controlled trial, I think I meant that more 9 just in direction opposition to having the 10 availability of -- of something by compassionate use 11 at the same time. 12 To me, it feels like there should be 13 one or the other. 14 And if I'm given the choice, I'd rather 15 have a prospectively -- prospectively designed no- 16 placebo trial than compassionate use 'cause at least I 17 have -- I think I have a better chance at interpreting 18 the data that comes out of the prospectively designed 19 trial than just us again just sort of based on the 20 whim. 21 It's -- it's -- it gets -- it's -- so 22 as a -- maybe as a comparator, when earlier we were</p>	<p style="text-align: right;">Page 280</p> <p>1 have a number of hands up; but before we jump in, I 2 just wanted to follow up on the comments that Dr. Vogt 3 and Dr. Viswanathan made. So with -- with respect to 4 the -- the looking at various doses, that is a very 5 typical drug development in many disease therapeutic 6 areas, including viral diseases. 7 But the difference, I would say, is, 8 you wouldn't intentionally study a dose that is a 9 microdose or lower than what you -- at least based on 10 invitro or cell contra-activity that you think is 11 lower than the minimal effective dose, at least based 12 on the nonclinical data. 13 And so the -- the dose finding is a 14 very reasonable Phase 2 looking at optimal-dose 15 selection; and I think that would be a reasonable 16 consideration, again, provided that ultimately we do 17 have a comparator arm in order to establish the 18 treatment benefit from the antiviral. 19 With -- with respect to the 20 compassionate use, the availability of compassionate- 21 use programs at the same time as when you're trying to 22 enroll patients into placebo-controlled clinical</p>
<p style="text-align: right;">Page 279</p> <p>1 talking about the epidemiology of enteroviruses this 2 morning, you know, there's those passive systems where 3 we get some data; and there's good data there. It's 4 not like that's useless data. There's absolutely good 5 data there. 6 And then there's the prospective 7 systems, and maybe that data gives us a little bit 8 higher quality or a little bit more precision for 9 certain other types of questions. I think when it 10 comes to rare diseases, I mean, this is that -- this 11 is why we're having a whole two-day symposium on it, 12 as this is tough. 13 But I do think that trying to interpret 14 compassionate use is tougher than it would be if we 15 had, you know, a trial that was no placebo. 16 That said, I'm going to talk about the 17 unicorn, which I said before I'd rather us hit a lot 18 of kids before they get super-duper sick and prevent 19 them from ever getting super-duper sick; but that's 20 maybe derailing this conversation too far. So maybe 21 forget I said that. 22 DR. BELEW: This is Yodit Belew. We</p>	<p style="text-align: right;">Page 281</p> <p>1 trials, just to kind of put this out there for the 2 group to discuss and consider is, you know, going back 3 to the ideal population and potentially the severity 4 of the illness at the time of enrollment. 5 What would you think about if, for 6 example, compassionate use would be limited to those 7 who are severely ill and don't meet eligibility 8 criteria to enroll into the clinical trial and the 9 clinical trial perhaps would focus on populations that 10 may be less critically ill? 11 And I don't know who had their hands up 12 first; but just going from left to right, Dr. Abzug? 13 DR. ABZUG: Thank you. I'm -- I'm not 14 sure which question I'm responding to now, but I'll 15 say a couple of things. 16 One additional flaw with the low- 17 medium-high trial design where all the arms are active 18 is if the outcomes are the same amongst the three 19 groups. You don't know if everybody derived benefit 20 or no one derived benefit. So that's -- that's a 21 problem. 22 Dr. Hincks mentioned, I think, whether</p>

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1 the natural-history study could be an appropriate
 2 comparator, if you will, of historical control but at
 3 least a contemporary-era historical control. I -- I
 4 think that's a possibility, except that we would have
 5 to subtract out those subjects who received a
 6 compassionate-use agent.
 7 And then now -- now remind me of the
 8 most recent question that you posed. Oh, people who
 9 don't meet inclusion criteria and get the
 10 compassionate use but others can't. I think that's a
 11 valid approach.
 12 I'll -- I'll tell you that when the
 13 pleconaril randomized study was going on we had it
 14 opened at one tertiary-care center in our city; but it
 15 wasn't opened at another tertiary-care center, which
 16 is a different hospital system in our same city.
 17 And before compassionate use would have
 18 been available, that baby might have been transferred
 19 to our hospital for the study; but when an alternate
 20 mechanism of having 100-percent access to the study
 21 drug was available, that removed the incentive for
 22 transferring the baby to the -- the center with the

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1 active study.
 2 So it -- it even gets murky when you
 3 try to define who meets or doesn't meet inclusion
 4 criteria because usually inclusion criteria for a
 5 study means being at a center where that study is
 6 available and open. Thanks.
 7 DR. PICA: Thank you very much for
 8 that. So I -- I -- we are running out of time; but
 9 given all of this robust discussion regarding use of
 10 natural-history data, we would like to give our real-
 11 world-evidence expert, Dr. Concato, an opportunity to
 12 comment.
 13 But before I turn it over to Dr.
 14 Concato, I did want to just read one of the comments
 15 in the Q-and-A from an attendee that I think is a nice
 16 segue for this.
 17 So the comment states: "Regarding the
 18 conversation about using the natural-history study as
 19 a comparison group, it seems like there would be an
 20 inherent bias because parents might be more likely to
 21 enroll in a new investigational drug trial if their
 22 child was sick and the current management wasn't

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1 working well, whereas many more patients' parents
 2 might agree to participate in a natural-
 3 history/observational study.
 4 It seems like it would bias towards
 5 underestimating the benefit of the treatment being
 6 studied." And so I think this highlights some of the
 7 many inherent challenges with natural-history data;
 8 and with that, I will turn it over to Dr. Concato to
 9 see what -- what comments he would like to make.
 10 DR. CONCATO: Thank you, and I'll --
 11 I'll leave my camera off as well due to connectivity
 12 issues, and yes. That was indeed a nice segue. I was
 13 already raising my hand to make a comment about the
 14 possible use of a comparator arm for a single-arm
 15 trial, whether it's the natural-history study that was
 16 mentioned or other sources of data.
 17 And unfortunately, I know no pleasure
 18 in saying this. The challenges are pretty -- pretty
 19 common. You know, oncology was mentioned; but the
 20 endpoint for oncology tumors don't tend to shrink.
 21 I'm an internist, not a pediatrician or
 22 a neonatologist; but listening to the earlier

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1 presentations the heterogeneity both within an organ
 2 system and across organ systems, CNS, heart, liver,
 3 lung, this is quite challenging to imagine how
 4 comparability is going to be assured, which is the
 5 crux of the matter for an externally controlled child.
 6 I will refer to an externally
 7 controlled child guidance that CDER, CBER, or OCE
 8 published last year for our -- our current thinking in
 9 this regard; and in particular, I don't have it open
 10 on my other monitor; but what comes to mind is the
 11 table of comparability.
 12 There's more than one way to -- to
 13 organize one's thinking; but I believe we settled on
 14 ten different domains; and just off the top of my
 15 head, again, deferring to the clinical division about
 16 whether this makes clinical sense or not.
 17 But even if it doesn't matter which
 18 enterovirus, at least even with a small child, you
 19 tend to get balance; but we believe we know which --
 20 which viruses were involved, would they be the same;
 21 but more -- more fundamentally, prognosis, as I
 22 mentioned, would be very -- very heterogeneric --

<p style="text-align: right;">Page 286</p> <p>1 heterogeneous.</p> <p>2 Even something as straightforward as</p> <p>3 the outcome, what is the endpoint; and is it measured</p> <p>4 the same in the single-arm trial versus the natural-</p> <p>5 history study? Supportive therapy could vary.</p> <p>6 And I think the -- I didn't see the</p> <p>7 question in the chat. I was getting -- preparing</p> <p>8 myself to -- to make a more general comment, but I</p> <p>9 think the commenter also had another concern.</p> <p>10 So again, our bar is -- is singular.</p> <p>11 Our evidentiary threshold is the same. We have</p> <p>12 regulatory flexibility, but it would take an awful lot</p> <p>13 of things to go well for an externally controlled</p> <p>14 trial to work out.</p> <p>15 That doesn't mean we shouldn't explore</p> <p>16 the possibility; but again, a -- sometimes a small</p> <p>17 randomized trial is better than a larger externally</p> <p>18 controlled trial because it conserves for bias. Thank</p> <p>19 you.</p> <p>20 DR. PICA: Thanks so much for that.</p> <p>21 Dr. Hincks, I -- I think you've had</p> <p>22 your hand up for quite a bit.</p>	<p style="text-align: right;">Page 288</p> <p>1 there's an ethical quandary there because if we really</p> <p>2 don't think it works and we're telling the patients --</p> <p>3 or we -- we think we'll get better enrollment because,</p> <p>4 you know, they -- they think it works, that's -- that</p> <p>5 -- that would be viewed as deceiving the patients.</p> <p>6 I mean, it's not only equipoise. It's</p> <p>7 also the standard of care. The drug could actually do</p> <p>8 more harm than good, which unfortunately sometimes is</p> <p>9 the case. So I'll -- I'll defer to the clinical</p> <p>10 trialists, but.</p> <p>11 DR. KIMBERLIN: And if I could respond</p> <p>12 to it, I -- I -- as I was developing the concept in</p> <p>13 real time, I guess one caveat, which may not sway</p> <p>14 people, this would not be a Phase 3 study I'm talking</p> <p>15 about. This wouldn't be where the drug had been --</p> <p>16 the dose had been determined in Phase 1.</p> <p>17 You've done a Phase 2 for, you know,</p> <p>18 feasibility and whether or not there's enough clinical</p> <p>19 evidence to move forward; and then you go to Phase 3.</p> <p>20 This would be more of a Phase 2A-ish level where</p> <p>21 you're still working on what the dose is, and you're</p> <p>22 trying to get with one trial enough information --</p>
<p style="text-align: right;">Page 287</p> <p>1 DR. HINCKS: Sure. So again, there's</p> <p>2 several questions that have been raised. The -- the</p> <p>3 one regarding compassionate use, Mark mentioned the</p> <p>4 issues that he had with pleconaril. We ended up</p> <p>5 shutting that down because it was an issue.</p> <p>6 We were getting a lot of calls for</p> <p>7 compassionate use because they didn't want to deal</p> <p>8 with the clinical trial. So I don't think that could</p> <p>9 continue if there's a clinical trial ongoing.</p> <p>10 As far as the various doses, there's a</p> <p>11 lot of variable already, as we mentioned: disease</p> <p>12 state, virus, viral load. Adding multiple doses on</p> <p>13 top of that, I think, would just dilute out any</p> <p>14 effects that we're trying to look for. My opinion is,</p> <p>15 you go in with your highest, safest dose to show</p> <p>16 effect. I think that was it for now. Responses?</p> <p>17 DR. CONCATO: As a nonclinical trialist</p> <p>18 -- this is Dr. Concato again -- I'll just say that</p> <p>19 I -- I agree that coming in with the dose that you</p> <p>20 think works.</p> <p>21 And also, a problem with the giving</p> <p>22 homeopathic doses, I think others have mentioned</p>	<p style="text-align: right;">Page 289</p> <p>1 DR. CONCATO: Then -- then it works.</p> <p>2 DR. KIMBERLIN: -- to get a drug --</p> <p>3 DR. CONCATO: Yeah.</p> <p>4 DR. KIMBERLIN: -- across the finish</p> <p>5 line.</p> <p>6 DR. CONCATO: Yeah. Thank you. And by</p> <p>7 the way, I hit the wrong button. My apologies. I was</p> <p>8 trying to type in an answer to the propensity-score</p> <p>9 question.</p> <p>10 So in fairness to the person who asked,</p> <p>11 propensity scores are indeed how externally controlled</p> <p>12 trials and observational studies would be done; but</p> <p>13 it's not a magic bullet.</p> <p>14 So the -- the data either do or do not</p> <p>15 support the comparability issue, and -- and we -- we</p> <p>16 can't wave a magic wand and have propensity scores</p> <p>17 provide comparability if it's not there to begin with.</p> <p>18 Thank you. Sorry for not typing it in the chat -- in</p> <p>19 the Q-and-A, I should say.</p> <p>20 DR. PICA: Thank you. Thank you for</p> <p>21 that answer.</p> <p>22 Wow, this has just been such robust</p>


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1 discussion. Thank you to all of our speakers and
 2 panelists for your participation, and many thanks to
 3 our meeting organizers and AV team for providing
 4 support today.
 5 We look forward to welcoming you all
 6 back tomorrow for Day 2 of the workshop tomorrow at 9
 7 a.m. Thanks so much.
 8 (Whereupon, the meeting concluded at
 9 3:30 p.m.)
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1 CERTIFICATE OF TRANSCRIBER
 2 I, SHANE WILLIAM SPRAWL, do hereby certify
 3 that this transcript was prepared from the digital
 4 audio recording of the foregoing proceeding, that said
 5 transcript is a true and accurate record of the
 6 proceedings to the best of my knowledge, skills, and
 7 ability; that I am neither counsel for, related to,
 8 nor employed by any of the parties to the action in
 9 which this was taken; and, further, that I am not a
 10 relative or employee of any counsel or attorney
 11 employed by the parties hereto, nor financially or
 12 otherwise interested in the outcome of this action.
 13
 14 
 15 SHANE WILLIAM SPRAWL
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1 CERTIFICATE
 2 I, ALEXANDRA HOBRECHT, the officer before
 3 whom the foregoing proceedings were taken, do hereby
 4 certify that any witness(es) in the foregoing
 5 proceedings, prior to testifying, were duly sworn;
 6 that the proceedings were recorded by me and
 7 thereafter reduced to typewriting by a qualified
 8 transcriptionist; that said digital audio recording of
 9 said proceedings are a true and accurate record to the
 10 best of my knowledge, skills, and ability; that I am
 11 neither counsel for, related to, nor employed by any
 12 of the parties to the action in which this was taken;
 13 and, further, that I am not a relative or employee of
 14 any counsel or attorney employed by the parties
 15 hereto, nor financially or otherwise interested in the
 16 outcome of this action.
 17 
 18 ALEXANDRA HOBRECHT
 19 Notary Public in and for the
 20 State of Michigan
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