UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

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OFFICE OF THE COMMISSIONER

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PEDIATRIC ADVISORY COMMITTEE MEETING

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September 19, 2023

9:00 a.m. EST

Via Web Conference

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Participants

Chairperson	Robert Dracker, MD, MHA, MBA, CPI	Associate Professor, Department of Pediatrics & Pathology, SUNY Upstate Medical College; Owner & Medical Director, Summerwood Pediatrics; Founder & Medical Director, Infusacare Medical services, P.C.	Syracuse, NY
Voting Members	Susan S. Baker, MD, PhD	Professor of Pediatrics, University of Buffalo, The State University of New York	Buffalo, NY
	Angela Czaja, MD, MSc, PhD	Associate Professor, Division of Critical Care, Department of Pediatrics, School of Medicine, University of Colorado	Aurora, CO
	Douglas Diekema, MD, MPH	Professor, Department of Pediatrics; Adjunct Professor, Department of Bioethics & Humanities, University of Washington, School of Medicine	Seattle, WA
	Gwenyth Fischer, MD	Associate Professor of Pediatric Critical Care; Associate Chair, Pediatric Research Partnerships; Director, Pediatric Device Innovation Consortium, University of Minnesota, College of Medicine	Minneapolis, MN
	Charleta Guillory, MD, MPH	Director, Neonatal-Perinatal Public Health Program, Texas Children's Hospital; Professor of Pediatrics, Department of Pediatrics, Section of Neonatology, Baylor College of Medicine	Houston, TX
	Richard Holubkov, PhD	Professor, Division of Critical Care, Department of Pediatrics, University of Utah	Salt Lake City, UT
	Steven Krug, MD	Former Head, Division of Emergency Medicine, Ann & Robert H. Lurie Children’s Hospital of Chicago; Professor of Pediatrics, Feinberg School of Medicine, Northwestern University	Chicago, IL
	Roberto Ortiz-Aguayo, MD, MMM	President and Chief Medical Officer, Complete Mind Care of PA	Abington, PA
	Michael White, MD, PhD	Pediatric Cardiologist, Ochsner Health System	New Orleans, LA

Patient-Family Representative (Voting)	Gianna McMillan, DBe	Associate Director, Bioethics Institute, Loyola Marymount University	Los Angeles, CA
Consumer Representative (Voting)	Randi Oster, MBA	Co-Founder and CEO, Help Me Health	Fairfield, CT
Pediatric Health Organization Representative (Non-Voting)	Jennifer Goldman, M.D., M.S.	Associate Professor, University of Missouri-Kansas City; Associate Program Director, Pediatric Clinical Pharmacology Fellowship, Department of Pediatrics, Children's Mercy Hospital	Kansas City, MO
Industry Representative (Non-Voting)	Robert Nelson, MD, PhD	Senior Director, Pediatric Drug Development, Child Health Innovation Leadership Department (CHILD), Johnson & Johnson	Raritan, NJ
Temporary Voting Members	Jeffrey Botkin, MD, MPH	Professor Emeritus of Pediatrics, University of Utah	Salt Lake City, UT
	Francis Sessions Cole, MD	Park J. White, M.D., Professor of Pediatrics; Professor of Cell Biology & Physiology, Washington University School of Medicine	St. Louis, MO
	Jonathan Davis, MD	Attending Neonatologist, Boston Children’s Hospital; Professor of Pediatrics, Tufts University School of Medicine; Chief of Newborn Medicine, Tufts Medical Center	Boston, MA
	Jeffrey Feinstein, MD, MPH	Director, Vera Moulton Wall Center for Pulmonary Vascular Disease, Stanford University Medical Center; Medical Director, Pediatric Pulmonary Hypertension Program, Lucile Packard Children’s Hospital; Professor of Pediatrics, Stanford University School of Medicine	Stanford, CA
	Christine Gleason, MD	Professor Emerita of Pediatrics, University of Washington	Seattle, WA
	Washington Hill, MD	Senior Physician, CenterPlace Health; Obstetrics & Gynecology/Maternal-Fetal Medicine; Professor, Department of Obstetrics & Gynecology, University of South Florida	Tampa, FL
	Sarah Hoehn, MD, MBe, FAAP	Chief Medical Officer, La Rabida Children’s Hospital	Chicago, IL

	Jennifer Lee-Summers, MD	Professor, Department of Pediatrics, Division of Pediatric Anesthesia, Department of Anesthesiology & Critical Care; Medicine Senior Associate Dean for the Office of Women in Science & Medicine, Johns Hopkins University	Baltimore, MD
	Marc Moon, MD	Denton A. Cooley, MD Chair in Cardiac Surgery; Chief, Adult Cardiac Surgery, Texas Heart Institute/Baylor St. Luke's Medical Center; Professor & Chief, Division of Cardiothoracic Surgery, Baylor College of Medicine	Houston, TX
	Mary Munn, MD	Professor & Chairman, Division of Maternal Fetal Medicine, Department of Obstetrics & Gynecology, The University of South Alabama Children's and Women's Hospital	Mobile, AL
	Mikael Petrosyan, MD, MBA	Associate Chief, General and Thoracic Surgery, Division of General & Thoracic Surgery; Director, Pediatric Surgery Fellowship, Children's National Hospital	Washington DC
	Caroline Zeiss, BVSc, PhD	Professor, Comparative Medicine & Ophthalmology & Visual Science, Yale School of Medicine	New Haven, CT
Designated Federal Officer	Marieann Brill, MBA, RAC, MT(ASCP)	Office of Health Technology 6 (OHT6), Office of Product Evaluation and Quality (OPEQ), CDRH, FDA	Silver Spring, MD
FDA Participants	Dionna Green, MD, FCP	Director, Office of Pediatric Therapeutics (OPT), Office of Clinical Policy & Programs (OCPP), Office of the Commissioner (OC), FDA	Silver Spring, MD
	An Massaro, MD	Supervisory Medical Officer, OPT, OCPP, OC, FDA	Silver Spring, MD
	Kalkidan Molla, MS	Lead Reviewer, Office of Cardiovascular Devices, OPEQ, CDRH, FDA	Silver Spring, MD
	Elizabeth L. Durmowicz, MD	Medical Officer, OPT, OCPP, OC, FDA	Silver Spring, MD

	Annabelle Crusan, DVM, MS	Veterinary Medical Officer, Office of Cardiovascular Devices, OPEQ, CDRH, FDA	Silver Spring, MD
Guest Speakers	Alan W. Flake, MD, FACS, FAAP	Ruth M. and Tristram C. Colket, Jr. Chair in Pediatric Surgery; Director, Center for Fetal Research Children's Hospital of Philadelphia	Philadelphia, PA
	George B. Mychaliska, MD	C.S. Mott Children's Hospital, University of Michigan Health; Robert Bartlett, MD Collegiate Professor of Pediatric Surgery	Ann Arbor, MI
	Mike Seed, MBBS, MRCPCH, FRCR	Head, Division of Cardiology, The Hospital for Sick Children	Toronto, Canada
	Gail M. Annich, MD, MS, FRCP	Professor of Pediatrics; Director of Resuscitation Oversight, The Hospital for Sick Children	Toronto, Canada
	Josef Neu, MD	Professor of Pediatrics; University of Florida	Gainesville, FL
	Mark Mercurio, MD, MA	Professor of Pediatrics; Director of the Program for Biomedical Ethics, Yale School of Medicine	New Haven, CT
	Peta M. Alexander, MBBS, FRACP, FCICM	Associate Professor of Pediatrics; Medical Director of Cardiac ECMO, Boston Children's Hospital	Boston, MA
	Susan R. Hintz, MD, MS, Epi	Robert Hess Family Professor of Neonatal and Developmental Medicine, Stanford University	Stanford, CA
Open Public Hearing Speakers	Dr. Elizabeth Chloe Romanis	Associate Professor, Durham University	Durham, England
	Theodora Scarato	Executive Director of Environmental Health Trust	Baltimore, MD

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Call to Order & Introduction of Committee — Dr. Robert Dracker

Dr. Dracker: Good morning, everyone. And thank you very much for attending. And I welcome all of you to a very interesting meeting today. I'd like to first remind everyone to please mute your telephone lines when you are not speaking. For media and press, the FDA press contact is Lauren-Jei McCarthy. Her email is lauren-jei.mccarthy@fda.hhs.gov. Her telephone number is (240) 702-3940. For members of the industry and press, please sign in by sending an email to PAC@fda.hhs.gov. Please direct all technical inquiries to the AV team at Virtual-WOCC-Support@fda.hhs.gov. I'd also like to comment that the AV support team has done an excellent job in coordinating this meeting and I appreciate it. This slide displays the link accessible for closed captioning. This link will also be shared in the chat section of the meeting throughout the day as well.

My name is Dr Robert Dracker, and I will be chairing today's virtual meeting. I will now call today's meeting of the Pediatric Advisory Committee to order. We will start by going over the meeting roster. I ask members of the committee to turn on their cameras now and keep them on for the duration of the roll call. When I call your name, please briefly introduce yourself and your primary area of expertise, institutional affiliation and role on this panel.

I will begin by introducing myself. My name is Robert Dracker. I am a Pediatrician, Hematologist, Transfusion Medicine and Advanced Biotherapy Specialist. I am the Medical Director of Summerwood Pediatrics and Infusacare Medical Services, Associate Professor of Pediatrics and Pathology at the SUNY Health Science Center in Syracuse, and Adjunct Professor of Pediatrics at Strong Memorial Rochester. I'm also the Chair of the Pediatric Advisory Committee. Next, we have, we could start, with Susan Baker. Thank you, Susan. Susan, are you there? All right, I guess we'll move on to Dr. David Balzer. Are you present? I

apologize, I'm having trouble hearing anything. All right, we will next move on to Dr. Jeffrey Botkin.

Dr. Botkin: Morning, I'm Jeff Botkin, Professor of Pediatrics at the University of Utah, Adjunct Professor of Genetics and Internal Medicine. My focus academically has been Bioethics. I am former Associate Vice President for Research Integrity at the University of Utah with the oversight for research ethics and compliance at the University. And also, former member and Chair of the Federal Secretary's Advisory Committee on Human Research Protections. I've been a member of the FDA's Pediatric Ethics Advisory Committee for a number of years as well. So, pleasure to be part of this group.

Dr. Dracker: Thank you, Dr. Botkin. Dr. Sessions Cole.

Dr. Cole: Hi, my name is Sessions Cole. I'm a Washington University in St. Louis Neonatologist. I've had a longstanding interest in the genomics of birth defects and interstitial lung disease. I've also had a number of both institutional and national responsibilities for overseeing and defining standards of care for Neonatal Intensive Care Units.

Dr. Dracker: Thank you very much, sir. Next is Dr Angela Czaja.

Dr. Czaja: Morning everyone. My name is Angela Czaja. I'm in Pediatric Critical Care Medicine here at the University of Colorado Children's Hospital of Colorado. In addition to Critical Care Medicine, I have a background in Pharmacoepidemiology to focus on off-label prescribing of medications in children. Happy to be here.

Dr. Dracker: Thank you very much. Dr Davis.

Dr. Davis: Good morning. I'm John Davis. I'm the Chief of Neonatology at Tufts University and Tufts Medical Center in Boston and an Attending Physician at Boston Children's Hospital. I'm Associate Director of our Tufts CTSA program and a Professor of Pediatrics at Tufts. I also

chair the Neonatal Advisory Committee in the Office of Pediatric Therapeutics at FDA and have been a Clinical Trialist over my 30-to-40-year career.

Dr. Dracker: Great, Thank you, Dr. Diekema.

Dr. Diekema: Hi, I am Doug Diekema. I practice Pediatric Emergency Medicine and do Bioethics at the University of Washington, where I'm a Professor of Pediatrics and an Adjunct in the departments of Bioethics and Humanities and The School of Public Health, and I also chair the IRB at the Seattle Children's Research Institute.

Dr. Dracker: Great. Thanks for being here. Dr. Feinstein.

Dr. Feinstein: Good morning. I'm Jeff Feinstein. I'm a Professor of Pediatrics and Cardiology here at Stanford. I also have a joint appointment with the Department of Bioengineering, expertise in Pediatric Pulmonary Hypertension Alagille Syndrome, also have extensive experience in the Medical Device Industry and worked with the Biodesign Program here at Stanford.

Dr. Dracker: Great. Thank you very much. Dr. Fischer?

Dr. Fischer: Morning. I'm Gwen Fischer. I'm an Associate Professor at the University of Minnesota. My focus is in Pediatric Critical Care and Pediatric Cardiac Critical Care. I also work in Pediatric Medical Device as well as Pediatric Drug Trials.

Dr. Dracker: Thank you. Dr Gleason.

Dr. Gleason: Hi I'm Chris Gleason, and I'm a Neonatologist and Professor Emerita at the University of Washington in Seattle Children's Hospital, and I'm a Temporary Member of the Pediatric Advisory Committee.

Dr. Dracker: Thank you. Dr. Goldman.

Dr. Goldman: Good morning. I'm Jennifer Goldman. I'm a Pediatric Infectious Disease Physician and Clinical Pharmacologist at Children's Mercy in Kansas City, and I serve as the Pediatric Health Organization Representative on this committee.

Dr. Dracker: Great. Dr. Guillory.

Dr. Guillory: Good morning, my name is Charleta Guillory, and I'm a Professor of Pediatrics in Neonatology at Texas Children's Hospital and Baylor College of Medicine. I serve as their Director, Neonatal Perinatal Public Health Program. In addition, I am Vice Chair, Chair Elect as of this November of the Texas Collaborative for Healthy Mothers and Babies, which is our state quality collaborative, and I'm presently the Chapter Chair President of the Texas Pediatric Society and of American Academy of Pediatrics. Thank you.

Dr. Dracker: Great. Thank you. Dr. Hill.

Dr. Hill: Good morning. I'm Dr. Washington Hill. I'm a Maternal Fetal Medicine Specialist in Sarasota, Florida. I practice at Sarasota Memorial Hospital and CenterPlace Health and I'm on the Volunteer Faculty at the University of South Florida. My interest for many, many years is maternal fetal medicine and of course, prematurity. Happy to be here as a Temporary Member.

Dr. Dracker: Thank you very much. Dr. Hoehn.

Dr. Hoehn: Hi, I'm Sarah Hoehn. I'm a pediatrician who does Pediatric Critical Care, Hospice Palliative Medicine, and Pediatric Ethics. I am a Clinical Associate at the University of Chicago Comer Children's Hospital, and I'm the Chief Medical Officer of La Rabida Children's Hospital, which is a subspecialty complex care hospital in Chicago, and I am a past member, but currently a Temporary Member of the Pediatric Advisory Committee for this meeting.

Dr. Dracker: Thank you, Sarah. It's nice seeing you again.

Dr. Hoehn: Thank you. You too.

Dr. Dracker: Thank you, Dr. Holubkov.

Dr. Holubkov: Hey, good morning. My name is Rich Holubkov. I am a Senior Biostatistician Clinical Trialist Professor of Pediatric, based in Pediatric Critical Care at the University of Utah, where I direct several clinical trials with a focus on Cardiology and Surgical Interventions. Glad to be here. Thank you.

Dr. Dracker: Thank you very much. Dr Krug.

Dr. Krug: Hey, good morning, everybody. This is Steve Krug. I'm a Professor of Pediatrics at the Northwestern University Feinberg School of Medicine. And I practice Pediatric Emergency Medicine at the Lurie Children's Hospital where I am the prior division head for that group. I've served on a number of different advisory committees, including those in federal agencies and happy to be here.

Dr. Dracker: Thank you very much, Dr. Krug. Dr. Baker?

Dr. Baker: Good morning. I'm Susan Baker. I'm a Pediatric Gastroenterologist with a PhD in Nutritional Biochemistry from MIT. I'm currently a Professor of Pediatrics at the University at Buffalo and former Division Chief. I've served on multiple federal committees and done a lot of drug trials and so on. Thank you.

Dr. Dracker: Okay, we have Dr Jennifer Lee-Summers.

Dr. Lee-Summers: Good morning. I'm Jenny Lee. I'm a Professor of Pediatric Anesthesia and Pediatrics at Johns Hopkins University. I'm a Temporary Member of the committee. I run a Translational Research Program to study Neonatal Brain Hypoxia.

Dr. Dracker: All right, Dr. Gianna McMillan.

Ms. McMillan: Good morning. I'm Gigi McMillan, Associate Director of the Bioethics Institute at Loyola Marymount University in Los Angeles. I'm a Bioethicist and a Patient-Family Representative for the Pediatric Advisory Committee.

Dr. Dracker: Great. Thank you for being here. Dr. Marc Moon.

Dr. Moon: Yes, I'm Marc Moon. I'm the Chief of Cardiothoracic Surgery at the Texas Heart Institute and Baylor College of Medicine. I've served on a number of panels as an ad hoc Reviewer, generally due to devices that involve heart and lung machines.

Dr. Dracker: Great. Thank you. Dr. Munn.

Dr. Munn: Hey, I'm Dr Mary Munn. I'm the Professor and Chair at the University of South Alabama in Mobile, Alabama and a Maternal Fetal Medicine Physician by-training with a big interest in prematurity. Happy to serve on the committee.

Dr. Dracker: Thank you very much. Dr. Nelson, it's wonderful seeing you again.

Dr. Nelson: Hi Bob, yeah. Skip Nelson. I'm currently the Senior Director of Pediatric Drug Development at Johnson & Johnson, and I am representing regulated industry as a non-voting member. Happy to be here.

Dr. Dracker: Thank you. Dr. Ortiz-Aguayo.

Dr. Ortiz-Aguayo: Hi, I'm Roberto Ortiz-Aguayo. I am former Associate Chair of the Department of Psychiatry at Children's Hospital of Philadelphia, current private practice, and I'm upcoming Chair of Psychiatry at Nemours Children’s Hospital, effective November 1st.

Dr. Dracker: Thank you. Randi Oster, it's nice to have you here.

Ms. Oster: Yes. Hi, I'm Randi Oster. I am the consumer representative for the PAC. I am also the President of Help Me Health, which focuses on the patient experience. And this is my second term on this particular PAC and I'm happy to be here.

Dr. Dracker: Thank you. Dr Petrosyan.

Dr. Petrosyan: Hi, my name is Mikael Petrosyan. I'm a past Chief of Surgery of Children's National Hospital, Washington, D. C. I'm also a Pediatric Surgeon and interested in neonatal surgery.

Dr. Dracker: Right, thank you. Dr White, it’s nice having you here.

Dr. White: Thank you. Happy to be back. This is Michael White. I'm at the Ochsner Health System in New Orleans, Vice Chair of our I.R.B., Vice Chair of our Ethics Committee, and Associate Professor at University of Queensland in Australia.

Dr. Dracker: All right. Thank you, Michael. Dr. Zeiss.

Dr. Zeiss: Good morning. My name is Caroline Zeiss. I'm a Professor of Comparative Medicine at Yale University. My specialty is I'm boarded in Laboratory Animal Medicine as well as an Anatomic Pathology. And I'm Chief of Pathology in Comparative Medicine. My Pathology Specialty is Neuropathology. And clinically, I specialize in translating animal models to human disease. Thank you.

Dr. Dracker: Great. Thanks. It'll be nice having you contribute to this meeting. On behalf of the FDA, I thank all the committee members for their participation. Now, I will pass the meeting to Marieann Brill, who will introduce the FDA representatives for today's meeting.

Ms. Brill: Hello, my name is Marieann Brill, and I am the DFO, the Designated Federal Officer for today's meeting. Now, I will ask our FDA participants to introduce themselves, beginning with Dr. Dionna Green.

Dr. Green: Good morning. My name is Dionna Green, and I am the Director of the Office of Pediatric Therapeutics.

Dr. Dracker: All right, Marieann, anyone else to introduce or no?

Dr. Farb: Good morning and thank you, I'm Andrew Farb. I'm the Chief Medical Officer of the FDA's Office of Cardiovascular Devices and Co-Leader of CDRH's Early Feasibility Studies Program for Medical Devices.

Dr. Peiris: Good morning, everyone. My name is Vasum Peiris. I'm the Chief Medical Officer and Director for Pediatrics and Special Populations for CDRH.

Dr. Hausman: Good morning. I'm Ethan Hausman. I'm a Medical Officer in the CDER's, Division of Pediatric and Maternal Health. My training is anatomic pathology, clinical pathology, transfusion medicine, and pediatrics.

Ms. Brill: Any additional FDA speakers or participants in today's meetings will introduce themselves when speaking during the day.

Dr. Dracker: Thank you, Marieann.

Ms. Brill: Sure.

Dr. Dracker: The FDA has convened today's meeting to discuss the development of Artificial Womb Technology devices, including regulatory and ethical considerations for clinical studies. The focus of this meeting is the development of Artificial Womb Technology devices as an alternative to current standard-of-care for infants who are born extremely prematurely with the goal of reducing morbidity and mortality for this vulnerable population. We will be focused on pediatric considerations during this meeting. While there are many notable maternal considerations, they are largely outside the scope of today's discussion. The term Artificial Womb Technology, or AWT, can mean many things to different people. In this meeting, we will not be discussing the use of this technology as a substitute for natural pregnancy, and we will not be discussing how these devices impact the limits of viability of preterm infants. This discussion is focused on the role of Artificial Womb Technology devices in optimizing the care of viable

infants who will be born prematurely despite efforts to prolong their pregnancy. There may be strongly held opinions regarding the topic being discussed at today's meeting. Our goal is that today's meeting will be a fair and open forum for discussion of the planned topic, ensuring individuals can express their views without interruption. With that said, if the discussion veers towards topics beyond the stated scope of this meeting, I may, as Chairperson, refocus the discussion as needed. As a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a very productive meeting.

In the spirit of Federal Advisory Committee Act, the government and the Sunshine Act, we ask that advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, the FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topics during breaks or lunch. Thank you. Now I will pass the meeting back to Marieann Brill, who will read the conflict –of interest statement. Thank you, Marieann.

Conflict of Interest Statement — Ms. Marieann Brill

Ms. Brill: Good morning, the Food and Drug Administration is convening today's meeting of the Pediatric Advisory Committee under the authority of the Best Pharmaceuticals for Children Act, the Pediatric Research Equity Act of 2003, the Food and Drug Administration Amendments Act of 2007, the Food and Drug Administration Safety and Innovation Act of 2012, and the Federal Advisory Committee Act. With the exception of the industry representative, all members and temporary voting members are special government employees or regular

government employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information and the status of this committee's compliance with federal ethics and conflict of interest laws, covered by, but not limited to: those found at 18 USC Section 208 is being provided to participants at this meeting and to the public. FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular government employees who have potential financial conflicts, when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest, or when the interest of a regular government employee is not so substantial as to be deemed likely to affect the integrity of the services, which the government may expect from the employee. Related to the discussions of today's topic, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves discussion about device development for artificial womb technologies, including regulatory and ethical considerations for first in-human studies. This is a particular-matters meeting, during which general issues will be discussed. Based on the agenda for today's session, and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued. To ensure transparency, we

encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue or the topic at issue. Dr. Jennifer Goldman is participating in this meeting as a Pediatric Health Organization Representative, and that is a non-voting position. With respect to FDA's invited industry representative, we would like to disclose that Dr. Nelson is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Dr. Nelson's role at this meeting is to represent industry in general, and not any particular company. Dr. Nelson is employed by Johnson & Johnson. In order to provide the expertise required to adequately address the topic covered at today's meeting, Doctors Botkin, Cole, Davis, Feinstein, Gleason, Hill, Hoehn, Lee-Summers, Moon, Munn, Petrosyan, and Zeiss will be participating as temporary voting members.

Dr. McMillan is participating as the Patient Family Representative, which is a voting position. We would like to remind members and temporary voting members that if the discussions involve any other topics not already on the agenda, for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. We also have with us today several experts who will be giving presentations to the committee. In the morning session about animal models of Artificial Womb Technology, Dr. Alan Flake will be providing an industry perspective and Dr. George Mychaliska and Dr. Mike Seed will be serving as expert guest speakers. Dr. Alan Flake from the Children's Hospital of Philadelphia will provide an industry perspective related to Artificial Womb Technology in a preterm lamb model. Dr. Flake has reported interests via Vitara Biomedical, including holding option shares, a sponsored research agreement, pre-clinical research, and paid medical consulting. Dr. Flake is a co-inventor of Vitara Biomedical's Artificial

Womb Technology and an inventor in multiple patents licensed from the Children's Hospital of Philadelphia by Vitara Biomedical.

Dr. George Mychaliska from the C.S. Mott Children's Hospital at the University of Michigan will be presenting an artificial placenta technology in a preterm LAMP model. Dr. Mychaliska has reported that he is a principal investigator on an NIH grant titled Miniaturization of the Artificial Placenta for Clinical Application and is also conducting research developing an artificial placenta for clinical application. Dr. Mike Seed from the Hospital for Sick Children in Toronto will be presenting on Artificial Womb Technology in a piglet model. Dr. Seed has reported no financial interests related to today's meeting topic. We have several additional expert guest speakers presenting in the afternoon. Dr. Susan Hintz, Dr. Gail Annich, Dr. Peta Alexander, Dr. Joseph Neu, and Dr. Mark Mercurio have reported no financial interests related to today's meeting topic. FDA encourages all other participants to advise the committee of any financial relationships that they may have regarding the topic that could be affected by the committee's discussions. And with that, I will turn the meeting back over to our chair, Dr. Dracker. Thank you.

Dr. Dracker: Thank you, Marieann. I will do all I can to try to pick up the speed a little bit so that we stay on time. We have a lot of material to cover. We will proceed now with opening remarks from Dr. Dionna Green, Director of the Office of Pediatric Therapeutics. Thank you, Dr. Green.

FDA Opening Remarks — Dr. Dionna Green

Dr**.** Green: Thank you, Dr. Dracker. I would like to welcome our committee members and guests who are joining us for today's Pediatric Advisory Committee meeting. At today's meeting, we will discuss the appropriate development plans for establishing safety and effectiveness of

Artificial Womb Technology devices, including regulatory and ethical considerations for first in-human studies. I would like to thank the committee for the time that you have taken to review the advanced materials. Your perspectives and input on topics brought before the committee are highly valuable to the agency.

I would also like to thank the following groups: the invited speakers who are providing presentations as part of today's agenda; all of the FDA staff members who are participating today; and those who have contributed to the planning for this advisory committee meeting. And last but not least, I would like to thank the public who are joining us today. As part of my opening remarks, I will be providing a few personnel updates regarding the Pediatric Advisory Committee and regarding the FDA Office of Pediatric Therapeutics. In addition, I will be presenting a summary of the Pediatric Research Equity Act noncompliance letters that have been issued since the last Pediatric Advisory Committee meeting.

Doctors Kelly Wade, Wael Sayej, and Benjamin Wilfond have completed their terms on the Pediatric Advisory Committee as of June 30, 2023. We thank them for their service and for contributing to the FDA's mission of protecting and promoting the public health.

Dr. Robert Dracker, a standing member on the Pediatric Advisory Committee serving in his second tenure, has been promoted to chairperson as of July 2023. Dr. Dracker is a Clinical Associate Professor in the Departments of Pathology and Pediatrics at SUNY Health Science Center at Syracuse. He serves as an attending pediatrician at four health centers and has faculty appointments at several academic institutions. Dr. Dracker is the Owner and Medical Director of Summerwood Pediatrics, and Founder and Medical Director of Infusacare Medical Services.

We have three new members joining the Pediatric Advisory Committee. Dr. Susan Baker has been reappointed for her second tenure to the committee. Dr. Baker previously served

from 2012 to 2016. She is a Professor of Pediatrics at the State University of New York in Buffalo. Dr. Baker is board-certified in Gastroenterology and Nutrition. Her research specialties include hepatology, nutrition, pediatrics, and pediatric gastroenterology. Dr. Douglas Diekema specializes in general pediatrics, emergency medicine, and bioethical issues related to children and adolescents. He currently serves as an Attending Physician as well as Professor in the Department of Pediatrics, Division of Bioethics, and Division of Emergency Medicine at the University of Washington. Additionally, Dr. Diekema is a chairperson for the Secretary's Advisory Committee on Human Research Protections. Dr. Charleta Guillory specializes in neonatal-perinatal medicine and she holds several roles within the field, including serving as the Director for the Neonatal-Perinatal Public Health Program at Texas Children's Hospital. Dr. Guillory is also a tenured Professor of Pediatrics at Baylor College of Medicine. We welcome these new members and we look forward to their contributions to the Pediatric Advisory Committee.

Next, I would like to introduce two new staff members in the FDA Office of Pediatric Therapeutics who are serving in roles that help facilitate and manage the Pediatric Advisory Committee. Allison Griffin, a Program Analyst and Conflict of Interest Specialist on the Pediatric Advisory Committee Logistics Team and Dr. Mohamed Mohamoud, a Senior Clinical Analyst on the Pharmacovigilance Team.

As required by legislation, I will now provide a summary of the PREA noncompliance letters. FDA has issued a PREA noncompliance letter to a sponsor if it failed to submit within the required timeframe a required pediatric assessment or report of a molecularly targeted pediatric cancer investigation, as appropriate. FDA has also issued such a letter if a sponsor failed to request approval for pediatric formulations as described in Section 505B of the

Food, Drug, and Cosmetic Act. Consistent with the Act, FDA has also made publicly available on FDA's website the PREA noncompliance letter and sponsor's response, with certain redactions. If a sponsor has requested a deferral extension or submitted a waiver request by the due date of the pediatric assessment or the report of the molecularly targeted pediatric cancer investigation, FDA has not issued a PREA noncompliance letter unless FDA subsequently denied the deferral extension or waiver request.

Since the last reporting on the PREA noncompliance letters at the September 2021 Pediatric Advisory Committee meeting, there have been three new letters issued by the Center for Biologics Evaluation and Research, or CBER, and 24 new letters issued by the Center for Drug Evaluation and Research, or CDER.

The information related to these new letters are listed on the following slides and can also be found on FDA's website.

Thank you for your attention and welcome again to this meeting of the Pediatric Advisory Committee. I will now turn the meeting back over to our chairperson, Dr. Dracker.

FDA Background Presentations

Dr. Dracker: Thank you very much, Dr. Green. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure that such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages all participants to advise a committee of any financial relationships they may have and with the firms that issue, such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interests and those based upon the outcome of the meeting. Likewise, the FDA encourages you, at the beginning of your presentation, to advise the committee if you do not

have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking. We will now proceed with the FDA's background presentations. You will have the opportunity to ask any clarifying questions after the third presentation. Thank you.

Regulatory Considerations for Artificial Womb Technology Development Programs — Kalkidan Molla

Mr. Molla: My name is Kalkidan Molla. I'm a Mechanical Engineer and a Lead Reviewer on the Circulatory Support Devices team in the Office of Cardiovascular Devices.

Here is a description of today's FDA's presentations. I'll be providing background information on Artificial Womb Technology or AWT devices. Dr. Durmowicz will offer comments on regulatory safeguards for children enrolled in AWT clinical studies. Dr. Massaro will review AWT benefit risk considerations, and Dr. Crusan will discuss animal study considerations for AWT.

This is an outline of my remarks. I'll begin by introducing background information on preterm births. Then the intended use of Artificial Womb Technology, or AWT, followed by regulatory considerations for AWTs, including device classification and information on CDRH's early feasibility study program, which FDA currently considers an important step for AWT development.

Preterm birth is a significant public health issue in the U. S. Infants born premature, defined as less than 37 weeks gestational age, represented 10 percent of all live births in 2020, but accounted for 65 percent of deaths in infants less than 12 months of age. The disproportionate contribution to infant mortality is most striking in the most premature infants, where 40 percent of all infant deaths occurred in extremely preterm infants born less than 28

weeks gestational age. Although these infants represented only 0.6 percent of all live births. Among survivors of extreme prematurity, morbidity rates are high in infants treated with the current standard of care.

Artificial Womb Technology devices are intended to treat extremely premature infants, or EPIs, after 22 weeks gestational age, by providing a bridge from extreme preterm birth to later gestation within a physiologic environment that mimics the womb. The following are some potential AWT benefits: to reduce high mortality and long-term morbidity rates in EPIs; provide an environment that promotes organ maturity; provide stable gas exchange and hemodynamic support; and reduce morbidity associated with mechanical ventilation.

To achieve the aims discussed in the previous slide, AWT systems generally have the following components: a system for sterile fluid for submersion of the infant, which mimics an intrauterine environment; a pumpless venoarterial circuit with a hollow fiber oxygenator to oxygenate blood; cannulas to connect to umbilical arteries and veins to oxygenate the blood and provide nutrients and medications; and display systems to monitor extracorporeal circuit flow and pressure, oxygen saturation, and vital signs.

Here are some device regulatory considerations relevant to artificial womb technologies. Medical devices are regulated by the Center for Devices and Radiological Health or CDRH. FDA's medical device classification is risk-based. That is, the risk the device poses to the patient and/or the user is the primary factor that determines the assigned risk class. Class 1 includes devices with the lowest risk, and Class 3 with the highest risk, requiring premarket approval, or PMA. Class 3 devices present the potential for serious risk to the health, safety, or welfare of a subject, and they may be an implant, a life supporting or life sustaining device, or a device of substantial importance in diagnosing, curing, mitigating, or treating disease, or in

otherwise preventing impairment of human health. Therefore, AWT devices are classified as Class 3.

An Investigational Device Exemption, or IDE, allows the investigational device to be used in a clinical study performed in the U. S., in order to collect safety and effectiveness data. It is important to note that IDE and IRB approval are required before initiating enrollment. An approved IDE provides protection to subjects via informed consent and study monitoring. Clinical study data collected under an IDE can be used to support a device-marketing application.

CDRH's EFS program is a voluntary program which facilitates conduct of early-stage clinical device studies in the U.S. The program is intended to increase early patient access to potentially beneficial medical devices in the U.S., expand U.S. site participation in the early clinical evaluation of innovative medical devices, and enhance collaboration among developers, industry, regulators, and investigators. Importantly, EFS utilizes current regulations to protect study participants.

All EFS, per FDA's guidance, is a small clinical study evaluating a device that may be early in development and before the design has been finalized. An EFS study is a type of IDE and is needed when information to advance device development cannot be practically obtained with additional non -clinical assessments or non-clinical tests are unavailable. During FDA's review of EFS IDE submission, we consider the target clinical condition, including the availability, effectiveness, and safety risks associated with alternative treatments, in this case, for extremely premature infants. In addition, EFS protocols incorporate risk mitigation strategies, augmented monitoring, and tailored consent process to enhance patient safety. Please note that an EFS IDE approval does not lower the fundamental regulatory requirements for initiating clinical

studies of investigational significant risk devices. For example, EFS must still comply with 21 CFR 812, which outlines requirement for clinical investigation of medical devices. And more importantly, in relation to AWTs, an EFS that enroll children must also comply with 21 CFR 50 subpart D, which outlines additional safeguards for children in clinical investigations. FDA anticipates that AWTs will follow the early feasibility study program pathway.

Here are some examples of clinical mitigation strategies intended to lower risks and increase safety for subjects enrolled in a EFS studies: study sites with the expertise and resources to manage adverse events and provide appropriate alternative therapies; and sites with highly qualified investigators with spatial training to conduct the EFS; follow-up assessments at frequent intervals to monitor subject safety and device performance, often more frequently than a traditional feasibility or pivotal study; timely reporting of serious adverse events to FDA, for example, after each occurrence rather than only in a periodic progress report; and early feasibility studies can include pre-specified plans for periodic patient outcome assessments and reporting to FDA prior to enrollment of additional patients, for example, as frequently as after each use for a particularly novel high-risk device. This risk mitigation strategy may be appropriate for particularly high-risk devices and interventions. In summary, considering the high mortality and morbidity rates associated with EPIs, the challenge in developing animal models that are representative of the clinical use conditions for EPIs and novelty of the AWT devices, FDA will consider relevant EFS principles to support initiation of first in-human studies for AWTs. In this presentation, I discussed EFS IDEs and their potential applicability to AWTs. I also stated that EFSs must still comply with IDE regulatory requirements, one of which being 21 CFR 50 subpart D, which outlines additional safeguards for children in clinical investigations.

Now, I'll turn our presentation to Dr. Durmowicz, who will discuss regulatory safeguards for children.

FDA's Regulatory Safeguards for Children Involved in Clinical Trials: Considerations for Artificial Womb Technologies — Dr. Elizabeth L. Durmowicz

Dr. Durmowicz: Good morning. I am Beth Durmowicz, a Medical Officer on the Pediatric Ethics Team in the Office of Pediatric Therapeutics at FDA. I will be talking to you today about FDA's human subject protection regulations that govern the enrollment of children in clinical trials, and I will be discussing ethical considerations for trials of artificial womb technologies.

I will begin my presentation by providing a brief background about why FDA has human subject protection regulations that are unique to children, and I will then provide a brief overview of these regulations. I will then move on to discuss ethical considerations for trials of artificial womb technologies, or AWTs, based on FDA's regulations. I will discuss considerations for analyzing the prospect of direct clinical benefit and the risks of a clinical investigation of an AWT device. This is important because we will be asking the committee members to discuss risk and benefit considerations for AWTs. I will also discuss potential challenges in obtaining informed consent for a trial of such a device.

Before discussing FDA's human subject protection regulations for children, I would like to briefly discuss the history and intent of these regulations. Since the 1970s, thought leaders have recognized that children should benefit from progress in medical care that is fueled by scientific research. However, these experts also recognize that children are a vulnerable population and that no child should be placed at a disadvantage by participating in research. To ensure balance between these potentially conflicting objectives, specifically to promote research involving children while also protecting children, government agencies and institutions

worldwide have published recommendations, guidelines, and regulations to guide enrollment of children in clinical investigations.

Let's talk a little bit more about ethical considerations and consensus that exists regarding enrollment of children in clinical trials. As discussed, clinical investigations in children are essential. We need data from clinical trials in children to understand if medical products are safe and effective in children for their intended use. We need these data to protect children from exposure to medical products that may be unsafe or ineffective in children or in a subpopulation of children. However, we recognize that children are a vulnerable population who cannot consent for themselves and therefore are afforded additional safeguards when participating in clinical investigations. Safeguards for children are considered essential requirements for the enrollment of children in clinical trials to support medical product development.

With the understanding that we need to conduct research in children, but we must do so in a way that protects this vulnerable population, FDA promulgated regulations governing the enrollment of children in clinical trials that embrace fundamental ethical principles. An important principle is related to necessity. This principle holds that children should only be enrolled in a clinical trial if the scientific or public health objectives are important to the health and welfare of children and cannot be met through enrolling subjects who can consent personally. Another principle is about limitations of risk. Specifically, if a trial does not offer the prospect or direct benefit to the individually-enrolled child in the trial, the risk to which the child may be exposed must be low. For children, there is a limit to the risk that knowledge alone can justify, and risks in a trial should be minimized. Also, children should not be placed at a disadvantage by being enrolled in a clinical trial, either through exposure to excessive risks or by

failing to get necessary health care or interventions. In addition, children should have a suitable proxy to provide permission or informed consent for them to enroll in a clinical trial.

I will now talk about FDA's regulations governing enrollment of children in a clinical trial, the Additional Safeguards for Children in Clinical Investigations. This slide is intended to provide a high-level summary of the basic concepts underlying our regulations. Our regulations require that the risk of a clinical investigation in children must be restricted to low-risk if the trial does not offer each individually enrolled child the prospect of direct benefit. Or if the risks are not low, the risks of the interventions or procedures must be justified by the prospect of direct clinical benefit to the child, and the balance of the anticipated benefit to the risks must be at least as favorable as available alternatives. In addition, a clinical investigation enrolling children must have adequate provisions in place for obtaining parental permission and assent of the child if assent is appropriate. So, to summarize, our regulations specify limits for the level of risk to which children may be exposed in a clinical trial and the level of acceptable risk is assessed based on the potential for direct benefit.

Under FDA's regulations, clinical investigations in children may be allowable if they present minimal risk. Or, if they present more than minimal risk, but offer the prospect of direct benefit. Or, if they do not offer prospect of direct benefit, but the risks are limited to a minor increase over minimal risk, and the investigation is likely to yield generalizable knowledge about the subject's disorder or condition. In addition, the regulations provide an opportunity for institutional review boards to refer protocols that are not otherwise approvable under these three pathways for federal review. The regulations also include requirements for obtaining permission from parents and assent from children when appropriate. I will focus the remainder of my talk on clinical investigations that offer prospect of direct benefit to subjects

and the requirement to obtain parental permission, because these regulations are particularly relevant to a discussion of a potential AWT device clinical trial.

Let's talk about clinical investigations that involve greater than minimal risk, but present the prospect of direct benefit to the child and begin by discussing prospect of direct benefit. The benefit is direct if it accrues to the individual subject enrolled in the clinical trial. We often modify the term benefit with clinical to identify that the benefit relates to the health of the enrolled child. The assessment of the prospect of direct benefit is based on data that support proof of concept or data that support that the intervention will have the intended treatment effect and on the structure of the protocol. In situations in which we determine that a trial intervention offers this prospect of direct benefit to each subject, our regulations then require that the risks of that intervention are justified by the anticipated benefit, and the relation of the anticipated benefit to the risk is at least as favorable to the subject as available alternatives.

Let's now talk about parental permission, or obtaining informed consent for participation of a child in a trial. The permission of the parent or guardian is required for a child to be enrolled in a clinical trial. Requirements for obtaining parental permission are the same as those for obtaining informed consent from a consenting adult. Obtaining informed consent, or parental permission, is a process that involves facilitating an understanding of the information, not just the signing of an informed consent document. The process should include the time and opportunity for the parent or guardian to ask questions and consider participation of their child in the proposed trial. And information should continue to be provided to the parent or guardian as the trial progresses and as the situation requires. The Parental Permission Form must contain adequate information to allow the parent or guardian to make an informed decision.

I am now going to move on to talk about ethical considerations for AWT trials based on FDA's regulations governing clinical investigations in children.

Ethical analysis of an AWT clinical trial begins with an assessment of how the trial may be able to proceed under our regulations. Given that an AWT device would be considered a highly innovative and novel technology associated with many potential risks and unknowns, the risks associated with an AWT would be considered to exceed the low-risk threshold. Therefore, according to our regulations, enrollment in an AWT trial must offer a prospect of direct clinical benefit to each enrolled neonatal subject. The risks of the AWT trial must be justified by the anticipated benefit to the subject, and the relation of the anticipated benefit to the risk of trial participation must be at least as favorable to the subject as that offered by standard clinical care. In addition, permission from the parent or guardian must be granted. Also, the benefits and risks of each research related intervention or procedure included in the trial should be evaluated to determine if the intervention or procedure offers the prospect of direct clinical benefit and to evaluate the associated risks.

As we just discussed, for a neonate to be enrolled in an AWT trial, each neonatal subject must be offered the prospect of direct clinical benefit from participation in the trial. To support proof of concept, evidence would be needed to determine that the AWT device and the associated interventions and procedures will have the intended beneficial effects. Proof of concept data could be obtained from animal models, for example, fetal animals placed in an AWT device, and/or relevant data from clinical trials or experience with device related procedures or interventions. For example, data on prostaglandin or anticoagulation use in extremely premature neonates. You will learn more in the presentations to follow about research being conducted to support proof of concept for an AWT. In addition to proof-of-concept data,

we would need data to support that the design of the AWT device and its performance are likely to result in the intended treatment effect, and data need to support that the proposed duration of the use of the device in the trial is likely to result in a measurable clinical benefit. To support prospect of direct benefit, data should demonstrate that the use of an AWT as proposed in a trial is likely to increase survival or reduce critical morbidities for the enrolled neonatal subject.

If data support that a neonatal subject enrolled in an AWT trial will be offered the prospect of direct benefit, we will then need to determine whether data are adequate to support that the risks of the AWT trial are justified by the anticipated benefit. We would want data that are adequate to evaluate the probability and magnitude of risks associated with the AWT device and the risks of other trial interventions and procedures. As discussed, the risks of the AWT must be justified by the anticipated benefit to the individual subject and the relation of the anticipated benefit to the risk must be as favorable as routine care for a neonatal subject of equivalent gestational age. As such, the survival and morbidity rates of the proposed study population should be carefully considered to ensure the benefit risk assessment of the AWT trial in the selected study population is anticipated to be at least as favorable as the care the neonate would otherwise receive in the neonatal intensive care unit. As discussed, the potential risks of the procedures and interventions in the trial must be evaluated both individually and collectively.

As per FDA regulations, parental permission or informed consent must be obtained from the parent or guardian. As we discussed earlier, when obtaining informed consent, the parent or guardian must be provided sufficient opportunity to ask questions and consider whether or not they will allow their child to participate in the trial. In addition, the circumstances for obtaining informed consent must minimize the possibility of undue influence. Obtaining parental permission for enrollment of neonates in a clinical trial may include inherent challenges,

and we anticipate these challenges may be accentuated for an AWT trial given the high-risk neonatal population and the novelty of these devices. In addition, there may be unique challenges in obtaining permission for an AWT trial. Some challenges may include a parent also being the pregnant person and as such also a research subject, therapeutic misconception or the parent not recognizing the difference between clinical care and enrolling their child in a research trial, the parent or guardian's perceived pressure to consent to experimental procedures, and the emotional circumstances under which informed consent may be obtained.

In summary, FDA's regulations governing enrollment of children in clinical investigations are not intended to delay or obstruct research in children, but they are intended to support evaluation of the safety and effectiveness of medical products to ensure the health and well-being of children. In addition, the regulations are intended to ensure that the risks of research participation are reasonable and that higher risks are justified by the anticipated benefit to each individual pediatric subject. Early feasibility studies and FDA's Early Feasibility Study Program may increase access for patients to potentially beneficial technologies and support device innovation and may be reasonable if there are limitations in the data that nonclinical studies can provide. However, the pediatric human subject protection regulations apply to all FDA regulated clinical investigations, and an AWT trial must be compliant with 21 CFR 50, subpart D.

Prior to enrollment of a neonatal subject in a trial of an AWT, data must be adequate to support that each individual neonate will be offered the prospect of direct clinical benefit, the risks of the trial are justified based on the anticipated benefit, and the benefit risk profile is at least as favorable as that afforded by routine clinical care. The process for obtaining parental permission for enrollment of a neonate in an AWT trial must address unique challenges.

This concludes my presentation. Thank you. We'll now move on to the presentation by my colleague, Dr. An Massaro.

Clinical Considerations for Evaluating Benefit versus Risk for Artificial Womb Technology Development Programs — Dr. An Massaro

Dr. Massaro: Thank you, Dr. Durmowicz. As mentioned, my name is An Massaro, and I am the Lead for the Neonatology Program in the Office of Pediatric Therapeutics. I will discuss the challenges in evaluating benefit versus risk for the development of Artificial Womb Technologies from a clinical and regulatory perspective.

As you heard from Dr. Durmowicz, regulations that we refer to as subpart D require us to consider several factors when evaluating a greater than minimal risk investigational artificial Womb technology device. We need to assess whether the potential risks of an AWT device are justified by the anticipated benefits of potentially improving mortality and morbidity in the extremely preterm infant. And this assessment needs to be favorable relative to outcomes with current standard of neonatal intensive care. As you've already heard from Dr. Durmowicz regarding important informed consent considerations, I will focus during this talk on the assessment of benefit versus risk for a potential AWT clinical trial.

In this sense, it is important to distinguish between the benefit-risk assessment that occurs later in the device development life cycle, where approval of a pre-marketing application would require support that the benefits of the device outweigh any associated risks to patients. This assessment is supported by data that is generated during clinical development of the device.

In contrast, when we are thinking about benefit versus risk to determine whether it's ethically permissible to proceed with a first in-human trial of an AWT device, we need to

make an assessment of the prospect of clinical benefits and potential device-related risks. And we need to make sure that this assessment is judged to be as favorable as known outcomes with standard-of-care in the neonatal intensive care unit. In order to make this assessment, we need to review the outcomes we are achieving currently in the proposed patient population, which in the case of the extremely preterm infant is variable by each completed week of gestation, as well as by the institution where care is received. We will hear more about this from Dr. Hintz later today. We also need to understand the available data to support prospect of benefit and safety of the investigational device. While data from animal models and relevant clinical experience may help inform this assessment, we recognize that there will always be some unknowns that will need to be accepted as part of the transition to initial clinical use. The most challenging question is to answer how much unknown is acceptable.

You heard an overview of general components of an Artificial Womb Technology system earlier, and you will hear further discretion about Artificial Womb versus Artificial Placenta Systems. But for the purpose of this discussion, to enable comparison to current standard-of-care of the extremely preterm infant in the NICU environment, I'll review general components with this schematic, where the neonate is cared for in a simulated womb environment and uses an ECMO circuit to provide gas exchange and access for parenteral nutrition and medication administration. This can be compared to postnatal care in the NICU that includes use of an incubator for thermoregulation and to provide a protective environment, respiratory support, either via endotracheal intubation or non-invasive methods to provide oxygen and/or positive airway pressure and intravenous lines for provision of parenteral nutrition and medications.

In the interest of time, I will not provide an in-depth review of the many morbidities that have been well described in preterm infants, but note that these conditions include bronchopulmonary dysplasia that can be associated with varying degrees of chronic pulmonary insufficiency, retinopathy of prematurity that can lead to vision problems or even blindness, necrotizing enterocolitis and sepsis that can both be immediately life-threatening and be associated with long-term complications, and intraventricular hemorrhage, periventricular leukomalacia, and other developmental brain injuries that can contribute to high rates of neurodevelopmental impairment in childhood survivors born preterm. In general, these morbidities occur across organ systems and are largely attributable to the vulnerability of the developing organs to injury and/or immature systems for repair. While the specific etiologies of some of these conditions are multifactorial and many not completely understood, the contribution of iatrogenic insults from standard care in the NICU to the development of prematurity associated comorbidities has also been well described. For example, ventilator-induced lung injury is a known risk factor for BPD, and oxygen toxicity has been implicated either directly or indirectly in the pathogenesis of BPD, ROP, and other conditions. Ventilator-associated pneumonia, sepsis, and NEC can lead to the need for long term venous access, which in turn can add risk for line-associated infections. Need for prolonged parenteral nutrition can lead to parenteral-nutrition-associated liver disease and other consequences such as delayed intestinal adaptation leading to feeding intolerance. In the case of the developing brain, despite best efforts by neonatologists, maintaining metabolic and physiological stability is not always possible, where management of glucose, electrolytes, blood pressure, and gas exchange is subject to the support devices and medications available in the clinical armamentarium. Finally, exposures to which the ex-utero preterm infant encounters on a regular basis in the NICU,

including light, sound, painful procedures, and medications, many of which have not been evaluated for safety or effectiveness in the neonatal population, can contribute to the relatively high rates of adverse neurodevelopmental outcomes observed in preterm infants. And while I focus on morbidity here, I'll emphasize that many of these conditions, either alone or in combination, may also contribute to the relatively high mortality rates seen in the extremely preterm infant as well.

These known risks associated with standard-of-care must be compared to the potential risks that may be associated with an Artificial Womb Technology Device. As described, transition from placental to AWT support requires relatively rapid cannulation and establishment of extracorporeal circulation, requiring administration of a paralytic agent to the fetus to prevent initial breathing, and possibly medications to prevent umbilical artery spasm to maintain circuit flow. The ECMO component is associated with an inherent risk for thrombosis and bleeding, requiring thoughtful management of anticoagulation. This is of particular concern given the underlying risk for intraventricular hemorrhage in the preterm infant and historical observations of increased intracranial hemorrhage in preterm infants managed in the early experience with neonatal ECMO. We will hear updates on this topic from Dr. Annich later today. Also of consideration is whether the preterm myocardium will be equipped to handle the additional load of the extracorporeal circuit with or without an incorporated pump, and whether there are potential consequences of maintaining fetal circulation, and of the medications required to do so, for a prolonged duration after delivery. We will hear perspectives on these considerations from Dr. Alexander. Given the need to maintain fluid-filled lungs either via submersion with artificial amniotic fluid or tracheal intubation with installation of perfluorocarbons, the neonate supported by AWT will likely require prolonged TPN and withholding of enteral feeds. While the risks

associated with TPN are not uncommon in the preterm infant, as I described on the previous slide, it is noted that standard of care in the NICU typically includes early initiation of enteral feeding and gradual discontinuation of TPN as soon as possible, given the recognized potential for associated complications. Thus, the potential consequences of the use of TPN in the setting of no enteral feeding for the first several weeks of life will need to be considered, and Dr. Neu will discuss these issues. Finally, just as with the NICU environment, externally contacting and indwelling devices can pose a risk for infection in the preterm infant with immature host defenses, and whether mitigation strategies are adequate to prevent infection will need to be considered.

Returning to the concept of conducting a benefit-risk assessment, we need to consider both whether there is support for prospect of direct benefit and adequate safety and mitigation of residual risk. With regards to benefit, we will look to animal models to provide data to support that the intended effect of the device can be achieved. That is, organ growth and maturation are supported while potentially reducing at least some of the iatrogenic insults that may contribute to adverse outcomes. With regards to risk, we will again rely on animal models to help inform risk. But note that, as we will soon hear from Dr. Crusan, differences between species may limit translation of safety, and we will also need to look, where possible, at relevant clinical experience to help fill gaps.

As I mentioned previously, even with the most comprehensive non-clinical program to develop an investigational AWT device, we expect that there will be unknowns at the time of initiating a first-in-human trial of such a highly innovative therapy. We will need to weigh the totality of the evidence to support that any proposed device has the data to support the potential to achieve the intended benefit of improving mortality and morbidity in the extremely

preterm infant, and that device-related risks can be adequately mitigated to ensure that the benefit risk determination is at least as favorable as current standard-of-care in the NICU. We look forward to the input from our invited speakers and the discussion by the PAC members to help guide FDA's consideration of all of these challenging issues. Thank you for your attention. We will now take clarifying questions regarding the three introductory FDA presentations before transitioning to discussion of non-clinical studies, which will start with FDA's overview by Dr. Crusan.

Clarifying Questions

Dr. Dracker: Are there any questions for our speakers? All right.

Dr. Cole: Yeah, Dr. Dracker?

Dr. Dracker: Hi, I'm sorry.

Dr. Cole: Yes, this is Dr Cole. I wonder if the FDA representatives could comment upon whether the known racial disparities in risk of preterm birth, inform the consent process in any way.

Dr. Nicole Gillette: I'm going to have Dr. Durmowicz start with that question.

Dr. Durmowicz: Thank you for the question, Dr. Cole. So, if I'm understanding, you're saying what – how will racial disparities inform the consent process? I think that's a very important point in a challenge that will need to be considered as the informed consent process, informed documents are developed for a trial in AWT.

Dr Cole: Thank you

Dr. Dracker: Randi Oster, do you have a question?

Ms. Oster: Yes, hi, this is Randi Oster, the Consumer Representative, and I would just like to understand in the informed consent, how long-term health consequences are discussed and the

support financially for those children who do have medical issues are covered or not covered and how that is presented or not in the informed consent process.

Dr. Durmowicz: This is Beth Durmowicz again, Medical Officer, Office of Pediatric Therapeutics. I think your points are well taken and those will be very important considerations when the informed consent documents and processes are developed for an AWT trial.

Dr. Dracker: This is Dr. Dracker, I'd like to ask a question as well. I think what was just mentioned with regards to sequelae following a subject for this procedure, I think the long-term follow-up is critically important and the response to the long-term follow-up should be considered by the by the investigators.

Dr. Durmowicz: This is Beth Durmowicz again, Medical Officer, Office of Pediatric Therapeutics. Thank you for your comment, doctor, I guess I think these are really supposed to be clarifying questions and we will have additional time for discussion of the informed consent process later this afternoon.

Dr. Dracker: Okay, great. Thank you.

Dr. Durmowicz: Thank you.

Dr Hill: This is Dr. Hill. I'm having trouble raising my hand, but I just wanted to go back to the question in regard to racial and ethnic differences in preterm birth. I think it will be very important as moving forward to make sure that this is rolled out in such a way that all groups, all ethnic groups, understand the benefit or non-benefit of this therapy. I hear the comments from the panelists, and we certainly would not want this type of therapy to be rolled out as an experiment on those who are at highest risk for preterm birth. Those are my comments. Thank you.

Dr. Green: Thank you, Dr. Hill, thank you Dr. Hill. I just wanted to also mention to everyone. Thank you so much for these comments. We are at the clarifying questions portion of the agenda. This is an opportunity for us to ask clarifying questions to the speakers based on their presentations, and we look forward to the discussion and comments in the later section of today's agenda. So, just a reminder, we're asking for clarifying questions at this stage.

Dr. Dracker: Nicole, are you available?

Dr. Gillette: Yeah, I was going to make the same comment as Dr. Green. So, we can keep going with clarifying questions. If there are no other clarifying questions, perhaps we can move on to the animal section?

Strengths and Limitations of AWT Animal Models

Dr. Dracker: Great. Thank you, Nicole. We're seven minutes behind, so we're catching up slowly, but we're doing alright. We will now proceed with presentations on AWT Animal Models. Committee members, you will have the opportunity to ask clarifying questions after the fourth presentation. We will begin with Dr Annabelle Crusan, Veterinary Medical Officer from the Office of Cardiovascular Devices in the Center for Devices and Radiologic Health.

FDA Perspective: Animal Study Considerations for Artificial Womb Technology Devices — Dr. Annabelle Crusan

Dr. Crusan: Good morning. I'm Annabelle Crusan, I'm a Laboratory Animal Veterinarian and Animal Studies Reviewer for CDRH. I will be giving FDA's current thinking on animal study considerations for Artificial Womb Technology Devices.

In today's presentation, I will cover animal study considerations for AWT to address safety and proof-of-principle endpoints. Then, I will highlight animal model considerations and historical use of the fetal lamb. In the last segment, I'll discuss comparative

anatomy and physiology in terms of exploring animal models for organ development and fetal circulation in humans and animals.

Non-clinical Device Evaluation. A comprehensive risk analysis is used to determine whether an animal study is necessary to evaluate the device. A device evaluation strategy can identify testing to address device attributes necessary for successful device performance. A series of bench testing such as engineering, simulated use, and a set of biocompatibility testing with defined decision points are used to evaluate device safety. This is also the time to investigate suitable and scientifically valid alternatives that may be performed in lieu of or to reduce and refine animal studies. Pilot animal studies can be very useful in guiding the design of subsequent larger experiments. They can include a targeted assessment of device function and attributes needed for the device to work as intended. Device design and procedures are often modified and optimized based on pilot's study results. Quality animal studies conducted are based on sound and valid conclusions from previous nonclinical studies to develop clinically translatable data. Large animal studies evaluate device safety and performance to support initiation of human trials. Throughout this process, the sponsor is encouraged to interact with the FDA via the pre-submission process so that FDA and the sponsor reach consensus on the non-clinical testing needed to support the clinical study.

Animal Study Considerations. Study quality and robust experimental design include careful selection of an appropriate animal model, which is essential to ensure the relevance of a particular model to human physiology and pathology. A comprehensive understanding of species-specific benefits and strengths and limitations are necessary to allow for a rigorous evaluation of medical devices that generate high quality data relevant to the endpoint being evaluated. Optimizing data generated by animal studies requires knowledge of

the biology of specific species and whether a given model can be used to simulate the clinical condition. This will help determine if the device will work as intended and to establish proof of principle. This will help establish basic device safety and performance to support a first in-human study. Animal study data are useful to support FDA approval of an IDE to conduct a clinical study of a significant risk device.

Animal Study Design. The objectives of the study should include the relevant proof of principle and safety endpoints. Study endpoints and acceptance criteria must be clearly defined in the protocol to help determine whether the study met its objectives. Sample size and grouping of animals can be based on a priori sample size calculation or scientific justification. This study should use the least number of animals that could provide a predictive outcome and meaningful interpretation of data. For AWT studies, a mid- to late-gestation fetus is the appropriate animal model, and it's also important to consider the number of dam or animal mothers that will provide their fetuses for this study. Determining the duration of a study can also be challenging, and this decision should be relevant to the expected duration of human use. Finally, it is important to consider data integrity and what assessments will be performed throughout the study to help define device safety. These range from periprocedural assessments, follow up period, and pathologic evaluation. Physiological assessments and clinical pathology are fundamental during the in-life phase. Postmortem assessments, such as gross and histological evaluation, as mentioned in the GLP regulations, is not only fundamental, but it is notably the distinguishing strength of the animal study that should be utilized fully and appreciated for its strong value in informing human safety.

Animal Study Insights. Animal studies designed to evaluate the AWT can give insights to how device function is intended in vivo, whether it provides acceptable hemodynamic

support, allow for critical organ system development and maturation in the fetal animal model, or even identify unintended effects. Animal studies can also assess the safety profile of the AWT in terms of hemocompatibility. If it can cause hemolysis, bleeding, and thrombosis, clinical chemistry stability, tissue injury, and organ dysfunction.

Animal model considerations. Selection of the best animal model is important to ensure that animal study data are most translatable to clinical use. Before selecting one animal model over another, one must consider each candidate's species' comparative anatomical, physiological, and pathological features and how these aspects of biology recapitulate those in humans. Although there may be well-established animal models for medical devices, there are rarely validated animal models for a specific device type. Additionally, it is important to remember that all animal models are inherently limited in their ability to comprehensively simulate the human-patient scenario. After all, animals, including us, are diverse. Choosing the best animal model for AWT may be based on feasibility of cannulation, adaptability to surgical manipulation, species size, growth rate, and movements that can be accommodated by the device. There's not one perfect animal model, but each model gives us a magnifying glass to increase our knowledge of safety of a medical device. The prenatal lamb is the most common fetal model, but fetal piglets and non-human primates are also considerations. It may be necessary to conduct studies in more than one animal model to fill safety and performance data gaps.

Fetal Lamb Model. The Fetal Lamb model and sheep as model for human reproduction dates back as early as 1937, and many scientific articles were published starting the 1960s. The Fetal Lamb has relevance to human anatomy, physiology and pathology, comparable

body weight and surface area, organ sizes, structures such as aorta and blood vessels, circulation, and responses to shear stress and blood contacting materials.

Comparison of lamb and human fetoplacental circulation is depicted on these top left two images and show the similarities in flow patterns and presence of two physiological shunts unique to the fetal circulation, which are the ductus venosus and foramen ovale. They show the preferential distribution of blood to myocardium, brain, and upper body. According to Lumber's book chapter,, fetal cardiac output is combined output of two ventricles where only seven percent of combined output is distributed to the lungs and the rest passes the ductus arteriosus into the systemic circulation. Around 58 percent of combined cardiac output is distributed to the placenta, which is the extracorporeal circulation. Fetal arterial pressure is low and in late gestation fetal lamb, the pressure is about half of the adult sheep arterial pressure. Top right is a table showing similar estimate blood volumes per body weight of fetal lamb and human fetus. The bottom tables are from Rudolph's 2018 paper that showed the differences between the distribution of cardiac output and organ blood flows in lamb and human fetuses, particularly in the later part of gestation. In Table 1, the lamb-human differences are largely related to variation in body configuration, organ size, and blood flow relative to organ weight, as the changes during gestational development are different in human versus the lamb fetus. For example, brain weight in the human fetus is 13 percent of body weight, compared to two percent in lamb. That is why cerebral blood flow increases dramatically in humans compared to lambs to support increasing vessel density in germinal matrix, gray matter, and white matter. Table 2 shows the umbilical placental blood flow and the oxygen content and glucose concentration of umbilical venous blood of lamb and human fetuses during development. The lamb fetus only has a small increase in hemoglobin concentration compared to marked increase in humans due to the differences in

decrease of umbilical placental flow in the latter half of gestation. Therefore, oxygen delivery is a critical component.

The left figure shows the five stages of pulmonary development correlated to the development of airways and capillaries. The 23-week-old, extremely premature infant, or EPI lung, is in the middle of canalicular phase of development. The canalicular stage is very important for EPI. At this stage, first, future air blood barriers are formed, and minimal production of surfactant is produced. The table shows that in fetal lamb, the mid-canalicular phase occurs at about 100 days, the macaque at 90 days, and the baboon 125 days. The timing of mid canalicular phases for each animal varies especially in comparison to the total time for gestation, which can create challenges in the interpretation of animal study results.

On the top left shows the development of human brain during gestational period and continued formation of synapses and myelin after birth. In comparing brain development of human, sheep, and rhesus, I took images from Halley's 2017 paper on brain growth in animals following a sigmoid pattern. The vertical color bars correspond to neurodevelopmental event estimates related to neurogenesis in green, tract formation in blue, and myelination in red. Compared to humans, sheep and rhesus are relatively mature neurologically at birth and have faster velocity growth curves for brain development. Sheep and rhesus fetus at about 75 days or younger are estimated equivalent of a 23-week-old human fetus. This stage of rapid growth represents the most vulnerable periods for developmental damage.

For mammalian renal development from pronephros, mesonephros to the functional metanephros, human, sheep, and non-human primates follow similar developmental pattern. Nephrogenesis is complete prenatally and glomerular capillary surface area will continue to increase. A human has a full complement of nephrons at about 30 weeks of gestation. Fetal

lamb completes nephrogenesis at late gestation of 130 days. Maturation of renal function occurs during different time frames for different species because of the differences in gestation lengths, which should be considered since the developing kidney has different periods of sensitivity to disruption of activity of fetal renal angiotensin system and susceptibility of renal sympathetic nervous changes to blood flow and glomerular filtration rate to chronic hypoxemia.

Considering the animal models I have presented thus far, the historical use of sheep and availability of singleton small sheep breeds that may be equivalent to mid- and late-gestation weights to human infant make the sheep fetus a potentially useful animal model. However, animal model limitations can confound an animal study include laboratory sheep breeds being larger than 23-week human infant at the equivalent canalicular stage of lung development, shorter umbilical cords comprised of two arteries and two veins compared to two arteries and one vein in humans, and growth rates approximately twice the rate of human fetal growth.

For cannulation, a fetal piglet is more advantageous to fetal lamb for simulating cannulation of umbilical arteries and vein in EPI. Fetal piglets are comparable in body size to EPI, vascular anatomy of fetal piglets, similar to humans of one vein and two arteries within the umbilical cord, and similar umbilical vessel diameters and length in relation to body size.

FDA has considered the advantages and limitations associated with Old World Monkeys. The Olive baboon infant has the largest body birth weight compared to other common NHP models such as rhesus, pigtails, and cynos However, the preterm baboon fetus, equivalent to canalicular stage of human lung development, is very small, which is a limitation for cannulation. Its smaller fetal heart cannot overcome the ECMO circuit resistance. The circuit volume is larger relative to the total blood volume of the fetus. For these reasons, while a fetal

NHP model may provide value due to similarities to humans, the model may add limited value for cardiopulmonary outcomes. Further, due to the anatomical differences at the equivalent stage of lung development with respect to EPI, it may logistically preclude application of the therapy.

I hope I was able to walk you through animal study design considerations for Artificial Womb Technology devices. A comprehensive risk analysis and finding valid alternatives are used to determine whether an animal study is necessary to evaluate the device. Robust and rigorous GLP animal studies, robust experimental design including identification of an appropriate animal model for AWT, I noted that size, including vessel sizes for cannulation, growth rate, and organ maturation are critical for animal models of mid- to late-gestation fetus. I presented similarities and differences in human and lamb fetal circulation, pulmonary, brain, and renal development of human, lamb, and NHP. Finally, I listed the fetal lamb and NHP animal model strengths and limitations and piglet advantage in umbilical vessel cannulation that may aid in the planning and development of AWT animal studies. This concludes my presentation. I'm very grateful for the opportunity to share FDA perspectives on animal studies and animal models for AWT. Thank you very much.

Dr. Dracker: Thank you, Dr. Crusan. Very interesting presentation.

Published Animal Models: Industry Perspective | AWT in a Preterm Lamb Model — Dr. Alan Flake

Dr. Alan Flake: Good morning. I was invited here to present our Preclinical Animal Study evidence supported by Safety and Efficacy Artificial Womb Technology.

So, what's the rationale for the artificial womb? We set out to design the technology to maintain normal fetal physiology and to mimic, as closely as possible, the environment of the maternal womb. By maintaining fetal physiology and extending gestation,

this technology is expected to improve the survival and wellbeing of extreme premature neonates. An important safety feature of the technology is that it allows the neonates to be quickly transferred to the standard-of-care if the technology fails for any reason.

The essential components of the Artificial Womb are, first, a sterile fluid environment maintained by continuous fluid exchange, that is, fresh fluid in and waste fluid out. Second, a pumpless, low resistance, low surface area, arterial venous oxygenator circuit. Powered by the fetal heart rather than a pump. And third, is the use of the umbilical vessels as a vascular conduit. Very simple in concept.

The role of each of these components in the potential prevention of mortality and morbidities of prematurity is shown here. The sterile fluid environment is essential to prevent developmental arrest of the lungs that occurs with any degree of gas ventilation. It allows normal liquid breathing and swallowing, maintaining the normal cyclic fluctuation of intrabronchial pressures regulated by the fetal larynx that is so important in normal lung development. There are also many non-pulmonary benefits of development in-fluid. It prevents thermal and septic stress, allows normal fluid balance, and provides buoyancy to prevent mechanical and pressure trauma. The combination of the AV pumpless circuit and umbilical vascular conduit mimics the placental circulation. The fetal heart is designed to develop under a very low workload, maintained by the low resistance placental circulation and the normal fetal circulation with its patent ductus arteriosus, ductus venosus, and foramen ovale. The fetal heart is very sensitive to afterload or preload imbalances, and the AV pumpless circuit allows some degree of auto regulation of blood flow. at the level of the umbilical vein ductus venosus, balancing circuit and systemic flows. The high flow that is uniquely allowed by the umbilical vessels allows normal O2 delivery at fetal saturations, critical to maintaining the fetal circulation. Finally, the use of the

umbilical cord provides full access to the fetal circulation, for monitoring, administration of nutrition or medications, it's painless and allows mobility of the fetus to prevent the need for narcotics, anxiolytics, or paralysis, thus avoiding catheter related complications and the neurodevelopmental impairment that is increasingly associated with these neuroactive drugs. In combination, the technology has the potential to favorably impact mortality and to reduce, essentially, all of the morbidities of prematurity.

So why the lamb model? Most of what we know about fetal physiology has been defined in the lamb model and for the most part has been validated in our understanding of human fetal physiology and development. The fetal lamb is the only model that I am aware of that is large enough at developmentally relevant time points to fulfill the surgical and mechanical requirements for development of the artificial womb. The primate models are simply too small, 100 to 200 grams at developmentally relevant time points. with umbilical blood flow too limited to utilize current oxygenator technology. The porcine model is size equivalent and has a very similar umbilical cord to human patients at 23-to-25 weeks, making it an ideal model for testing clinical techniques for conversion from placental to circuit support, but it's developmentally advanced near term, making it unsuitable for developmental studies or studies requiring prolonged circuit support. In summary, there is no perfect animal model. We have therefore done our best to use a combination of animal models to address specific questions in the most relevant animal models available to approximate clinical application.

After evolution of our technology through a series of prototypes, our initial studies in the artificial womb utilized the 105-to-113-day gestational age lamb model, which is developmentally equivalent from a lung developmental perspective to the human 23-to-25-week gestational age infant. In our initial publication, and in a number of publications since that time,

we demonstrated in this model, at least to the resolution of our analysis, that the artificial womb could maintain normal fetal physiology, growth, and organ development for up to four weeks. Specifically, we demonstrated maintenance of the fetal circulation, normal cardiovascular and oxygenation parameters, and normal lung, brain, and gut development. Given that the fetal lamb grows at approximately twice the rate of human infants, four weeks is a very clinically relevant duration of support.

However, the 105-to-113-day model is very large and has relatively advanced neurodevelopmental status compared to the 23-to-25-week human. Specifically, the germinal matrix is mature, and medullation, the process of neuronal migration and myelination, is near complete, making it a poor model for assessment of white matter susceptibility to ischemic injury and intraventricular hemorrhage. In addition, the large, more mature cardiovascular system might not mimic the human cardiovascular system's tolerance for the pumpless AV circuit. In contrast, the 90-to-95-day lamb model is more similar in size, although there's a lot of variability in lamb weights, to the human premature infant and neurodevelopment. Specifically, medullation in its early stage, making it a more relevant model for white matter ischemic injury. It should be mentioned that the 90-to-95-day lamb in general is much less mature than the 23-week human infant, more like a 17-to-19-week human infant in most respects. Note the gelatinous and fragile appearance of this lamb and the cutaneous ecchymosis just from placement in the bag. The next slides focus on comparison of the hemodynamic and oxygenation parameters of the early gestation model versus the late gestation model and includes data from the Nature Comms paper as late gestation controls and data that is pending publication for the early gestation labs.

This slide demonstrates that we can maintain physiologic circuit flow and stable hemodynamic parameters in the early gestational model for 14 to 21 days. An important observation is that the early gestation animals do not auto regulate their circuit flow like the later gestational animals do. We learned that to balance systemic and circuit flow, a circuit resistor was required. And with circuit flow restriction, the animals remain hemodynamically stable for the duration. The animals in the study were euthanized when they met study endpoints at 10 to 14 days for brain and tissue analysis, except for one animal which we allowed to continue to 21 days for a long term thrombogenicity study. My point in saying this is that we can maintain early gestation lambs for up to four weeks. For instance, we just had a 720-gram animal run physiologically for 29 days. For this study, however, we were most interested in neurodevelopmental endpoints at the 105-day time point, bridging the gap between 90 and 105 days.

This data shows that we were able to maintain stable oxygenation and cardiovascular parameters in the early gestation model. Interestingly, these graphs include data from three serendipitous late gestational IEGR animals, between 710 and 820 grams, that we ran as pilot animals to work out the flow restriction parameters prior to the study. They are included for interest and were maintained for 8 to 24 days on circuit. The bottom line is that the small animals tolerate the AB pumpless circuit, as well as the late gestation group, with appropriate management. I particularly like this analysis that shows cardiac dimensional growth over the continuum of 90 to 130 days. By all echocardiographic parameters, cardiac function, chamber size, and growth are normal in the early through the late gestational model.

What about the brains? They were assessed by independent veterinary radiology and pathology consultants. The MRI assessment included, among other things, diffusion

imaging, which is widely utilized to identify white matter injury and progression of white matter maturation. The analysis demonstrated normal brain growth relative to age matched controls, as well as normal maturation of all regions relative to age matched controls, with no evidence of intra-ventricular hemorrhage or ischemic injury.

Similarly, the histologic assessment demonstrated no evidence of ischemia or inflammation, with normal GFAP and IBA-1 staining, normal cortical and cerebellar histology and medullation, and no evidence of IVH or ischemic injury in the developmentally more relevant early gestational model.

As evidence supporting safety of Artificial Womb Technology, we have witnessed that in the animal models studied, the technology is robust and stable. We've now run over 300 lambs in the artificial womb, and the runs are generally remarkably smooth, with one trained fellow or technician able to monitor and care for up to three animals on circuit without difficulty. Over the course of our experience, we've observed no acute irreversible events that threaten survival or neurologic injuries, such as irreversible cord spasm, circuit thrombosis, cannula issues, major bleeds, or organ failure. In other words, lambs do not suddenly die on circuit. There's always a prodrome or indication that the lamb is approaching the end of the run, hours or even days before major deterioration. Finally, the ultimate safety feature is the fact that the potential patient can be immediately removed from the circuit for a standard of care or resuscitation if oxygen delivery is threatened.

The data I've just presented may support potential clinical benefit for the extreme premature infant that is treated by Artificial Womb Technology. We've shown in relevant animal models that the artificial womb maintains fetal physiology and the fetal circulation, avoids mechanical ventilation and oxygen exposure, prevents thermal and septic stress, avoids invasive

monitoring and central catheters, and dramatically reduces or eliminates the need for narcotics, anxiolytics, and paralysis. All of this would be potentially beneficial for reduction of mortality and the major morbidities of prematurity. These data may support feasibility, proof of principle, and safety for consideration of a clinical study of Artificial Womb Technology.

So, in conclusion, in the animal models described, the Artificial Womb can maintain normal physiology and support normal organ development. We believe that our preclinical data supports feasibility and safety, and that it's adequate for consideration of a carefully designed clinical study of Artificial Womb Technology.

Finally, I would like to acknowledge the Children's Hospital of Philadelphia for the sustained and generous support of the Artificial Womb Project over the past decade, as well as the dedicated personnel of the Center for Fetal Research that made our progress possible. Thank you.

Dr. Dracker: Thank you, Dr. Flake. We will now hear from Dr. George Mychaliska, Professor of Pediatric Surgery at C. S. Mott Children's Hospital in Ann Harbor, Michigan.

Published Animal Models: Expert Guest Speaker Perspective | Artificial Placenta in a Preterm Lamb Model — Dr. George Mychaliska

Dr. Mychaliska: Good morning. I'm George Mychaliska, a Pediatric and Fetal Surgeon and Researcher in the ECLS Laboratory at the University of Michigan. Thank you for this opportunity to present artificial placenta technology in a preterm lamb model.

In this presentation, I will present the clinical rationale and principles of extracorporeal support in premature infants. I will discuss the evolution to the VV-ECLS configuration and our approach to lung management. Using this model, I will present our data on long-term support and assessment of organ development. I will highlight recent work developing

non-thrombogenic surfaces, making extracorporeal support possible without systemic anticoagulation. I will conclude with our work developing clinical risk stratification, our clinical approach, and remaining scientific milestones prior to clinical application.

Optimal treatment of prematurity remains an unsolved problem. Mortality and morbidity of ELGANs remains disproportionately high. The predictable complications including chronic lung disease, neurodevelopmental problems, IVH, necrotizing enterocolitis, retinopathy of prematurity, and sepsis are due to both organ immaturity and the unintended iatrogenic consequences of conventional postnatal therapy. Given significant organ prematurity, optimal growth and development should occur in a fetal environment.

A radical paradigm shift in the treatment of prematurity would be to recreate fetal physiology in the form of an artificial placenta.

The key principles include maintaining fetal circulation, a low oxygen environment, no mechanical ventilation with fluid filled lungs, and either a VV- or AV-ECLS cannulation configuration.

This slide represents a decade of evolution in our laboratory. We began with a pumpless trans-umbilical AV-ECLS approach with a submerged premature lamb who also underwent a thoracotomy with placement of invasive monitoring, picture at the top left. Despite a smooth transition during an exit procedure to the artificial placenta, we encountered umbilical artery spasm, which led to cardiac failure and diminished flows. Despite adding a pump and other refinements, we were limited by persistent hypotension, picture at the top right. Given these constraints, and with an eye towards eventual clinical application, we transitioned to a VV-ECLS approach, with inflow through the umbilical vein and outflow through the jugular, demonstrating 24 hours of support. Picture at the bottom left. As you can see, we continued with

an amniotic bath for lung management, but despite many maneuvers, we had persistent problems with infection. The bottom right picture demonstrates our latest model with a fluid filled endotracheal tube for lung management.

The data I will present are based on the 118-day model, term equal to 145 days. We chose this gestational age since the lung maturity is similar to a 24-week human infant. As mentioned, this is a pump driven system with umbilical vein reinfusion and jugular drainage. After trying various liquid mediums, we found that perfluorocarbons were superior in terms of lung protection and development. Furthermore, partial liquid ventilation may serve as a protective bridge after AP support before air breathing. These animals receive empiric antibiotics, steroids, prostaglandins to maintain ductal patency, and TPN for nutrition.

In this video, you can see a comfortable animal on the artificial placenta in a standard neonatal isolate with inflow into the umbilical vein and outflow through the jugular. As noted previously, we instill perfluorocarbons to a meniscus, which allows fetal breathing movements.

In this video, the sweep has been turned off, the lungs suctioned, and the sheep is breathing supplemental oxygen.

Using this VV-ECLS approach, we compared optimal medical treatment with an oscillator and surfactant to the artificial placenta. The premature lambs on the AP survived for one week, compared to only a few hours for the mechanical ventilation controls. You can see the artificial placenta provides remarkably stable hemodynamics and gas exchange in the normal fetal range.

Since the artificial placenta is intended to be applied after birth and clinical risk stratification, the next question we ask is, can the artificial placenta rescue animals after

ventilatory failure? These experiments demonstrated fetal lambs who failed mechanical ventilation could be stabilized with re-initiation of fetal circulation with stable hemodynamics, gas exchange, and minimal lung trauma.

When clinically translated, the artificial placenta would provide hemodynamic stability, gas exchange, and the fetal milieu for organ protection and ongoing development until the organs are mature enough for conventional treatment, including air breathing or minimal ventilatory support. As such, our next major goal was to examine many organ systems, including the lung, brain, GI tract, liver, spleen, heart and kidney. Overall, the data suggests that major organ systems are protected and continue to show evidence of development.

Given its central importance to gas exchange, we published several studies on lung development and management during AP support. Histological data indicate the lungs continue to mature, and functionally premature lambs are able to transition to mechanical ventilation after 10 days of AP support. Compared to other fluid mediums, including artificial amniotic fluid, perfluorocarbons minimize lung injury and promote lung development.

Given the serious intracranial complications and neurodevelopmental sequelae of extreme prematurity, we studied brain perfusion with NEARS and carotid flow probes on AP support, as well as post-mortem MRI to assess for white matter injury. It is acknowledged that the fetal lamb model at 118 days is not a good model for IVH. Since the germinal matrix is mature, it is still a good model for white matter injury. Data demonstrate that cerebral oxygenation and blood flow is maintained on AP support, and no white matter injury was noted with normal cortical folding.

Given the baseline risk of IVH in premature infants, and also experience with elevated intracranial hemorrhage with application of preemi-ECMO, from 29 to 33 weeks with

systemic anticoagulation. We developed a novel, non-thrombogenic surface coating we termed NOSA, Nitric Oxide Surface Anticoagulation. The polymer surface with the top coat of argatroban elutes nitric oxide at the same flux units of endothelial cells preventing thrombosis locally in the circuit without systemic anticoagulation. Since the oxygenator cannot be coated, as this would impede gas exchange, we use NO in the sweep flow to prevent thrombosis. In a recent published manuscript, we demonstrated five premature lambs survived for one week with no systemic anticoagulation. There was no significant bleeding or thrombosis with normal fetal gas exchange, hemodynamic stability, and maintenance of fetal circulation. Not only is this approach optimal for clinical application of the artificial placenta to LGANs, it could be applied to standard ECMO for infants greater than 28 weeks estimated gestational age to mitigate risks of intracranial hemorrhage.

A milestone for clinical application of the artificial placenta is miniaturization. The premature lamb model at 118 days is approximately 2.5 to 3 kilograms. We have performed unpublished experiments in two different premature models. The left picture shows our early work in a standard 95-day fetal lamb model, which you can see is quite immature developmentally, but is still 1.5 kilograms. The right picture shows a 105-day, one kilogram mini sheep model, which we are using for further miniaturization experiments. The artificial placenta will require small cannulas and we demonstrated in preliminary studies the feasibility of using six French cannulas with adequate flows and support.

The artificial placenta is intended to be applied after birth, and our group is targeting an 80 percent expected mortality for initial clinical application, consistent with the initial criteria when ECMO was introduced clinically. If this technology demonstrates safety and efficacy, the inclusion criteria would be adjusted accordingly. Retrospective analysis from the

University of Michigan demonstrated that SNAPPE II at four hours of life had an AUC of 0.8 and was the best predictor of mortality. We are currently in the midst of a prospective study including other variables, including markers of morbidity.

Clinical application would utilize existing NICU and ECMO platforms with modifications such as perfluorocarbon-filled lungs, which we have used in a previous clinical trial of congenital diaphragmatic hernia patients on ECMO. Early application of the artificial placenta on the first day of life, after risk gratification, would be expected to re-initiate fetal circulation with minimal barotrauma. For premature infants not captured on the first day of life and subsequently fail maximal medical therapy, the artificial placenta would be applied as a rescue therapy. We recognize there are many ethical and regulatory considerations prior to clinical translation. Thank you very much for your attention.

Dr. Dracker: Thank you, Dr. Mychaliska. We will now hear from Dr. Mike Seed, who serves as the Head of the Division of Cardiology at the Hospital for Sick Children in Toronto.

Published Animal Models: Expert Guest Speaker Perspective | AWT in a Piglet Model — Dr. Mike Seed

Dr. Seed: Thank you for this opportunity to present our experience with Artificial Womb Technology. Our main findings have been reported in two publications, which are shown at the bottom of this slide.

Compared with the prior speakers, our group has less experience with Artificial Womb Technology, having embarked on setting up a lab following the publication of the sheep research conducted by Dr. Flake and his team at CHOP. Our choice of a pig model was primarily a practical one, as the animal research facilities at our institution are not equipped to house pregnant sheep. Indeed, our only option in terms of a large animal model was to use miniature

pigs. And this has had implications for our research, including some potential advantages such as their umbilical cord anatomy, which is similar to humans. In addition, towards the lower limit of viability, which is around 95 days gestation in pigs, many pig fetuses weigh around 600 grams, which is comparable to human infants born extremely preterm. Term gestation in swine is approximately 115 days.

One disadvantage of working with pigs is that there is relatively little in the way of reference data available regarding the fetal pig circulation or fetal pig development. And so, our experiments have needed to include the collection of some control data, including fetal MRI scans like this one to measure their umbilical blood flow.

Our initial approach was modeled on the sheep experiments described by Dr. Flake's team using a commercial neonatal cardiopulmonary bypass oxygenator. Successful cannulation of the umbilical cord vessels required a learning curve. And even in more recent experiments, we are still not consistently able to achieve transition to the system in every animal.

Nevertheless, we did successfully initiate support in 12 animals at a mean gestational age of 98 days and birth weight of 740 grams. We compared blood gases and hemodynamic parameters between animals supported on the system and in utero controls. The most striking and consistent observation was that our artificial placenta subjects were markedly tachycardic and had significantly diminished umbilical blood flow compared with their in-utero controls.

And we observed an inverse relationship between these two parameters. whereby lower umbilical flow was associated with faster heart rates. In this initial set of experiments, our animals deteriorated over a matter of hours, becoming visibly edematous, with pleural effusions and ascites.

Echocardiography revealed enlargement and reduced contractility of the right ventricle, and we concluded that abnormal myocardial loading conditions imposed by the circuit were causing cardiac failure in our subjects.

Our initial reaction was to consider trying to develop a miniaturized oxygenator, but following discussion with some engineering colleagues, we decided first to experiment with adding a pump to the circuit and continuing to use a commercial neonatal ECMO oxygenator. This figure shows the second setup, whereby a small centrifugal pump was placed between the umbilical artery cannulas and the oxygenator.

The addition of the pump resulted in a marked improvement in the circulatory physiology of the animals, at least for a period of hours.

This graph shows a comparison of the circuit flow on the pumped circuit, shown in red, versus the pumpless circuit, shown in blue.

And we saw significant improvements in the duration of our experiments, which now averaged 48 hours, with one animal lasting a full week.

This plot shows how the circuit flows of 12 animals supported on the pumped circuit compare with in-utero umbilical flow. indicated by the dashed red line. As you can see, the animals on the pumped artificial placenta circuit initially exhibit supraphysiologic flows, but then ultimately settle out with sub-physiologic flow.

However, the animals supported on the pump system were similarly tachycardic as those supported on the pumpless system.

And over the course of several days, we continued to observe a steady increase in the size of the heart and myocardial thickness and the development of fluid collections. In this

second set of experiments, we also collected more data in terms of arterial and venous blood pressures.

And this diagram synthesizes some of that data with existing reference information regarding normal human and sheep fetal physiology, whereby the numbers in black are the reference data and our findings in pigs supported on the pumped circuit are shown in red. The most informative differences are probably the tachycardia, the systemic hypertension, and the differences in umbilical venous physiology, including a reduction in umbilical vein flow and an increase in umbilical vein pressure.

And we have speculated that the mechanism leading to circulatory failure in our pumped circuit could start with elevated post membrane pressures generated by the pump, inducing vasoconstriction in the umbilical cord and ductus venosus. The associated fall in umbilical flow may then impair venous return to the heart, resulting in a drop in cardiac output, which would trigger a sympathetic response, including peripheral vasoconstriction and tachycardia, placing additional afterload on the right heart and resulting in cardiac failure.

In conclusion, we have yet to achieve consistent, physiologic fetal circulatory parameters in our model. We believe this is due to our circuit imposing abnormal cardiac-loading conditions on the fetal heart, which is perhaps not surprising considering our use of devices that were not designed for this purpose. However, we remain extremely enthusiastic about the potential of Artificial Womb Technology and are about to embark on a new set of experiments using a third iteration of our circuit. Thank you very much.

Clarifying Questions

Dr. Dracker: Thank you, Dr. Seed, and to all our speakers who are available to answer any clarifying questions until we take our morning break. Our morning break is at 11:20. Normally, I

will allow it to go to 11:25 and we'll decrease the break to 5 minutes so that we can begin the open hearing at 11:30. Thank you.

Dr. Lee-Summers: I have a question.

Dr. Dracker: Go ahead. Is this Dr Steven? Who's that?

Dr. Lee-Summers: This is Jenny Lee from Johns Hopkins.

Dr. Dracker: When you do ask a question to all of you, please identify yourself prior to asking your question. Thank you.

Dr. Lee-Summers: Hi, this is Jenny Lee from Johns Hopkins. Were the brain MRIs in the lambs obtained in-vivo or ex-vivo?

Dr. Mychaliska: This is George Mychaliska from University of Michigan. In our studies, these were postmortem MRIs. Which, to my knowledge, working with experts in our group, are quite accurate at defining white matter injury.

Dr. Lee-Summers: May I ask, were they perfused brains? Did you perfuse them?

Dr. Mychaliska: They were perfused, this was a number of years ago, they were perfused very specifically to a certain pressure with formalin.

Dr. Lee-Summer: So they were fixed, perfused brains, ex vivo MRI?

Dr. Mychaliska: Correct.

Dr. Lee-Summers: Okay, thank you. Thank you.

Dr. Flake: I'll answer. This is Alan Flake from CHOP. We also used fixed perfused MRIs for FDA-related studies that I presented in the earlier gestation lamb model. We've done earlier MRIs on lamb survivors of the system up to six months of age and those were done in living lambs.

Dr. Lee-Summers: And was this like a three-T or 1.5-T clinical magnet or what? What type of magnet were you using for the ex-vivo?

Dr. Flake: I believe it was a three T for the fixed studies.

Dr. Lee-Summers: Okay.

Dr. Flake: And 1. 5 for the living ones, there.

Dr. Lee-Summers: Thank you very much.

Dr. Dracker: Thank you for this information. Dr. Hoehn, you had a question?

Dr. Hoehn: Yes, Sarah Hoehn from the Pediatric Advisory Committee. My question was, I believe it was doctor umm from Michigan talked about how they compared the outcomes when they used oscillator and surfactant to the artificial placenta with perfluorocarbon. But my question is specifically when in the animal models, when they're doing the fluid in the lungs and keeping them in the fluid, have any of the models, either the lamb or the piglet, included surfactant in that fluid, as opposed to waiting till they're coming off to get surfactant? Have any of the models incorporated giving them surfactant when their lungs are still filled with fluid?

Dr. Mychaliska: So, that's a great question. This is George Mychaliska from Michigan. It depended on our studies. We did a number of studies because our device is intended to be used after a birth and after the patient is intubated. So, in those cohorts, we would give surfactant and if they failed mechanical ventilation and we went on the artificial placenta, we would then instill perfluorocarbons in.

Dr. Hoehn: Okay, thank you. And then I just had a follow up question. Were they also getting steroids,

Dr. Mychaliska: Yeah.

Dr. Hoehn: Or were there any concerns if they got steroids when initiating the artificial womb, if that made anything worse?

Dr. Mychaliska: It actually made things better in general. We have been giving steroids to our animals. The vast majority.

Dr. Hoehn: Thank you.

Dr. Dracker: Dr Davis.

Dr. Davis: Thanks very much. Following up on some of those comments, I appreciate Dr Flake's comment that there is no perfect animal model and it's probably a big reason why there's been such limited drug and device development for neonates over the past 30 years. But my question for our FDA discussant and some of the other folks is about the animal model as we're trying to assess risk benefit. You know, certainly when you are talking about 22 and 23-week gestation fetuses with mothers in preterm labor, probably 60 to 80 percent of them, there's either inflammation or infection in the placenta. And that is going to have a significant impact along with many of the medications, like steroids, as you mentioned, or magnesium antibiotics, other medications that the mother's getting while pregnant. So, can you comment with the lack of all of that, I don't know that any of these models are really simulating the human condition in a way that is going to allow you to really be able to predict things until you actually do the human trials.

Dr. Dracker: Any further comment to Dr. Davis's question?

Dr Crusan: Yes. Go ahead Dr. Flake.

Dr. Flake: I'm sorry. This is Alan Flake. Yeah, I just agree with you completely. There are no models of preterm labor related to human pathophysiology in the lamb or other systems that are applicable here. I will say that, in general, the preterm delivery is related to maternal

pathophysiology, and the fetus is a relatively healthy individual in that process. Now, there may be impacts on the fetus from these pathophysiologic conditions, but in general, they're stably surviving on placental inflow at the time of delivery, and we would be replacing that placental inflow. So, it doesn't really answer your question, but I think it also doesn't negate the information provided by normal animal models related to the ability to support the fetus for their system.

Dr. Crusan: I also would like to add that for animal models, like Dr. Flake has mentioned we would like the animal model to be as healthy as possible to minimize variables and other confounding factors. And also, as far as the animal study design, is we would like the animal study to be to mimic the clinical condition as much as possible. I think in that way, we will be able to review the animal study whether it demonstrated evidence of safety.

Dr. Dracker: Thank you. To our members again, I'd like to remind you to please identify yourself and not to turn on your camera until you are asking a question. Dr. Cole.

Dr. Cole: Thank you. This is Dr. Cole from Washington University. This is for Dr Crusan. Are you – you did a great job comparing the anatomy and physiology of sheep and human. I wonder, has there been a direct comparison of placental function and placental contribution to fetal development between a human and sheep?

Dr. Crusan: Honestly, I haven't seen a paper with regards to the placental function, and also the factors that are present in the sheep placenta comparing to the human placenta. But I think that later on in the presentation, one of the guest speakers will be able to at least discuss the factors that are present in the human placenta. But as far as I'm concerned, I haven't seen a study comparing sheep and human.

Dr. Cole: Thank you.

Dr. Dracker: Randi Oster, you had a question?

Ms. Oster: Yes. Yes. My question is for Dr. Crusan, and I just want to first point out that Dr. Mychaliska, he did talk about how the long-term medical problems are common. And so, the question that I had is knowing that and the CR, 21 CR 50 subpart D, we are looking for no mortality and morbidity and trying to understand that when you gave your presentation, the end point seemed to be for the survival of the machine. And my question is, how long after the animal came out of the machine, are they followed up for morbidities? And is there any correlation between the morbidities you see in the animals that we can then use for understanding known morbidities in infants?

Dr. Crusan: I think that will be a question for Dr. Mychaliska and Dr. Flake as well as Dr. Seed with regards to their animal studies.

Dr. Flake: This is Dr. Flake. I can start if you wish. That's one of the limitations of the animal model, is that sheep are quite difficult to survive after any intervention in which they are not normally delivered and placed on ventilation, et cetera. And that relates to their multiple stomachs, swallowing air when they're on the ventilator, competing with their respirations, et cetera. So, we have survived four lambs after being in the system, one of them was followed up for over 6 months and we saw no obvious morbidity in the lamb. Now, that's a limited assessment, obviously, we did do a neurocognitive assessment in the lamb and some other testing, but we could see no evidence of abnormality. But this isn't obviously relevant to long-term human morbidity after the use of the artificial womb. And I think that's going to rely on long-term follow up of any subjects that are placed on the artificial womb for many years, actually, to see what its long-term effects may be.

Dr. Dracker: Thank you, Dr. Flake. Uh, Dr. Fischer, you had a question?

Dr. Fischer: Hi, yes. Gwen Fisher from University of Minnesota. This question is for Dr. Flake from CHOP. The data that you provided was very comprehensive. I'm wondering specifically about the cardiac growth data you shared if there – specific question being if there is a human or a comparable lamb data that you guys have looked at to compare that growth rate with what would happen in standard-of-care NICU therapies, and then a more general question around that being in a clinical trial, what kind of comparison data do you imagine we would be using for this therapy?

Dr. Flake: Well, thank you for that question, Dr. Fischer. So, we've used primarily fetal standards to assess normal cardiac growth and our echocardiographer, Dr. Jack *Rychik* has generally compared our lambs to same gestational control lambs in terms of their cardiac dimensions and function. I think in the NICU, the comparator is appropriately also normal fetal heart growth and development because we're trying to maintain the fetal state and the fetal circulation. And so, comparing it to the postnatal cardiac parameters in a premature infant would be difficult. The premature implant has undergone some degree of transition to the postnatal circulation. They have stresses, cardiac stresses from afterload, et cetera, that are not present in the fetus. And so, I think their cardiac dimensions will be different than the normal developmental dimensions that you see in a fetus.

Dr. Dracker: Thank you very much. Trying to stay on schedule. We will not take further questions at this time. We will have time later on today to address those issues. Please make notes so you remember what you wanted to ask and Marieann will make sure we ask the questions in the order that they were received. We will take a 10-minute break and we'll resume at approximately 11:32. There will be two open hearing speakers and I'll see you in 10 minutes. Thank you very much.

Open Public Hearing

Dr. Dracker: Welcome back everyone. We will begin the Open Public Hearing session. We originally had three speakers. We now have two, so I am hopeful that at the end of the public hearing session, we will still have time before lunch to address the remaining questions. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee Meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, the FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with parties engaged with the topic of today's discussion. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the Open Public Hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for the Open Public Hearing to be conducted in a fair and open way, where every participant is listened to carefully, and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by myself, and thank you for your cooperation. Speaker number one, your audio is now connected. Will speaker number one introduce yourself? Please state your name and the organization you are representing, for the record.

Dr. Romanis: Hi, my name is Dr. Elizabeth Clary Romanis. I'm an associate professor in Biolaw at Durham University in the UK.

Dr. Dracker: Thank you. And your question?

Dr. Romanis: Great. So I have no financial relationship to declare before I begin. And thank you for allowing me the time to speak today. I've been researching the ethical and legal implications of artificial womb and placenta technologies for the last six years, and have published over 15 peer reviewed publications on the subject. I firmly believe that the development of this technology could revolutionize our treatment of pregnancies that become dangerous, and premature human entities, with substantial benefit. My position is, however, that there are ethical and legal implications of this technology that need to be considered in advance of its first use. And some of those are broader than the immediate ones that are talked about when it comes to clinical translation. These devices mark a paradigmatic shift in the approach to care, and they are clearly conceptually distinct from existing conventional methods of care. These artificial wombs or placentas are an alternative to neonatal intensive care.

But we must not lose sight, when we're thinking from an ethical or legal perspective, of the fact that these devices aren't just an extension of existing methods, but they're something fundamentally different. Entities gestating outside of the human body, as the devices are designed to facilitate, are human entities that we've never seen before, and this has all sorts of implications and raises new questions. Because I only have a short time, I'm just going to focus on some of the implications I think are most significant in relation to human use, but a full account of these questions and some others are included in the written comments I submitted, along with a list of relevant publications. So firstly, while it's easy to focus on the fetus or premature human entity when discussing artificial wombs, the pregnant person should be at the

center of how decisions are made. I appreciate it was noted at the beginning of this meeting that maternal considerations were outside the scope. However, it's hard to cleanly separate the issues of pregnant people and their wanted fetuses, and I think there are clear dangers in doing so.

The care pathway for artificial womb technology clearly starts before the pregnancy has ended because the entity must be extracted from the pregnant person. And there may be, for some people, psychological implications for parents, and especially some pregnant people in using the artificial womb. We know that people who experience prematurity sometimes report a sense of loss and grief about the loss of their pregnancy, even if their fetus survives. I have a paper forthcoming with a colleague, Victoria Adkins, in which we suggest that this loss might be exacerbated by the artificial womb. Now, we don't suggest that's the reason not to develop the technology, but it is something that needs to be considered in how care pathways are developed and tested. In doing clinical translation, we think that we need to make sure that we're evaluating the care pathway as it's experienced by pregnant people and parents, with supplementary social science research, as well as looking at the potential implications for preterm neonates.

Secondly, there are large disparities in maternal morbidity and mortality in the United States. Prematurity is far more likely to affect racialized groups and people from lower socioeconomic backgrounds. This potentially means that the technology is more likely to be tested on people or premature neonates with some structural disadvantages and from a group that may be less likely to access the technology if it were clinically translated in future. This is an important context that needs to be considered in all aspects of the ethical and legal issues that are raised.

Third, in my work I've argued that an entity undergoing gestation outside the body is a unique human entity. It has fetal physiology, but it's not part of a pregnant person. I called this

subject a gestateling in my work, which literally means ‘of gestation’. Others have used different names since. While this is not a matter which determines whether the process of gestation outside the body is permissible or not, it is something that we need to think through, because this new entity is being created in this process. That it is different, means that there may be subtle ways in which the protection afforded to it should be different, or there are novel ethical dilemmas that are raised by its existence, and complex legal questions. For example, how can it be or should it be treated if there is a complication? What happens if there were a serious mistake made, and the gestateling suffers severe complications while in the artificial womb, during clinical translation, or as it comes for future use? Thank you so much for your time. More information substantiating these thoughts and other questions are in my written comments, as I mentioned, and I would welcome any opportunity to discuss the ethical and legal implications of these devices further in the future. I think it's really important to incorporate the perspectives of legal and ethical experts. Thank you so much.

Dr. Dracker: Thank you for your comments and your very important insight. We look forward to your publication. I'm sure we will consider that as well. Thank you. Speaker number two, your audio is now connected. Will speaker number two introduce yourself? Please state your name and the organization you're representing, for the record. Thank you.

Ms. Scarato: Thank you. Theodora Scarato, Executive Director of Environmental Health Trust, with no financial relationships.

Dr. Dracker: Welcome.

Ms. Scarato: Thank you. Thanks for the opportunity. We are a scientific think tank and our experts have published extensively on the issues of environmental health as well as bio electromagnetics. So, plans to establish the safety and effectiveness of artificial womb

technology devices, or any technology involving premature infants, must consider the non-ionizing electromagnetic field environment. I'm referring to the following non-ionizing electromagnetic field sources, the magnetic electric fields, the extremely low frequency fields emitted from the electrical equipment of the technology itself, as well as technology near the infant in the womb, and even from outside sources. So, in addition, there are the wireless emissions, the radio frequency electromagnetic fields, and they're present in the room, not just from devices that may be on the equipment, but also used by staff, also Wi-Fi and wireless networks, which are in the room and vicinity, as well as sources that may be outside the room, from exterior sources like base station antennas or cell towers and so forth. Now, metal can reflect radio frequency and create unexpected exposures. There's also, liquid is conductive, and all of these sources and exposures need to be assessed and addressed and mitigated, because of the growing and substantial body of evidence indicating adverse effects at low levels. And also ways that this exposure can impact – you know – impact development.

So, I'm sure you're aware of the researchers at Penn State Medical Center, that found reducing electromagnetic fields improved health outcomes in the preterm infants in NICU equipment. The EMF levels are linked to various impacts on the autonomic nervous system, including heart rate. So, there have been many recommendations to mitigate levels related to incubators, and redesign them to reduce exposures to the babies and caregivers. Now, this issue has not been explored previously or adequately researched in terms of the equipment that's being discussed here. But what we do know is that children have proportionately higher exposures to any one device, like a cell phone and wireless devices, because they have thinner skulls and higher water content in their tissue. They have smaller heads, resulting in a shorter distance for the radio frequency to travel, from the skull to critical brain regions important for learning and

memory. And modeling has found, when they've looked at comparing adult and children models, you know, a tenfold greater radio frequency absorption into the pediatric cerebellum, tenfold greater into the bone marrow of the skull, 30 folds greater into the hippocampus, and two to almost five-fold in the eye. So, we also know that even if the exposure were the same, that the child's developing brain and eyes and organs are more sensitive. They have more active stem cells, and those have been found to be more impacted by radiofrequency. And of course, there'll be a longer lifetime of cumulative exposure starting before birth. So, as the 255 scientists with expertise in the field of electromagnetic biology state in the EMF scientist appeal, numerous scientific publications have shown that electromagnetic fields affect living organisms at levels well below most international and national guidelines. Effects include increased cancer, cellular stress, increasing harmful free radicals, genetic damages, structural and functional changes of the reproductive system, learning and memory deficits, neurological disorders, and negative impacts on general well-being in humans. And I will be submitting extensive documentation for you on these publications.

But the issue is that we have a regulatory gap and regulatory deficiencies that are quite extensive. The FCC limits, for human exposure to wireless radio frequency, were set in 1996 and remain unchanged since then. The EPA was the lead researcher in development of safety limits, until it was fully defunded in 1996. The FCC then set limits based on industry group recommendations that protect for heating effects, of short-term radio frequency exposures only. In fact, the studies that underpin these limits used antiquated behavior studies with small sample sizes, where animals were exposed to radio frequency frequencies for under 60 minutes of exposure. And the level of harm was identified by internal temperatures noted when they stopped pressing the lever for food. There was not long term, you know, chronic low level exposure

studies that had been completed at the time, certainly. Current FCC limits do not protect against non-heating related biological effects, nor for effects from chronic long-term exposures. And they certainly never considered children or developing fetus. Now, federal agencies, such as the EPA, CDC, FDA and NCI, have not formally evaluated the totality of the up-to-date scientific evidence. There are no risk assessments, no systematic reviews, nor transparency in what activities even exist. In 1999, the FDA requested that the National Toxicology Program perform large scale animal studies to test for health effects from chronic low level cell phone radiofrequency radiation. And in 2018, the NTP released its final report, finding significantly increased tumors in the brain, as well as Schwann cell tumors in the hearts of exposed male rats. And in addition, they found DNA damage in the brains of exposed rats and mice, reduced pup weights, as well as the induction of cardiomyopathy of the right ventricle, in male and female rats. And the levels were all below levels that FCC limits would consider the heating thresholds of harm. So, FCC limits cannot be understood as resting on accurate assumptions in terms of what level causes harm.

Now, a 2021 analysis of the NTP study concluded that FCC limit should be strengthened by 200 to 400 times to protect children, according to current risk assessment guidelines. However, the FDA has disagreed with the NTP findings and released a limited literature review, which is only on phones, only on cancer, dismisses the NTP study, and notably, it's not a risk assessment by any formal procedure that is used in risk assessment, despite the word being used. And all non-cancer issues are omitted. Importantly, issues such as impacts to memory, brain development, and the endocrine system, they're completely absent in this review.

So, there needs to be, this issue needs to be addressed. Now, we did file suit against the FCC and had a favorable ruling in 2021 and the D.C. circuit, U.S. Court of Appeals D.C. circuit,

ordered the FCC to provide a reasoned explanation as to how these safety limits, that are in place, are adequate in light of the ambiguity of wireless radio frequency, current use patterns, children's vulnerability, and the research documenting long-term effects. The FCC has not complied with that mandate. Now, the FCC limits that we have, test for heat, in a large adult male phantom, 220 pounds with a 12-pound head, certainly not an infant. There are no federal regulations when it comes to those lower frequencies, the magnetic fields frequencies from the electrical system. And there also is the issue of harmonics in the electrical system from whatever is plugged in, which needs to be measured. We would recommend any technology involving infants, ensure non-ionizing electromagnetic fields being measured and mitigated, due to the lack of regulatory safeguards in place. And just as an example, the Archbishop Makarios Hospital in Cyprus piloted an RFR reduction program in the pediatric intensive therapy units and neonatal units. They removed the Wi-Fi access points, installed wired networks, and launched a multimedia educational program. And they measured before and after, and were able to document the reduced levels. Thank you so much for the opportunity.

Dr. Dracker: Thank you very much. I think you brought forward a subject area that we don't normally think of, especially in ex vivo applications. Perhaps we should put the artificial womb in a Faraday cage, and that might reduce some of the risks. So I think your contribution is very important and something that many researchers don't always keep in mind. So I appreciate your comments. Thank you.

Ms. Scarato: Thank you.

Additional Q & A For Morning Speakers

Dr. Dracker: We have the Open Public Hearing session until 12:30, but we can take additional questions that we did not address earlier. And then, if there are any other speakers that would like

to make a comment or join in, please let us know. And again, if you do, identify yourself and your relationship to the entity that you're representing. So, I will wait a few minutes to see if anybody has additional public hearing concerns. If not, I'd like to move ahead with Dr. Gleason's question, before we got to this segment. Dr. Gleason, are you still interested in asking a question?

Dr. Gleason: Sure, thanks very much. Christine Gleason, University of Washington. I had a question for Dr. Flake. I don't know if he's still on, but it was a question about the advantage of the AWT that he referred to, as did another speaker, that the lambs could immediately put, be put, or transition to standard of care, if that was needed, for whatever reason. And so, I just wondered in the 300 lambs that he presented on AWT, how many needed to be transitioned immediately to standard care? And how, how was that done? With, you know, fluid filled lungs and so forth. How was it done? Were there any complications from it?

Dr. Flake: Thanks Dr. Gleason for your question. My comment was really related to clinical application of this technology, not to the lamb model per se. Now, we have, in efforts to survive lambs, we have taken them out of the system and transition them to ventilation, to demonstrate lung function for the FDA related study that we did. And that, that transition is very possible and seamless. You simply clamp the umbilical cord. If you want, you can leave them on the circuit for a transitional period, or you can just clamp the umbilical cord and ventilate the lamb in this case. But in terms of clinical application, it would be much easier to simply open the device and transition the infant to what would be a normal neonatal resuscitation. There's nothing that we do with the technology that should interfere with that capability.

Dr. Gleason: Thank you, Dr. Flake.

Dr. Dracker: Dr. Moon, you had a question.

Dr. Moon: Yeah, mine had to do with the pump itself. Maybe I missed it, but is that a proprietary new pump, or is this, these old pumps and oxygenators and circuits that have been used and tested before? Because one of the questions is, I've got a lot of experience with these pumps and they occasionally go bad. And, is a pump exchange not a terminal event of having to be off the pump, or is it possible to exchange the pump to extend the period of time?

Dr. Flake: I'm not sure who you addressed that question to Dr. Moon, but we don't use a pump. That's one of the fundamental aspects of our system, is that we allow the fetal heart to be the pump, and that allows for some autoregulation of blood flow within the system by the fetus. I will refer any pump questions to the Toronto group, Dr. Seed if he wants to comment on it. Or Dr. Mychaliska.

Dr. Mychaliska: So, we do use a pump in our system. It really is a veno-venous type of ECLS configuration. And we use a pump developed in our lab, an M pump, a rotational pump. We've not had issues with it, having to replace it, but obviously a great question. The circuit would need to be interrupted briefly to replace it.

Dr. Moon: And the oxygenators, what's their durability period? They must have an end point.

Dr. Mychaliska: We've used them successfully up to three weeks, but, in certain experiments, we've had problems with oxygenators just like we would in standard provision of neonatal ECMO. If they have a clot burden or not functional, they need to be replaced.

Dr. Moon: And you can replace the oxygenator without having to take the individual out of the bag. I mean, you can carry on.

Dr. Mychaliska: Well, yeah, at least I'll defer that to Dr. Flake or the Toronto group. We provide our care in a standard isolate. And the animals, as I noted, they're intubated with a fluid column of perfluorocarbon. So, to just chime in on the other question, in our system, should the system

fail, the extracorporeal circuit, we would simply suction the perfluorocarbon and ventilate the animal.

Dr. Moon: Okay.

Dr. Flake: So, we use standard oxygenators for our sheep experiments. We have a clinical oxygenator that we have tested within the sheep system, that's smaller with a much smaller priming volume. We've tested in a parallel arrangement with a standard oxygenator and sheep, that human anticipated, human flows, et cetera. And the oxygenators can last the duration, in terms of the duration of our planned clinical runs, and we've actually run sheep independently on them with the earlier gestational model. And we can run those labs. We've run one up to 29 days, as I've mentioned, without needing to change the oxygenator. We have changed oxygenators or exchanged them. We use a bridge for that. We don't need to take the animal out of the bag. We can do it very quickly. Just like you can on an ECMO circuit. And have done that safely and quickly in the lab model multiple times.

Dr. Moon: Okay, thank you very much.

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Dr. Dracker: Thank you. Dr. Zeiss, if you're still there, you had a question.

Dr. Zeiss: Hi there. I'm Caroline Zeiss, Yale University. I have a question for Dr. Seed, and possibly also for Dr. Flake. You know, translating the success in the lamb to the pig model, using similar technology, would provide confidence that we could then translate it to humans. I was curious about the difference in outcome between the pig and the lamb, and I wonder if you could comment if that is due to differences in technology, or if it's due to differences in species. For example, the smaller size of the pig, which is more similar to the human, the intended size of the human patient. Differences in fetal circulation, blood volume, umbilical size. Is there anything

we can learn from the pig outcomes that could inform our confidence that this could translate to people?

Dr. Seed: Should I start, perhaps? Thank you for the question. I think that our conclusion has been that this technology is more difficult to apply, the smaller the animal. And so, I think that's the reason why we have been less successful than the groups using the larger sheep model. The latest research I've seen, from a group working in Perth, is with, has been published with animals more comparable size to the pigs that we are using. And they seem to be achieving a more stable outcome than we have. Although, I would still suggest that those small animals are still not having completely normal fetal cardiovascular physiology, they're still tachycardic, and they seem to develop edema. I think the big difference in terms of the approach that we're using is that we're still using a large neonatal ECMO oxygenator, which I think is probably part of the issue for the small pigs that we are using. We tried to overcome that with a pump, and essentially run into other problems, to do, directly to do with sort of a non-physiologic circuit. And it may be that my colleagues in Philadelphia or Michigan have overcome that limitation by producing a customized smaller oxygenator as has also been reported by the group in Perth.

Dr. Flake: I would respectfully disagree with Mike. I don't think that it's size related. If you think about normal fetal physiology, the normal fetus at whatever size, tolerates a pumpless AB system. So it's a matter of circuit specifications, circuit resistance, circuit volume, etc. We've been able to maintain animals that are equivalent in size to the human infant, meaning in the six-to-700-gram range, meaning lambs, for long durations on our system. And the Perth group was able to maintain them for approximately two weeks, although they did have some issues with maintaining physiologic flows for that period of time. We've been able to maintain, as I said, a 700-gram animal for 29 days, in fairly normal physiologic conditions. So, I don't think it's a

matter of size. I think it's a matter of the circuit specifications. With respect to the pig model, I'll have more to say about that tomorrow, but we've been able to rapidly convert pig fetuses that are human in size from placental support to circuit support, with physiologic blood flows. And, I'll discuss more about that tomorrow, but it has not been a limitation in our system to run pigs for short duration, physiologic.

Dr. Dracker: Alright. Thank you. Dr. Cole, you had a question.

Dr. Cole: Yes, thank you. This is Dr. Cole from Washington University in St. Louis for Dr. Mychaliska. It sounded as if the nitric oxide producing circuit eliminated the need for systemic anticoagulation. Is that right?

Dr. Mychaliska: Yes, that’s correct Dr. Cole. Thank you for the question. So, there's a polymer surface that's been in development. For well over a decade, with Dr. Bartlett and Dr. Meyerhoff, a chemist at the University of Michigan that we collaborate with. And the paper we published, we had five animals with one week of total support with no systemic anticoagulation. So, the obvious, in my mind, that's a seminal advance for this technology. But, obviously, we'll have applications to the use of ECMO in more premature infants as well.

Dr. Cole: Yes, I agree. That's a step forward, and the clot burden et cetera were all acceptable.

Dr. Mychaliska: Very minimal. I showed in my presentation a representative slide of the circuit and oxygenator. And, as I noted, we can't coat the oxygenator. So, nitric oxide is placed in the sleep flow. And that effectively prevented thrombosis of the oxygenator for a week.

Dr. Cole: Thank you.

Dr. Dracker: Dr. Seed, you had wanted to make some additional comments.

Dr. Seed: Just want to respond to one of the questions earlier, in the earlier session, that was about whether there's been a direct comparison of sheep and human placental function, because we have undertaken that comparison. I don't know if you'd like me to share my screen to show that. But we used MRI techniques to measure placental oxygen transfer in sheep and human, in late gestation sheep and humans. I guess the major findings were are actually previously known, essentially that oxygen delivery to both species is pretty similar. And oxygen consumption, in the sheep, this is achieved with higher umbilical flow. And in the human, it's achieved with higher oxygen carrying capacity of the umbilical blood. And that is due to the higher hemoglobin concentration in the human, in the human fetus compared with the sheep fetus. So, I can certainly provide that paper, which is published in the Journal of Physiology, if anybody would be interested.

Dr. Dracker: Thank you very much. Since we're still in the open hearing session, I'd like to again ask if there are any individuals who would like to make a comment or ask a question in the open hearing. I guess not. Are there any other questions from the panel?

Dr. Hill: Dr. Hill here. I did have a question.

Dr. Dracker: Sure.

Dr. Hill: Dr. Flake, you mentioned several times that you were able to maintain an animal for four weeks. What was the range, using your technology, for extending animals? Maintaining animals.

Dr. Flake: Well, if you include the entire experience, the range is very broad. So, I wouldn't say that we're able to maintain all animals for four weeks. That's not true. But we can typically, I would say, in 80 percent of our mature model, and perhaps 70 percent of our less mature model, maintain them for three weeks, on the circuit. And there are many lamb specific reasons for

shorter runs than you might encounter with the human patient. So, I don't have time to detail those, but the lamb is different in a number of respects that can contribute to shorter runs than you might have in a human.

Dr. Hill: So, in your most recent work, you indicated you were able to get four weeks.

Dr. Flake: Yes. I mean, again, not in 100 percent of animals. So…

Dr. Hill: Yes, sir.

Dr. Flake: But we've, for instance, we just ran a 720-gram lamb for 29 days in physiologic conditions.

Dr. Hill: Thank you.

Dr. Dracker: Thank you very much. Were there any other clarifying questions regarding the FDA presentations?

Dr. Hoehn: I had a question. This is Sarah Hoehn from the University of Chicago. Dr. Crusan had talked about the fact that there's differences in growth between the lamb and the human, in terms of the percentage of change of cerebral blood flow. So, specifically, she said the lambs went, it increased from two to three, which was about a third. And then in humans, over the same period of time, when the cerebral blood flow was increasing by a third, in humans, in that same gestational period, the blood flow increases from eight percent to 35%, which is a four times increase. So I just wanted to hear from Dr. Flake and everybody who has been presenting about this, if there's been, I know when the MRIs were done, there were not risks of hemorrhage, but given the differences in the maturity of the germinal matrix of the lamb versus the human, versus the difference in change in cerebral blood flow, in the ratio of the change from lambs to humans, just if they could comment on any, what they would suspect would be any differences in risks of hemorrhage, from the human baby compared to the lamb. Does that question make sense?

Dr. Flake: Sure. Thank you for the question. First, I think blood flow is obviously driven by brain growth. And so, that change in blood flow is analogous to the difference in brain weight between humans and sheep. With respect to the risk for hemorrhage, we anticipate that maintenance of the fetal circulation, prevention of the transitional circulation, with fluctuations in blood pressure that occur, et cetera, the lack of the need for ventilation, all of those things will reduce the likelihood of interventricular hemorrhage in our system. If, in fact, it is fetal physiologic, as we anticipate, the risk should be comparable to those of the fetus in the womb, during the period of time that we're talking about.

Dr. Hoehn: Thank you.

Dr. Dracker: Thank you. Dr. Hill, did you have a question?

Dr. Hill: No, I do not. I'll try to lower my hand.

Dr. Dracker: Okay. Thank you. Any other questions? I have a question, out of curiosity. With the animal models using fluorocarbons, are there any changes in lung compliance over time? I know there is some uptake by histiocytic like cells in the lungs over time. Did it affect the efficiency of diffusion in any of the animals?

Dr. Mychaliska: Thank you very much for that question. So the first thing I'll just say is that we have used and published clinically, using perfluorocarbons, in CDH patients who were on ECMO, and those were, we were looking at mechano-transduction. So they had a certain amount of pressure applied to help stimulate growth of the lungs. But we also did animal experiments in the artificial placenta model, and showed that compliance improved, with those animals who had perfluorocarbons and when they were transitioned to mechanical ventilation.

Dr. Dracker: Okay. Thank you. Dr. Gleason, did you have a question?

Dr. Gleason: Oh, hi, yes. Chris Gleason, University of Washington. Just a quick clarifying question for Dr. Mychaliska. You showed that wonderful video of that comfortable lamb on the artificial placenta, and I just noticed while you went through it, I saw no fetal movements. And I saw no fetal breathing, or at least it didn't look like it when you showed the liquid in the tube. It just didn't look like there was any movement of the liquid. So, was the animal on paralytics, or sedating, or was it just, it just didn't happen that the animal was moving or breathing at that point.

Dr. Mychaliska: Yeah, it's a great question. So I will say that we do need to, we don't paralyze the animals, but we do give them benzos and some narcotics, to keep them comfortable. And in those video clips, the animals don't move very much. And I didn't capture, in that video. We have early in our experience, we would cap the endotracheal tube, so it was more akin to sort of a tracheal occlusion model. But we've started leaving the perfluorocarbons to a meniscus. And we usually see that meniscus moving with simulated fetal breathing movements. Now, obviously they have an endotracheal tube in their trachea, so it's not exactly the way it happens in nature. But they are moving that fluid. And we've noted, and this is well known, that lungs in a fetus need to be filled with fluid to stimulate normal growth and development.

Dr. Gleason: Great. Thanks very much.

Dr. Mychaliska: Sure.

Dr. Dracker: Thank you. Any other questions? There has to be more questions from this brilliant committee. So, think of something you can ask. We have another 20 minutes to go, 19 minutes I should say, to close the public hearing. So we have opportunities to get further clarification.

Dr. Hill: I'd like to ask a question, if I could, of Dr. Flake and whoever else may want to chime in. So, where are we with this technology? Are we kind of in the middle, or, we certainly aren't at the end. I ask that question because we may think about, and have mentioned, moving this to a study or the clinical round. So, Dr. Flake, you've done a lot of work in this area. Where are we on this journey?

Dr. Flake: Respectfully, I think that exceeds the scope of this discussion of animal models, etc. And I will defer my answer to that to our discussions tomorrow.

Dr. Hill: Thank you.

Dr. Dracker: Additional questions?

(Speaker's name unidentified): Dr. Davis and Dr. Guillory both have their hands up, Dr. Dracker.

Dr. Dracker: Alright, go right ahead. Whoever was first.

Dr. Guillory: This is Charleta Guillory from Baylor College of Medicine. My question is, and I think I missed it, but I definitely heard some discussion about rescue, using this method in a rescue mode. Can, I do not remember the person who said it, but could you tell me, if you did use the rescue mode, how would that change the outcome? And the reason I'm saying that is because we have small baby units all across the country. We've really improved our data with these very small babies. And so, as we look at benefit risk, you know, I'm in my mind determining which babies would really go on, be placed on this machine, versus using the conventional method. So, if you could explain to me, is the rescue method that was used, if used at all. Thank you.

Dr. Mychaliska: Thank you, Dr. Guillory, for that question. I presented that the artificial placenta, the way we're envisioning clinical translation, is twofold. One way would be on the

first day of life, and that would be with a clinical risk stratification system, where we would preemptively put infants at a high predicted mortality on the device. In that application, based on our animal work, we believe that fetal circulation would be reinitiated, and there would be minimal barotrauma from the initial resuscitation. The rescue mode, you know, I think we can all acknowledge we may not capture all of the patients on the first day of life. And clearly, extremely premature infants die at various time points. On the first day, maybe the most premature from respiratory failure, but then later in their course they may exceed maximal medical management. So those patients could be placed on the artificial placenta, their lungs filled with perfluorocarbons to protect their lungs and continue the maturation process. And I would acknowledge that fetal circulation likely would not be reinitiated. And there would be a greater degree of barotrauma. So this would be, in my mind, you know, sort of extending what we think of conventional ECMO, to a more premature group of infants that definitely need it. And, you know, so that's why we also focused a lot of our work on developing non-thrombogenic surfaces, because as we're all aware here, we typically don't provide ECMO for premature infants, even at 27, 28, 29 weeks.

Dr. Dracker: Thank you. Dr. Davis, do you have a question?

Dr. Davis: Yeah, thank you. John Davis, from Tufts University in Boston. I'm curious if you could comment and give us a little bit more information on the cannulation procedures of the umbilical cord. I know how complicated it is for me, although my eyes aren't as good these days, to cannulate a 500-gram umbilical artery and try to slowly dilate it to get a catheter in. You've sedated or paralyzed the animals, and so they're not breathing. There's no blood flow. And you're establishing these connections in the umbilical vein and artery. And then those connections have to be maintained for up to 28 days without bleeding, without coming loose, and I'm just curious

to get a little bit more information. Some of our speakers have said they weren't able to cannulate all the animals. So, I'd be curious as to how successful you are on average, how long it takes. How complicated is the procedure? Because I'm having trouble visualizing how easy it is for the cannulation of the umbilical arteries and potentially a fetus at 500 grams.

Dr. Flake: Thanks for the question. You know, you need to realize that the animal cannulation is entirely different than the human cannulation. So, I won't discuss the human cannulation. The animal cannulation, sheep have four umbilical vessels. We actually do a direct operation on the umbilical cord. We cannulate an artery and vein, and establish blood flow through that connection, those connections, before we cannulate the second artery. So during that period, we actually have placental profusion from the other artery and vein, which provides the luxury of time to place the animal on a circuit. So our cannulations typically last 15 to 20 minutes. We're able to uniformly do it in all sheep, even small lambs, that are equivalent in size to human fetuses. The only ones we can't cannulate is you sometimes see a marked arterial size discrepancy in sheep, and it may, one artery may be too small for the cannulas that we have available. But, generally speaking, we're able to successfully cannulate almost all sheep that go on to the circuit. But it's very, it's completely different than the human cannulation will be.

Dr. Davis: And I imagine the vessels are much larger, since you talked about 10 or 12 French catheters that you're able to put in those vessels.

Dr. Flake: Well, it's interesting, you know, the standard perception of umbilical vessels is that of neonatologists, when they're trying to put in umbilical vascular catheters. And that umbilical cord is entirely different than what you see in the fetus, that's actively connected to the placenta. As a fetal surgeon that does open fetal surgery, for instance, on 23, 24 weekers, the blood flow through those vessels is tremendous. And they're actually quite large. So, in our

system, for instance, in sheep, we can cannulate, you know, using 10, 12 French arterial cannulas and 14, 16 French venous cannulas, in the later gestational model. And 10 French and 14 French in the earlier gestational model. So the sizes of these vessels are surprisingly large, compared to most people's perceptions of the umbilical vasculature.

Dr. Dracker: Thank you. Dr. Fischer, did you have a question?

Dr. Fischer: Yes, thank you. Gwen Fisher from the University of Minnesota. My question is related to Dr. Davis's question. I'm wondering about whether the animal model lends itself well to potential human clinical trials for weaning ECMO and also decannulation in those patients.

Dr. Flake: Well, as I mentioned earlier, I think when we have, and with our initial study, for instance, we compared animals that were, necropsied after three to four weeks on support, with animals that were ventilated for 24 hours, to look at pulmonary function. And so all of those animals underwent transition from the circuit to ventilation. And it's really very straightforward. The animal's lung function after three or four weeks on the circuit was equivalent or better to age matched gestational controls. And we were able to simply intubate the animals and initiate ventilation, and establish ventilation, and then divide the umbilical cord, take them off circuit. So, I don't anticipate that the human decannulation procedures... It's the umbilical cord, remember? So decannulation is simply dividing the umbilical cord, clamping the umbilical cord like you would in a normal delivery. I anticipate the resuscitation would be the same in a human patient as it would be after premature infant delivery, with graded efforts at ventilation, and determining what the patient needs basically. We've documented that surfactant production proceeds on schedule within our system. So, if in lambs that have been maintained for three to four weeks in the system, we have active surfactant production. We have ongoing lung development. And we would anticipate the same in humans. So, at 28 weeks, some infants may

need surfactant. Some infants may require intubation and mechanical ventilation. Some may require minimally invasive ventilation.

Dr. Dracker: Thank you. Dr. Hill, you had your hand up before. Do you still have a question, or no?

Dr. Hill: I do not.

Dr. Dracker: Great. Thank you. Are there any other questions?

Dr. Gleason: Hi, Dr. Dracker. I just shot my hand up just for a quick, yeah, just a quick clarifying thing from Dr. Flake. And thinking about, you know, when it's time to transition to standard of care, and he said, well, you just, you know, you decannulate but you don't have to de-, you just clamp the cord. But, so, what's the plan for, I mean, that's, they're catheterized. So, like Dr. Davis said, you know, we usually have umbilical catheters in. So, are the catheters left in and then just hooked up in the normal way we do in the NICU? Or, what happens to the umbilical cord vessels after the plans, you know, human is taken off the circuit?

Dr. Flake: You kind of have to sort of see the whole transition process to fully grasp it. But, so, our cannulas are not inserted centrally into the animal, or even into the abdomen of the animal. The cannulas are almost like an end adapter sort of connection. So there's only two or three millimeters of cannula that extends into the cord vessels. So, we can actually clamp the cord near the animal without interfering or dealing with the cannulas. And if you wanted to, following the decannulation with the circuit cannulas, you could easily put in umbilical arterial and venous cannulas. And in fact, we've done that in our animals when we've transitioned them to standard ventilation. So, you have the availability of the umbilical cord stump, just like you would with a normal preterm delivery. You can place catheters at that time if you wish to. And it should be very analogous to a preterm delivery.

Dr. Gleason: Got it. But they won't have vascular access until that's done. So one assumes that everything's, you know, whatever they're on, you know, is interrupted for that period of time until vascular access is obtained, which should be easier at 28 weeks than at 23 weeks. But still…

Dr. Flake: So, yes, you would need to establish vascular access. Now, theoretically, you could leave them on circuit if they're stable, if it's not a precipitous transfer from circuit to ventilation. You could leave them on circuit and transition them off of circuit while you initiate ventilation. And initiate your catheterization or even peripheral access at that time, during that interval.

Dr. Gregor: Got it. Thanks very much.

Dr. Flake: You got it.

Dr. Dracker: It's Dr. Dracker. I have a question. I find the physiology very interesting, to think of taking a fetus from an intrauterine physiology to an extrauterine physiology, and if there are any vascular events that occur in between. Because you're almost having the animal ex utero and then transitioning immediately into an in-utero-like environment. Are there any other issues that come up?

Dr. Flake: Well, again, turning to our animal experience. We do a few things to prevent transition to the fetal circulation. Some of them I don't know are absolutely necessary. Some of them we do to maintain normal development. So, for instance, we do give, we do administer a paralysis agent, short acting paralysis agent, prior to delivery and to air, so that the fetus doesn't take a breath, fill its lungs with air. Which, there's a lot of evidence to support arrest lung development in the canula phase. The simple act of filling the lungs with gas. And so, we do that to prevent lung inflation. And that is one of the triggers of transitional circulation.

We also get PGE1 immediately after putting the animal on the device, just as a prophylactic measure to maintain fetal circulation. We really haven't tested the system without PGE1 to know whether that's absolutely necessary. Theoretically, if you maintain fetal saturations, you should maintain the fetal circulation. We've uniformly seen, in all of our animals on circuit, maintenance of the fetal circulation. We don't see ductal closures. We don't see those sorts of alterations in fetal circulation. And so, at the time of delivery out of the circuit, you should have an intact fetal circulation and the individual should transition to a postnatal circulation in the same way that a premature infant would, that was being delivered out of the womb at whatever gestational age you're delivering the patient.

Dr. Dracker: I really asked that question in consideration of a human application. You don't always have the luxury, obviously, of cannulizing on the infant, although premature is stable in utero and it comes out. You're faced with the issue of a child being born at 22, 23 weeks and then potentially applying the technology in a fastidious manner. I just wondered, you know, what issues were being considered?

Dr. Flake: Well, I think in our initial human application, it would be a very selected population, that would not be precipitous premature deliveries or mothers with severe pathophysiology, like severe pre-eclampsia.

Dr. Dracker: Right.

Dr. Flake: We'll start with a selected population. Ultimately, I see no reason that this technology could not be applied with vaginal delivery on the perineum, with delayed cord clamping you maintain non spastic vessels for a period of time after delivery. And you can potentially cannulate those vessels and put the patient on the device. So, there are various scenarios that we've thought about, that we anticipate, that would expand the application of the

technology. It's probably not applicable to all deliveries and all premature infants. Certainly not in its original form. Or we are expecting to do it with a cesarean section just to have more controlled circumstances. But I think ultimately a lot of those scenarios will turn out to be possible.

Dr. Dracker: Great. It is 12:29. So I'm going to hold further questions at this point. At 12:30, we will be closing the Public Hearing, and I'd like to ask if there are any other individuals that would like to make a comment in the Public Hearing period. If not, we will close for lunch and I want to remind the panel members not to discuss the issue at hand, and that we are on Eastern Standard Time so that we will resume again at 1:30. We will now take a one-hour lunch. Panel members, again, no communication between each of you and we'll see you in one hour. Thank you.

Relevant Clinical Experience Data

Dr. Dracker: Welcome back, everyone. We have a very busy afternoon, so I'm going to try to keep everybody online on track and we will now proceed with the afternoon presentations summarizing clinical experience relevant to AWT. You will have the opportunity to ask clarifying questions after the fourth presentation. We will begin with Dr. Susan Hintz, Professor of Neonatal and Developmental Medicine at Stanford University.

Contemporary Outcomes for Extremely Preterm Infants (EPI) — Dr. Susan Hintz

Dr. Hintz: Thank you very much for inviting me to speak with you today about the outcomes of infants born extraordinarily preterm. As an overview, we will be discussing survival and in-hospital morbidity and two-year corrected age, neurodevelopmental outcomes using data from the NICHD Neonatal Research Network, and we will touch on school age outcomes using data from Victoria, Australia and from Sweden. For context, the NICHD Neonatal Research Network

was initiated in 1986 to conduct clinical trials, but also for observational studies. And this included the initiation of what is referred to as the Generic Database, and this collects data from delivery to NICU discharge at network hospitals for those born between 22 plus zero and 28 plus six weeks. The ongoing follow-up study was launched soon thereafter. In its current iteration, it follows children in the GDB born at less than 27 plus zero weeks gestation or in a trial and follows these children to 22 to 26 months corrected age.

Starting with survival, this is from the recently published paper, and this was a birth cohort for survival in in-hospital morbidities between 2013 and 2018, and you can see on the left on the figure that survival is represented both for all infants in blue and for those that were offered active treatment at birth separately in red. So, we will focus on 22 to 24 weeks and on the actively-treated infants. And for that, you can see that at 22 weeks, about 30% survive to discharge or 1 year if still hospitalized, for 23 weekers about 55%, and for 24 weekers, about 71%. You can see on the right, just for context, I gave you the denominators for infants in those gestational ages. So, for infants actively treated at birth at 22 weeks, about 200 infants during that cohort. A very limited number of in-hospital morbidities are shown here, again, focused only on those gestational ages before for severe intracranial hemorrhage or IVH grade three or four, about 38% of those born at 22 weeks, and about 36% of those born at 23 weeks experience that outcome and surgery for NEC ranged from six to nine percent for these groups.

For bronchopulmonary dysplasia, this is an outcome that is only assigned for survivors to 36 weeks postmenstrual age. And you can see for the most severe BPD grade three, which means that invasive mechanical ventilation is still ongoing at 36 weeks postmenstrual age, about 20% of those born at 22 weeks had that outcome and about 18% at 23 weeks. I also provide here length

of hospitalization information for you for surviving infants only at 22 weeks, for instance, about 156 days is the mean with a wide interquartile range and to 23 weeks about 143 days is the mean.

Moving on to neurodevelopmental outcomes at about two years corrected age. Just to provide a definition of sorts, neurodevelopmental impairment, or NDI is a composite outcome. And this combines the presence of findings, one or more, from several domains. The severe NDI definition for the network at this period was defined as a cognitive or motor composite score on the Bayley scale's third edition of more than two standard deviations below the standardized mean, or gross motor impairment that was consistent with non-ambulatory cerebral palsy or bilateral deafness or blindness. And you can see on the right, the figure is showing no or mild, moderate, or severe NDI. And for these gestational ages, you can see, first of all, that there are very few patients that make it to follow up to two years in the 22-week category. But among those 29 children, about 30% had severe and about 22% had moderate NDI. For 23 weeks, severe NDI was present in about 34% with 69% having either moderate or severe NDI. And then at 24 weeks, about 60% had either moderate or severe NDI. Again, just a very high-level view of functional and resource needs at two years. And this is showing you that among those 22 weeks about 19% had limited or no oral feeding at two years, about 18% for the 23-week group. The equipment needs also align with this. You see here with gastrostomy or other tube feeding at two years in 14 to 19% of this overall group and mobility aids and supportive equipment also needed any more than one or more was seen in about a quarter to a third of this group at two years.

So, the outcomes at school age and beyond for those born at this extraordinarily preterm group are obviously crucial to understand for both the child and the family. But there are a number of challenges and limitations, including the lag time between the birth cohort period and the time to follow-up. And also the fact that there are care changes across the years, so outcomes

may not be reflective of current cohorts. And I would say this is particularly true for 22 and 23-week EGA infants as the initial stance for intensive care in the delivery room has changed over the years. Having said that, there are a number of excellent examples of population-based, extremely preterm follow up studies, and this includes the Victoria, Australia Infant Collaborative Study Group. They've undertaken long term, really truly long-term follow-up for a number of birth cohorts, and eight-year outcomes are available for three of these birth cohorts as published in 2018. So, this is a figure showing in the manuscript the combined mutually exclusive outcomes by EGA. But just to highlight the major disability rates among survivors, you can see that the number of 22-week survivors is so low as that it's really not reported. But at 23 weeks, it's about 30% of these children have major disability at eight years and at 24 weeks, about 20%. Again, these investigators indicated that there was no difference across the eras in major disability among survivors, so these cohorts were combined.

So, this is from the Swedish National Extremely Preterm Study. This is the Express-1 or the first birth cohort. There is another birth cohort, which is data that is coming, but this is from birth years 2004 to 2007. The definition for this group for severe neurodevelopmental disability was even more severe, so I'm showing all levels of disability. And just to highlight that there were only five children who survived to evaluation at six and a half years at 22 weeks, but you see the outcomes here. At 23 weeks more than 20% had severe neurodevelopmental disability and about 55% had either moderate or severe. And that is compared to the 24-week group with a still high rate of 40% having moderate or severe disability at six and a half years. And if there is a temptation to look at the outcome at toddler age and assume they perfectly align or predict school age outcome, that's not the case. This is from the Swedish national cohort again. Less than half remained in the same category between two and a half and six and a half years, and they

moved in either direction. And just looking at the data, this is an example that among those categorized at two and a half as mild, about 37% of them moved to a moderate or severe category. And among those that were categorized as moderate at two and a half years, about 20% moved to severe and about 17% moved to a no disability category at six and a half years.

So finally, I'll just say we focused on neurodevelopmental outcomes. But particularly for school age and beyond, there are clearly numerous other important health-related outcomes and quality of life-related outcomes that need to be urgently explored for this extraordinarily preterm group. Thank you very much.

Dr. Dracker: Thank you, Dr. Hintz. We will now hear from Dr. Gail Annich, a pediatric ECMO specialist and Professor of Pediatrics at the Hospital for Sick Children in Toronto.

Hemostasis in Preterm Infants Undergoing Extracorporeal Membrane Oxygenation — Dr. Gail Annich

Dr. Annich: Good afternoon. My name is Gail Annich. I'm a pediatric intensive care physician at the Hospital for Sick Children. I have expertise in anticoagulation, extracorporeal technology and a research interest in the development of non-thrombogenic surfaces. I want to thank the FDA for asking me to present and participate in this advisory meeting.

Challenges with ECLS are multifactorial. The ones to focus on today in this talk are principally related to hemostasis and anticoagulation, and that is what I will primarily present upon. But this picture and cartoon is just to demonstrate how many different types of factors are affected and the significance of that, which include inflammation, fibrinolysis and other activated inflammatory parameters.

Blood surface interactions. So, the interaction of the blood against an artificial surface is what we are trying to prevent. We are trying to prevent this activation clot formation because it is

important to maintain patency of this circuitry to provide life support for the patient. Ultimately, though, we would like this response to be normal or as normal as possible within the patient to prevent a life-threatening hemorrhage within the patient. The platelets are the first order line of defense against bleeding within the patient, and they are activated by a multitude of different activators, as you can see here in the blue box. Once the platelet is activated, a number of different actions occur. Adhesion of the platelet via receptors bolster von Willebrand factor and fibrinogen, the release and secretion of granules that allow for more chemotaxis and more platelets to arrive at the site of primary injury. And ultimately, also, the presence or the adhesion of coagulation factors to the phospholipid membrane of the platelets to allow the activations of coagulation cascade and the conversion of prothrombin to thrombin and ultimately a cross-linked fiber and hemostatic clot. It is not without regulation so that we don't continue to form clot. There has to be a regulatory response in inhibiting further clot formation once bleeding has been abated. And this is done by both platelet inhibition, inhibitory mechanisms like nitric oxide and prostacyclin and those of the cascade that can inhibit further production of clot, antithrombin protein C and S.

The fibrinolytic pathway is also a very important pathway in the maintenance of hemostasis within the human. Once clot is formed over a period of time, it is dissolved. And this fibrinolytic pathway is not simplistic. It's not just over a certain number of days that clot has broken down. Once there is some disruption, in the normal feedback loop, then fibrinolysis can occur and can become difficult to control. So again, something that we have to be very concerned about, and certainly in the preterm neonatal populations can even be more concerning and difficult to manage.

Hemorrhagic complications are by far the most common complications in extracorporeal life support. All the complications in grey are every possible complication that can occur on ECMO, both in the circuitry and within the patient. And so, you can see that about 40% of those complications in the neonate are hemorrhagic about 30% in the pediatric population, and then less so in the adult, about 25%. But ultimately, we would expect if we had a column for preterm neonates that this would be an even larger proportion.

It is important to understand the in-utero development of the coagulation factors so that we understand at the different types of fetal age or preterm infant age, where these factors may be. As you see the graphs that are coming up in the next several slides, it's important to understand that I have adapted them from a paper by Toulon et al. and another paper by Andrews et al. And these will have citations on each of them. At five weeks of age, the fetus has already demonstrated the presence of platelets. And by 22 weeks of age, it has the normal number of platelets that you would see in an adult. By 11 weeks of age, it begins to start to have the development or the presence of coagulation factors. So, just taking primary hemostasis of the preterm neonate to begin with, as I said, at five weeks gestation, there's presence of platelets by 22 weeks, they are at adult levels. Given that these platelets, however, are not as functional like adult platelets, they have a more hypo reactive type of response due to a lack of alpha-adrenergic receptors. There's also much lower levels of high molecular weight kininogen, which are important to the activation of platelets and the chemotactic response to the site of bleeding. Compensatory to this, however, and is known, is that they have much higher levels of von Willebrand factor. And the more preterm the neonate, the higher the level of von Willebrand factor. So it appears that within that it provides some compensation that allows for somewhat of a normal primary hemostatic response. This is just to further elaborate or demonstrate how the

levels are quite divergent at early birth within a neonate who is 30 to 33 weeks of age, but over a course of even six months, they come into almost normal range with the adult.

Coagulation factors as expected in the neonatal population are low. Again, these are term neonates in this graphic, but you can even see in the preterm neonates that over a period of six months, between 30 to 36 weeks gestation, they have quite low levels of a significant number of the different coagulation factors and the different factors that we see, you can see that factor ten is quite low. Fibrinogen is within a more normal level, but factor ten is quite low. Factor two is quite low. These are all the big areas in terms of activation and the ability to form clot and cleave fibrinogen to fibrin.

As I had said with the platelets, physiologic regulation of coagulation and the development and the presence of fibrinolysis are important or the fibrinolytic cascade and system is also very important. And as we have seen with coagulation factors, these factors are also quite low in the term neonate and lower in the preterm neonate. The only one that I can demonstrate from the Andrews paper that was measured was plasminogen. But again, you can see it is lower in range compared to where the term neonate sits. So again, fibrinolysis is somewhat reduced or does not have the same levels of factors to provide appropriate response. Regardless of this, upon further study and a lot of study in the preterm neonate, if they're healthy, they seem to have a reasonable balance. Although we do know that they have some significant increased risk to bleeding once that's disrupted or if they become unwell and have organ system dysfunctions.

Anticoagulant choice is also important to understand and most certainly the most common anticoagulant used in this population is unfractionated heparin. Experience in the use of direct thrombin inhibitors is becoming more common across human populations and across all age groups, even neonates. But it's exposure and experience in the preterm neonate has yet to be

further characterized given that we're still characterizing it in the neonatal population. This is just to demonstrate a slide of what unfractionated heparin is, won't go into further details on it at this time. And this is to demonstrate the variability and the need for customization in anticoagulation, as we can see metabolism and rates of metabolism have significant effects as does each patient responds differently to the different types of dosing for anticoagulation for direct thrombin inhibitors.

There is significant variability in the coagulation anti-coagulation testing, and we have to expect this and probably further characterize this in the preterm infant and understand it because a neonate is very different at 15 days of age, even compared to five months or to six to 11 months of age. There are challenges with our present monitoring tests. These are the most common of these tests. And if we are to further understand it in terms of the neonatal or preterm neonatal population, we will have to perhaps develop testing that is relevant to that population, not testing that is adapted from the adult population.

Surface modifications are as demonstrated here. The most common ones that are used are those within the biomimetic surface functionalization with heparin surfaces, but perhaps we need to design further types of surfaces that will allow for a less need for systemic anticoagulation. Ideally, the best type of circuit would be one that the entire circuit can be covered that has longevity, that requires no systemic anticoagulation, that has the ability to be manufactured in the normal stream, prevents thrombosis, preserves platelet function, and reduces inflammation.

And with that, I want to thank you, and I'm happy to field any questions.

Dr. Dracker: Thank you, Dr. Annich. We will now hear from Dr. Peta Alexander, a pediatric cardiologist and medical director of Cardiac ECMO at Boston Children's Hospital.

Cardiovascular Considerations for AWT in the EPI — Dr. Peta Alexander

Dr. Alexander: Thank you for the opportunity to present cardiovascular considerations for artificial wound technologies in the extremely premature infant. My name is Peta Alexander, and I'm a pediatric cardiologist and intensivist at Boston Children's Hospital. All images in my presentation are used with permission or with reference to the original citing article.

By way of overview, we'll start with cardiovascular development through embryonic, fetal life, and into the early postnatal period, including transition of circulation. Disorders of that transition in extremely premature infants will be reviewed. And then we'll move on to the use of ECMO in small and premature infants, and the consequences of that care. Precipitating potential alternatives to ECMO for the rescue of extremely premature infants. We'll then review preload, afterload, and ventricular function during prolonged support, as well as monitoring considerations for this therapy.

The human heart is one of the first organs to form and function during embryogenesis, and it's vital for oxygen and nutrient distribution to the developing embryo. By the end of week four, the recognizable four chambers of the heart, the right atrium, the right ventricle, the left atrium, and the left ventricle connected to their appropriate outflow tracks are formed by gestational week seven. So that's all during this embryonic stage, which extends up to ten weeks of gestation. And beyond that, the late first trimester, second trimester, and third trimester make up the rest of the fetal period. You can see the growth in this period is mainly via hyperplasia, the increase in the number of cells contributing to the cardiovascular system. And over the course of the second and third trimesters, the cardiovascular system gradually increases in workload as well as oxidative capacity.

This diagram demonstrates fetal circulation, which is optimized to ensure that the most oxygenated blood is delivered from the placenta to the heart and brain. The structural anatomy of the four-chambered heart, the right atrium, right ventricle, left atrium, left ventricle, is as previously described. And the descending aorta connects to the very low resistance placenta. Oxygenated and well-nourished blood is delivered back through the umbilical vein, bypasses the liver via one of the structural shunts -in the fetal circulation, the ductus venosus - and is delivered back to the right atrium where it's diverted across the flat valve foramen ovale into the left atrium and delivers oxygenated blood into the left ventricle, where it's ejected into the upper body circulation to deliver the most oxygenated blood to the heart and brain. Deoxygenated blood from the upper body is returned via the superior vena cava into the right atrium. At this stage, it's deoxygenated and mixed with IVC flow that did metabolize in the liver. This blood is then pumped by the right atrium, right ventricle across the pulmonary valve into the pulmonary artery. But because the pulmonary vascular resistance is very high at this stage through a combination of biochemical factors, as well as collapse and atelectasis of the lung fields themselves, the blood mainly traverses across another shunt in the fetal circulation, the ductus arteriosus. This vessel connects the pulmonary artery to the aorta and facilitates the majority of that deoxygenated blood traversing across into the descending aorta where it flows into the placenta in that low vascular resistance state and returns to the rest of the body. So, both biochemical factors and anatomical shunts ensure that oxygenated blood is delivered from the placenta to the heart and brain directly.

Normal transition for circulation from fetal circulation on the left to early neonatal circulation on the right occurs after the first early breaths following delivery of the patient, where both increased oxygen in the lungs and a surge of nitric oxide results in decreased pulmonary

vascular resistance such that when deoxygenated blood is traversing the right ventricle into the pulmonary artery, more blood traverses through the left and the right pulmonary artery, flows through the pulmonary vascular bed, and returns to the left side of the heart as oxygenated blood into the left atrium. In addition to the catecholamine surge associated with delivery, increasing heart rate and contractility of the heart, this left atrial preload increases LV ejection and the cardiac output overall increases. Oxygenated blood now flows through the ascending aorta and down the descending aorta with the shunts in the circulation that facilitate mixing of blood in fetal life, closing over the first few days post-delivery.

So, in this transition to the postnatal period, from embryonic to fetal life, you can see that at the point of delivery, there's an increase in the cardiac output, seen as cardiac workload. Oxygen availability increases because the oxygen saturation of the blood is now much higher in the context of oxygenation of the pulmonary vascular bed and closure of those shunts. And so, the oxidative capacity of the heart is higher. Over time, cardiovascular hyperplasia, the growth by increasing cell number, is replaced by hypertrophy of individual cardiomyocytes in this postnatal phase, and that's how the cardiovascular system achieves the rest of its growth. Factors influencing cardiac development in fetal life and in postnatal life are very similar to those that precipitate early delivery in that early preterm phase. Nutrition, intrauterine environment, placental function, angiogenesis can all precipitate early delivery and are also influencing cardiac development. And in the postnatal life, the gestational age at birth, birth weight, intrapartum factors, and the intrauterine environment also impact longer term cardiac development. So, when we look at the transition of circulation in extremely preterm infants, it's apparent that the immature cardiovascular system impacts transition to the neonatal circulation. The ductus arteriosus is unresponsive to the constriction associated with hyperoxia, and the foramen ovale

may remain open. In combination, this can result in pulmonary congestion, left to right flow of blood from the systemic blood flow to the pulmonary blood flow, and ultimately result in inadequate blood flow to end organs, to the tissues, resulting in hypoperfusion.

Prematurity is obviously associated with bronchopulmonary dysplasia, the failure of the lungs to be well developed at the time of delivery, but it also impacts myocardial structural development, which alters cardiomyocyte maturation. The sudden onset of high systemic vascular resistance, coupled with hyperoxia, leads that growth pattern of the cardiovascular system to move from hyperplasia to hypertrophy of individual myocytes, and thus, abnormal postnatal development. And this can affect the relaxation of the left side of the heart with impaired diastolic dysfunction and persistent reduction in right ventricular systolic function.

As such, many innovators have considered ECMO or extracorporeal life support as a potential strategy to support critically ill patients who are born prematurely, as well as those with pulmonary or cardiopulmonary disease. This is most commonly used in VA configuration, and in this baby, that cannulation strategy would be via the carotid artery into the ascending aorta with a venous cannula cannulating the right internal jugular vessel, but the end of the cannula draining down to the right atrium. This has also been considered for pulmonary support, VV support of the extremely premature infant.

This is what ECMO cannulation looks like in my setting. It's a surgical intervention that's often done at the bedside with an ad hoc sterile field applied. The team involved in ECMO cannulation in this picture includes the intensive care physicians, the cannulating cardiac surgeons, bedside nurses or anesthesiologists maintaining care to the patient during the procedure, operating room nurses for the equipment, and an ECMO specialist who manages and troubleshoots the ECMO circuit and the components themselves. And you can see when we look

at this term three kilogram infant that even in this child, the dimensions of the aortic cannula that we use are quite diminutive. This is a six or eight French cannula with a diameter of about a tenth of an inch. As such, it is rare to offer ECMO support to children less than two kilos or below that 32-week gestation mark due to the complexity and the dimensions when compared to other patients supported. This is a 1.8 kilo patient in our center that was cannulated with a six French aortic cannula and a 12 French venous drainage cannula compared to an adult sized patient who's cannulated with much larger supports.

In addition to the small cannula dimensions, the ECMO flow required to support a patient is calculated according to body weight. Usually, we'd start at about 100 mls per kilo per minute of flow in a small child. The ECMO circuit components generally not optimized for the pump flows required for even term neonates. This bench study comparing the red cell destruction as measured by hemolysis that occurs across three different commercially available pumps at different flow rates. With the higher flow rates used in adults, four liters per minute, and these lower flow rates used in small children, neonates, at three to five kilos. And it shows that there's increasing hemolysis with lower flow rates. This is even worse when higher resistance to flow is applied. That's when you can really see the hemolysis index increase. That's of particular relevance to pediatric and neonatal circuits because neonatal oxygenators tend to have higher resistance to flow than adult circuits. So, it may not be surprising then that the consequences of ECMO occur more frequently in infants and children than in adult populations. These data from the ELSO Registry international report demonstrate higher rates of cannula malfunction, circuit hemolysis, circuit change, and oxygenated failure in small children than in adults and patient-related consequences also occur with much higher frequency. Seizures occur ten times more frequently and brain hemorrhages even more frequently in neonates than children and adults.

There is interest in the ECMO community in pushing the limits of viability for ECMO-supported premature infants. In this recent systematic review of published studies of small and premature patient outcomes, this population's survival to hospital discharge has improved over the past decades, and the frequency of brain bleeds has also improved. That's reported here as intracranial hemorrhage. Even at the rate of improvement, 21% of patients have intracranial hemorrhage. That remains twice as common as if we look at larger non-premature infants. And the patients included in these studies were all closer to that 32, 34-week gestation and nowhere near approximating the mid-gestation prematurity considered for this conference. As such, it does seem reasonable that there are alternative extracorporeal strategies being explored to bridge through artificial womb technology. The NIH Human Placenta Project included the language that the placenta is arguably one of the most important organs in the body, influencing not just the health of the woman and her fetus during pregnancy, but also the lifelong health of mother and child.

In the absence of such a placenta, two main strategies of artificial womb technology have been described. The strategy of cannulation and ECLS support has implications for patient cardiovascular development and function. On the left, one described option presents a veno venous ECMO circuit, including surgically-placed internal jugular cannula connected via a blood pump to an oxygenator before being returned to the recipient via an umbilical vein. The alternative strategy on the right uses the umbilical artery to power flow across a low-resistance oxygenator with oxygenated blood returning to the fetus via the umbilical artery. In addition to cannulation strategies, the isolation and pulmonary management of these patients are approached differently.

This table compares some of the characteristics of relevance to the cardiovascular system from the described artificial womb technologies. The cannulation strategy as mentioned requires surgical intervention for the VV ECMO group with less manipulation for those pumpless oxygenators. In the pumpless oxygenator, the anticoagulation strategy much more approximates that used in postnatal ECMO, with unfractionated heparin, targeting ACTs, and biologically-coated circuits, whereas the VV ECMO circuit described includes an innovative nitric oxide eluting circuit. In VV ECMO, the pump flow is basically dialed up on the pump and a proportional volume is delivered. Whereas in the pumpless oxygenator circuit, the flow is determined by the umbilical artery pressure and the resistance across the oxygenator circuit. Thus, if the resistance is low, high volumes can be achieved in terms of flow, and that can result in high output cardiac failure, a very inefficient circulation. If the resistance across the circuit is too high, however, the right ventricle, which provides much of the lower body, previously, placental flow can be impaired in the early echocardiology imaging series, a small series of patients on this support, median right ventricular function, appears to reduce over the first week of support before improving to baseline and remaining stable through the four weeks of documented support. In both systems, the recipients managed with long term prostaglandin E1 for ductus arteriosus patency and maintenance of the fetal circulation. While there are case reports of individuals with tissue edema while managed on long-term prostaglandins, this therapy is often used for subacute durations in other populations, particularly those with ductal dependent congenital heart disease and those with congenital diaphragmatic hernia with severe pulmonary hypertension and right ventricular dysfunction.

Recipients of artificial womb technology have been monitored with serial cardiovascular assessments, which include fetal vital signs of heart rate and mean arterial pressure, general

appearance, monitoring for peripheral edema, ascites, and pleural effusions, which might be signs of right ventricular dysfunction. Fetal ultrasound, specifically looking at pulsatility indices and the cardiovascular system supplying middle cerebral artery, umbilical artery and ductus venosus, and fetal echocardiography, which is quite achievable in either system. The Doppler echocardiography-derived cardiac output can be assessed, and qualitative assessment of biventricular systolic function is feasible in both support strategies. Speckle tracking, a more sophisticated derivation of global longitudinal strain and strain rate, was performed in studies of the pumpless oxygenator support, and it's what was able to show differences in the right ventricular systolic function over the first week of support, which recovered over time. Any of the cardiovascular monitoring should be performed sequentially in frequencies that could be included between daily in early support through to weekly once support is established.

In summary, cardiovascular immaturity puts extremely premature infants at risk of long-term biventricular dysfunction. Disorders of transition of circulation contribute to the complexity of care for early premature infants. And ECMO is probably not a good support strategy in isolation for the extremes of prematurity. So, alternate ECLS modes for rescue of extremely premature infants are in evolution, and they're described here as the artificial womb technologies. Preload, afterload, and ventricular function during prolonged support depend on the strategy of support being used, and monitoring considerations are reflecting the strategy of support system used.

Thanks for your attention, and I'm happy to be contacted at any time.

Dr. Dracker: Thank you, Dr. Alexander. We will now hear from Dr. Josef Neu, a neonatologist and professor of pediatrics at the University of Florida.

Gastrointestinal Considerations for AWT in the EPI — Dr. Josef Neu

Dr. Neu: I would like to thank the organizers for inviting me to give this talk. The title of my talk is Gastrointestinal Considerations for Extremely Preterm Infants Treated with Artificial Womb Technology.

Here's my disclosure, I have no conflicts of interest to disclose that pertain to this lecture. The objectives are to review nutritional requirements for extremely preterm infants in an extrauterine NICU environment. To discuss nutritional challenges for extremely preterm infants in an artificial womb environment. To provide background and historical perspectives on the effects of prolonged parenteral nutrition and lack of enteral nutrition. And to provide a perspective on the benefits of natural amniotic fluid and other therapeutic strategies for artificial womb environment.

The fetus receives large quantities of nutrient in utero. Receives a continuous supply of glucose. Protein is taken up at around four grams per kilogram per day and lipids at three grams per kilogram per day. When we consider the energy stores in the fetus and newborn, when we get to the extremely low birth weight newborn or fetus at around 24 weeks gestation, as you can see in the first row here, the weight is 690 grams on the average. And this fetus and baby is largely made up of water. And if you go down the columns, lipid is only 0.1% which provides a storage of energy of 19.5 calories, which is not very much. These babies have to get food from the extra uterine environment if they are born prematurely, and the amount of food that a baby like this requires in terms of energy is approximately 120 calories per kilogram per day. In an adult, and here we see an adult Tour de France bicyclist who is riding his bicycle over 120 kilometers per day. And this cyclist requires around 7,000 calories per day. And that is the equivalent in terms of energy intake that this premature baby requires.

So, when we think about the in-the-bag-of-water environment, and this is work that was done at Children's Hospital of Philadelphia, we see that the fetus in the bag here, the extra uterine fetus, requires food from some sources, and one of the sources is through the umbilical pathway. And this is the same pathway that the fetus is getting oxygen. This fetus is also bathed in a water environment, and it is possible to provide some food through the amniotic fluid. Now, the type of food that is provided to this fetus is very important because here's the brain at around 22 to 24 weeks gestation. Here's the brain at term. And here we see some of the developmental phases and there's a tremendous amount of development that occurs during this period of time. And if we don't provide enough adequate nutrition and types of nutrition, then there will be abnormalities in terms of brain development.

So what are some of the consequences of not giving enteral nutrition in a premature baby in a neonatal intensive care unit? Here we see the problems with no food in the gastrointestinal tract. TPN associated sepsis, mucosal atrophy, lack of trophic hormones, systemic inflammatory response syndrome, decreased mucosal IgA from the Peyer's patches, and increased adhesion molecules, and PMN attraction. This is some work that was done at Baylor University in the early 2000s, and this was done in piglets. And here we see on the right, piglets receiving TPN for seven days, and on the left piglets receiving enteral nutrition. And you look at the histology of the liver in these two groups of babies, we see increased problems with H & E staining, ballooning of the hepatocytes, increased fat staining, increased diastase glycogen staining, all suggestive of liver injury with only seven days of TPN.

Here's another study that was done at Baylor in the late 1990s, and this was done on premature babies with a birth weight of approximately one kilogram and gestational age at 28 weeks. And the purpose of this study was to determine the effects of TPN only versus putting a

small amount of food in the gastrointestinal tract early. And here we see two groups. The group in the gray was given small amounts of food, less than 20 milliliters per kilogram per day between days four and 14. And the blue group was given TPN only up until day 15. And in these babies on day ten, lactulose and mannitol ratio were evaluated. And lactulose to mannitol ratio, if the lactulose to mannitol ratio is high, that suggests increased permeability of the gastrointestinal tract. In other words, breakdown of the tight junctions between the intestinal epithelium. And here we see in the TPN only group, a greater permeability or leakier gut that can lead to perhaps more translocation of various substances, including bacteria that can cause inflammation in a highly immunoreactive subepithelium.

Here we see amniotic fluid fluxes. And the fetus is bathed in this lung fluid and is swallowing large quantities of amniotic fluid. The swallowing begins at around 13 weeks gestation, and at term it's around 450 milliliters per day. And this amniotic fluid contains nutrients, trophic factors, and immunomodulatory components. It is thought that the amniotic fluid contains approximately 0.5 grams of protein per 100 milliliters. Work that was done in the mid-1980s by a surgical group in Los Angeles discussed and showed the role of amniotic fluid in fetal nutrition. And some of the work done by this group showed that if you ligate the fetal esophagus, you get 32% reduction in gastric weight, 40% reduction in serum gastrin. The gastric acid was 43.7 micromole per milliliter in controls, but 0.5 following ligation. Infusion of bovine amniotic fluid intragastrically resulted in normal gut development, whereas Ringers lactate did not. Epidermal growth factor in amniotic fluid was shown to have a potent effect on both somatic and intestinal growth. So, what are some of the trophic factors present in amniotic fluid? Well, these include EGF, HGF, TGF beta, IGF-1, EPO, and the various cytokines. And these are all thought to be important in promotion of intestinal integrity.

What about calcium and phosphorus? Well, in the Neonatal Intensive Care Unit, this sometimes happens, and it's very embarrassing for the neonatologist to have to tell the parents that your baby's arm broke in our Neonatal Intensive Care Unit. This is highly problematic, and largely because we have a hard time supplying calcium and phosphorus to these babies, and they are also frequently getting steroids and diuretics, which all cause weight loss of calcium. Human milk is not enough for these babies, so it's usually fortified. But what about in the artificial womb situation? What do we know about calcium and phosphorus in the artificial womb situation? I think at this point, very little. A lot of work needs to be done in that area.

So, I'd like to stop here, because I'm out of time, with some take home messages. The fetus is in an artificial womb environment and this presents a unique set of challenges. It may be possible to supply nutrients parenterally, but to provide them in quantities similar to those obtained in utero that provide for optimal growth and development, and these are not known. The fetus swallows large quantities of amniotic fluid, but provides nutrition about 15% of requirements. But we have to also take into consideration bioactive factors, such as epidermal factor and other trophic factors that we have to try to be able to provide in the artificial womb environment to be able to provide optimal nutrition to these extremely preterm infants. Thank you for your attention.

Clarifying Questions

Dr. Dracker: Thank you very much Dr. Neu, and to all of our speakers, who are now available to answer any clarifying questions. I'd like to mention though that we will take questions and discussions until 2:45 when we have our final presentation. Thank you. Please raise your hand if you have any questions.

Dr. Hoehn: There are four hands up.

Dr. Dracker: Okay, whoever was first. I cannot see it right now on my screen. I'm sorry, but one of them —

Dr. Hoehn: I think I was first. This is Sarah Hoehn, University of Chicago. Sorry, mine hopefully is a quick question. It's for Dr. Neu who presented about the GI data. You were talking about how the lack of calories impacts brain development and I didn't know if any of you in the panels had seen retrospective studies looking at the timing of intraventricular hemorrhage and caloric intake in the 48 hours prior to when they had neurological changes. I had not previously connected GI intake or caloric intake to independent risks for interventricular hemorrhage, so I just didn't know if there was any specific data linking caloric intake to temporaly related to intraventricular hemorrhage.

Dr. Neu: So, to try to answer that question I don't think that we have very good data in relation to intraventricular hemorrhage per se. There is some work that has been done when Cami Martin was at Harvard. Dr. Konnikova was working with her and they did a retrospective study looking at early enteral nutrition. In other words, starting before four days of age versus starting after four days of age, and they saw some very important differences in those babies in terms of adverse outcomes. And one of the adverse outcomes did include intraventricular hemorrhage. So, whether this had something to do with blunting of an inflammatory response with food in the gastrointestinal tract, that could be speculated upon. Especially since at two weeks, there were lower IL8 levels in those babies who were fed earlier by the enteral route. So, I think that using the GI tract is probably important. It's not just the calories, it's the immunoreactivity that you find in the intestinal mucosal immune system that I think we need to take into account. So, it's not just macronutrient calories or energy intake.

Dr. Hoehn: Thank you very much.

Dr. Dracker: I want to remind all of you to please state your name and affiliation. The next is for Ms. Oster.

Ms.. Oster: Yes, this is Randi Oster and I'm with Help Me Health. I have three questions. The first one is for Dr. Hintz and I just wanted her to clarify. One of the first charts she showed was for the 24 weeks and she had compared the babies who had been put in the NICU to not the NICU, but the results seem to be about the same. And then when she was doing the neurodevelopment outcomes, it was unclear to me if the outcomes were for the treated babies or the non-treated babies or for both at this 24-week period. And that becomes critical because I think it's important for us to understand the differences of treatment or not treatment. And so, I'd like that clarified. And then I have two follow-up questions for two other doctors.

Dr. Hintz: Yes, this is this is Susan Hintz. Yeah, that was data, I think, if you're asking about the survival to discharge or to one year, if they were still hospitalized. The red bars that I showed were those that were actively treated in the delivery room. And you're absolutely right at 24 weeks, there's really not a difference between actively treated and not actively treated in the delivery room because there are very few that are not actively treated. The point I was making is that at 22 weeks, and to some extent at 23 weeks, there is a different stance that has been taken in various sites, and it is quite site specific. So, that active treatment, not active treatment was really specific to the survival data that I showed. The neurodevelopmental outcome data that I showed, those were the patients that made it to 22 to 26 weeks. Really not a 22 or 23-week baby would not survive to that point. I'm not aware of any data that demonstrates that they would survive to two years. So, those data that I showed were patients that survived to have a complete neurodevelopmental outcome assessment at 22 to 26 months in the Neonatal Research Network.

Ms. Oster: Okay, thank you. Thank you. And then I have a question for Dr. Annich. And the question is she talked about heparin and I just wanted to understand the understanding we have for long-term impact of heparin on babies that we currently have, and then how we would then extrapolate that to these babies that are younger if they are using heparin. And I'm not clear on that and I just want to understand do we have enough data at this point for the babies we have and or not? And so, if she can just answer that question

Dr. Annich: Hi, so Gail Annich from the Hospital for Sick Children. I'm sorry, I'm not a hematologist so I don't follow infants out beyond about who've been on extracorporeal technologies beyond about sort of month or that time period. So, given that, obviously, we place a significant number of our neonates onto some type of heparinization or anticoagulant for thrombus afterwards, I don't have the answers to that. I think in the acute time period, I'm not sure that influence of those long-term effects in terms of when we're thinking about osteopenia and fragility of bones, given that the premature infant already has those and that risk. I don't know that answer whether it would escalate the potential for further loss of integrity to the skeletal structure of the preterm infant or a very preterm infant, but I would think in that time period, my suspicion would be no, I think it's more of a prolonged effect. But again, I would be speaking out of turn since it's not my area of expertise.

Ms. Oster: That's okay. That's so I was trying to get a clarification on our knowledge. So I appreciate that. And my final question is for Dr. Neu, and it has to do with nutrition. And my question there is the earlier discussions we had on pigs and on lambs, they didn't talk about food and nutrition. And would you advise that maybe that is something we should be studying so that we'd have that data for this next stage for human development? And so, I just want to get a sense of that because it was such an unknown for us. Is that an opportunity for animal research?

Dr. Neu: Absolutely. Yes, I think that this is a very important area. No more needs to be said.

Ms. Oster: Thank you.

Dr. Dracker: Okay. Dr Cole. You had a question.

Dr. Cole: Yes, this is Dr. Sessions Cole from Washington University in St. Louis. Just to add to what Dr. Neu said, I do think that there are species-specific differences in both placental function and amniotic fluid composition that need to be integrated into the kind of research that he was referencing. But my question, first of all, is for Dr. Hintz. I wonder if the network has looked at the impact of the social determinants of health on long-term outcomes for the very small babies. And then for Dr. Alexander, I wonder if she could comment upon the reduction of prostaglandin E1 by the placenta. And is placental production of PGE1 the reason why PGE1 is required to maintain ductoral patency in these animal models?

Dr. Hintz: This is Susan Hintz from Stanford. Thank you, Dr. Cole. Yes, the Neonatal Research Network, as well as many other networks, including the California Perinatal Quality Care Collaborative and many other groups around the country have looked at social determinants of health and neurodevelopmental outcomes and indeed social determinants of health and even being able to get to follow-up. So, first of all, there are disparities by race, ethnicity, by insurance, by socioeconomic factors, about children even being referred to high-risk infant follow up, that's data from California. And getting to the high-risk infant follow-up clinic appointments. So even getting access is obviously different. And there are associations certainly in terms of insurance type. And other socio-demographic factors with challenges to neurodevelopmental outcomes at two years, certainly. And from the Australian group these factors seem to continue on and in fact, may impact life course issues even more significantly

than some clinical factors that we focus on in terms of much later outcomes and achievements. So, yes.

Dr. Cole: Thank you. And Dr. Alexander, could you comment on the source of PGE1 in the human fetus? And whether the absence of the placenta in the animal models accounts for the need for PGE1 infusions to maintain ductal patency.

Dr. Alexander: I'm certainly happy to make a comment. This is Peta Alexander from Boston Children's Hospital and Harvard Medical School. As a pediatric cardiologist and intensivist, I'm very confident using at prostaglandin E1, the exogenous source to maintain ductal patency in my patients and have to admit, I've not spent a lot of time thinking about the endogenous source in utero. But at the time that I was reading around the topic of discussion today, my understanding is that the placenta is the source, but I really can't claim to be an expert on that. That's not within my field. But yes, exogenous PGE1 often used in patient populations that I'm familiar with.

Dr. Dracker: Alright, thank you. Dr. Michael White. Michael, do you still have a question?

Dr. White: You did. Let's try this. Okay. Michael White, Ochsner Health System. Dr. Hintz, my buddies next door have just sent a mother to me at 24 weeks for a fetal echo anticipating she's going to be admitted for delivery. What can I tell her is the likelihood this kid's going to survive to two years of age based on what we currently know, not on historical data from several years back?

Dr. Hintz: Ah well, so, one thing I would suggest, and I think this is recommended broadly, is that one looks at their own site data. So, I would probably suggest that you look at your own site data certainly. And I would also just take this opportunity to say all of these networks that publish broadly, whether they are population-based, whether they are academic sites that come together to do trials and prospective studies are made up of many sites. And so, as someone

mentioned, I don't recall who this was, there is quite a bit of site variability. So, I would say that it's important for you to look at your own site and to look at your own numbers as a first step. If you have access to a quality care collaborative in your state, you can also look at the most recent—

Dr. White: I'm going to interrupt you for just a moment because I'm aware of all the things that go on here locally. But I'm thinking in general, if we proceed with some sort of program to deliver these babies, we're going to assume that this is a very sophisticated site. What would you tell those mothers that might be considering enrolling for any studies that we might anticipate as survival rates for today?

Dr. Hintz: Are you asking about 24-week—

Dr. White: 23, 24 weeks, anywhere in that area where we might be considering treatment options for a baby using any of these devices, any of these technologies, what will we use for contemporary data for survival?

Dr. Hintz: So, first I can't really speak to what the added impact or challenges would be based on the technology that's being discussed today. But, I would say that survival is, in terms of what I've shown you today, I think it's going to be fairly consistent in the next two years' birth cohort because I've looked at some unpublished data for 23 weeks in terms of survival to discharge in an academic center for a 23-week gestational age infant all-comers, just those who are actively treated would be probably 50 to 55%. But I would also very strongly caution that that's not the only thing, as we know that we counsel about. And some of the other data that I showed, I think many families would be very interested in those data as well. And many families who have children and adolescents and adults who were born at 23 weeks would probably hope

that they could have had some more time based on the morbidities that they've had since that time. So, I'm not sure that it's only survival that would be counseled.

Dr. White: I would agree with you and I thank you for that answer. I'm just trying to get a better idea for survival. And then I had one more question, or actually two questions please, for Dr. Neu. Dr. Neu, Is there any data to tell us how much nutrition a fetus gets through the gut?

Dr. Neu: I think that the information that I showed you from that paper that was published in the 1980s actually provided some information in terms of what the composition of amniotic fluid is and what happens when you close off the esophagus. And you have some pretty significant effects occurring if you do not get that nutrition through the gut. So yes, I think that we do have some clues that if the infant does not get any food through the gastrointestinal tract via the amniotic fluid, that this may actually cause some problems in terms of gut development and perhaps even problems after the baby is taken out of the sac and with long-term complications.

Dr. White: And another question, is there any exocrine function to the developing gut in the fetus that might affect lung development?

Dr. Neu: I'm not sure about exocrine, but certainly there are numerous hormones that are secreted by the gut. Modulin is an example of a hormone that's secreted by the gut, and that is responsive to some food in the gastrointestinal tract. I would be a little bit more concerned and not so much at in terms of exocrine hormones. I'd be more concerned about the inflammatory response that you might be getting if you have a lack of tight junction integrity with the lack of food in the gastrointestinal tract, so if you have much more permeability in the gastrointestinal tract.

Dr. White: Okay. Thank you very much. Appreciate that—

Dr. Neu: It's a leakier gut. Yeah. Thank you.

Dr. Dracker: We have the next question from Dr. Gleason. Unfortunately, we do have four or five questions after that, which we will not be able to get to. So, I ask that you have your question prepared, that it be brief and that we have a brief succinct answer. So we can get to one more. Thank you. Dr Gleason.

Dr. Gleason: Yes, very succinct. About amniotic fluid the artificial commercial preparations for Dr. Neu. I know they're used for various indications and so forth. I couldn't find very much about them. Do you know if any of them have done research and including some of these trophic factors and so forth that you've talked about in amniotic fluid? Those various products, do you know anything about those?

Dr. White: No, Christine, I'm not aware of them. I don't think that they contain a good cocktail of some of these trophic factors.

Dr. Gleason: Okay. Thanks. Great concise answer.

Dr. Dracker: Great. Thank you all. Dr. Fischer.

Dr. Fischer: Thank you. This is Gwen Fischer from University of Minnesota. I have a question for Dr. Hintz. That was really comprehensive data that you presented. Thank you. My question is a little bit like what Dr. White was referring to and that's obviously older data because these are patients who are now being followed up later on in life. My specific question is whether or not there is newer data coming out of centers that tend to be more aggressive in resuscitation. I'm aware that Iowa, some areas in Japan, some areas in Sweden tend to resuscitate all of their 22-week premature infants and whether or not there's any follow-up data that we should expect soon from those areas.

Dr. Hintz: Yes, thank you. So, this is Susan Hintz. I have no doubt that there will be some newer Japanese data. As you know that the Japanese data is quite delineated from almost all data in the United States. You mentioned the group in Iowa, they have about two, three years ago, published their experiences with 22 and especially 22, 23-week EGA babies. I suspect they will be coming forward with further data. The neonatal research network certainly will be coming forward with more recent data as well. Certainly as I said, I've seen some of that survival unpublished data. But as you know, even with more recent cohorts, there is a lag, even in two-year follow-up data. So, there will be certainly more data coming forth.

Dr. Dracker: Thank you. Dr. Botkin. You have the last question of the session.

Dr. Botkin: Great, thanks. Jeff Botkin, University of Utah, also for Dr. Hintz. How much variability is there between centers for both mortality and morbidity? And it sort of relates to the question of, as a non-neonatologist, to what extent is there a standard of care out there, or is there quite a bit of variability in how different centers will manage a 23-week patient?

Dr. Hintz: Yes, there is there is a difference in how some sites would manage a 22-week or a 23-week patient. There have been some modifications to the ACOG standard to provide some additional flexibility. Of course, as you know, this is a mother and a baby in terms of the approach and in terms of delivery options. So yes, there is variability in terms of approach, especially at the lowest ends of gestation for sites, but how the site's stance in terms of what is offered, and there are some sites that are certainly much more aggressive.

Dr. Botkin: And do you see that reflected in the outcome data? Do you have centers that consistently have better outcomes in other centers, or is there fairly uniform data across centers?

Dr. Hintz: So, when you say outcomes, are you speaking about survival, or are you speaking about neurodevelopmental outcomes?

Dr. Botkin: Yeah, I guess both. But—

Dr. Hintz: Okay. So survival, as you asked yourself, obviously has a lot to do, if you take all comers as the denominator, has a lot to do with decisions that are made by families and approaches to 22 and 23-week gestation pregnancies. And that's obviously a very complex question that families make. And there are complex stances that institutions take. In terms of neurodevelopmental outcomes there is wide variability because as discussed in a previous question, there are many neonatal and perinatal factors that impact neurodevelopmental outcomes, particularly at two years. And there are many social determinants of health that impact the neurodevelopmental outcomes that we measure at two years. I would also just reiterate strongly, if I can get up on my soapbox, that it is a very early window into outcomes for children at two years. And there's really actually quite a limited number of things that we can measure well at two years. So, I would really say that especially when we're talking about 22 and 23-week, about children who are 22 and 23-week gestational age, we recognize that those outcomes are limited at this point because we have a small number of survivors and we have quite a lag in terms of getting to that time point as we have more survivors.

Dr. Dracker: Alright, thank you all for your excellent questions and insightful answers. We will now need to proceed with the final afternoon presentation by Dr. Mark Mercurio, Professor of Pediatrics and Director of the Program for Biomedical Ethics at Yale School of Medicine. We'll have an opportunity to ask clarifying questions after this presentation. If I did not give you an opportunity to ask questions at the last session, please retain them so that if we have an opportunity later, we can cover them. Thank you. Dr. Mercurio.

Ethical Considerations for a First-in-Human Trial of Artificial Womb Technology — Dr. Mark Mercurio

Dr. Mercurio: My name is Mark Mercurio. I'm a pediatric ethicist and a neonatologist at Yale School of Medicine and Yale New Haven Children's Hospital. Let me get right to it. I've been asked today to speak about ethical considerations for a first-in-human trial of artificial womb technology. I'd like to start with a brief overview of some of the ethical considerations given the time restraints that we have. I'd like to discuss some relevant ethical principles and guidelines, patient/subject eligibility criteria, terminology and moral status, and then finish with some specific recommendations and questions I feel still need to be answered. There are, if you will, dual goals of this work, which are both laudable and which at some point may be in conflict. One is the best interests of the child subject, and the other is the science to benefit others, obviously future patients. In pediatric ethics, we understand the importance of working with vulnerable populations and clearly in situations like this, there's much to be gained, there's also a risk of exploitation. So, the question then becomes, which way should the balance tip?

Rick Kodish, the bioethicist, has stated that individual beneficence must take precedence over collective notions of beneficence. And the pediatric research community must remember that our responsibilities to individual children outweigh more speculative concerns about potential benefits to future generations of children. So, we must pay close attention to both, but our emphasis has to be on the child subject. The federal guidelines, commonly referred to as the Common Rule, recently revised in 2018, actually I think, have a very good ethical grounding, and I'd like to begin with that. The HHS has laid out three requirements for research involving greater than minimal risk, but presenting the prospect of direct benefit to the individual subjects. Note the three, it is an *and*, and not an *or*, A, B, and C, all three need to be fulfilled.

So first, the risk is justified by the anticipated benefit to the subjects. So, just a brief reminder, I think everyone here realizes it, there are two research subjects. These protocols can involve cesarean delivery in a setting where it otherwise would not have been clinically indicated, which is to say that the protocol carries risks to the pregnant patient as well as to the future newborn. There's also, because of the cesarean section, risks to future pregnancies and future newborns, and these all need to be considered.

The second requirement is that the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches. Now, the creators of one of these technologies in Philadelphia, De Bie et al. here, have written out a very nice summary of the ethical considerations regarding artificial womb technology for what they refer to as the fetonate. And they divide this into four different domains. As you can see in the red box, the domains are essentially defined by the gestational age associated with each. And this work primarily focuses on domain three, which is 22 to 25 weeks. And this, in neonatology, is sometimes referred to as the gray zone or sometimes the zone of parental discretion - 22 to 24 or 25 weeks. Now, if we consider the ethical permissibility within domain three or in pediatric ethics decision in general, we would say that anything we're considering should be considered or could be considered either ethically impermissible, permissible, or obligatory. If it's permissible that implies that it's neither impermissible nor obligatory and in this setting, parents are given a great deal of discretion, right? So Lynn Gillam, the bioethicist, has referred to this as the zone of parental discretion, and it's commonly referred to in neonatology as the gray zone. I think that the limits of that zone of ethical permissibility are best determined by prognosis, feasibility, and the relevant rights. And these thresholds are often described in terms of gestational age. So, let's take a look, if you will, at some gestational age and survival data.

These are data from the NICHD, the Neonatal Research Network from the epoch of 2013 to 2018. And we see the different columns represent different gestational ages. So, we're looking at survival at 22 completed weeks, 23 completed weeks, 24, and 25. And if we look inside the red box, we see that at 22 weeks, survival was 10.9% and at 23 weeks, it was 49.4%. We can see the others there as well. But for a moment the focus on those two, 10% and 49%. But it's important to recognize these are all live births at all the hospitals participating in the neonatal research network, I believe this number was 24 at the time this was done.

Now, importantly, if we're trying to compare this to artificial womb technology, we should really compare the results, not for all live births, but rather those who received active treatment, active attempts at resuscitation. And importantly, during that time period, many kids, particularly at 22 weeks and at 23 weeks, did not receive active resuscitation. So, though we saw, for example, if we look at the red box, we saw that at 22 weeks, 10.9% survival. But if we looked at just those infants who were actively treated at birth, survival to discharge of one year was not 10%, but 30%. And at 23 weeks, again, looking at the blue box, we see the survival is actually up to 55%. Now, if we look at the Canadian data from their neonatal network, we see that numbers are quite similar. Survival at 22 weeks was 32%, and at 23 weeks was 50%. The Japanese neonatal research network, here we have much larger numbers. But if we look specifically at survival, at 22 weeks, at three years, we see that there was a survival of 46% overall, and of those admitted to the NICU, perhaps a proxy for those who received active care, 51% survived. So they save, in Japan, again, this is going back more than a decade, they save about half of those kids at 22 weeks.

Here, in the United States, at the University of Iowa, which is a center that is well-known for aggressive care and highly successful care of kids born at borderline gestational age, we see

survival to discharge at 22 weeks was 64%. And at 23 weeks, 82%. So, at 22 weeks, they save about two thirds of these kids. Of course, we see the numbers are low. It's 14 out of 20, recognizing that this represents data just from one center. Now, at Nagano Children's Hospital, again, one center, for similar years, we see survival at 22 weeks for all live born was 81%, and of those admitted to the NICU was 93%. That's at 22 weeks. This is really quite extraordinary. And as you can see quite different from the data reported overall for the United States and Canada for our neonatal research networks.

So, a question we have to ask ourselves is what current survival data should be used for determination of that relevant risk for that second requirement from HHS? Should we use the data from the center where the artificial womb technology is to be trialed? Should we use US overall data, such as that from the Neonatal Research Network, or perhaps the Vermont Oxford Network? Should we use the data from the centers with the best outcomes, and should we emulate the centers with the best outcomes before trying artificial womb technology? Importantly, gestational age alone is a poor proxy for survival. And this is not new information.

Folks in the US, the Neonatal Research Network, this article led by John Tyson back in 2008 in the New England Journal, which he basically described the fact that intensive care for extreme prematurity, he talked about moving beyond gestational age, that if we use five factors, if we talk about gestational age, but also the weight, the sex, the presence or absence of antenatal steroids, and plurality. These five things together are a much better prognosis for survival than gestational age alone. The bigger kids do better than the smaller ones. The older ones do better than the younger ones. The girls do better than the boys. Those who receive steroids do better than those who don't. And singletons do better than twins or triplets. Now, if we look at the data from the Neonatal Research Network, they've created an online tool, the Extremely Preterm

Birth Outcomes tool, where one can enter the specific information about an anticipated delivery to get a likelihood of survival. And if we take a look at this, you can see how much it can differ even within a specific gestational age, again, illustrating how gestational age alone is a poor proxy for prognosis. So, if we look at a 22-week male, 500 grams, singleton with no antenatal steroids, the likelihood of survival with active resuscitation is 15%. A 22-week female, 500 gram singleton who did receive steroids, it's more than twice that, 37% likelihood of survival. And if we just go up to 23-week female who's a bit bigger at 650 who got steroids, the likelihood of survival is up to 60%. So, within that range of 22 to 23 weeks, we see a fourfold change in the likelihood of survival based on this information.

Now outcomes, of course, are not just about survival. And we're very interested with this technology and prevention of disability. Pulmonary morbidity is a big, big issue in neonatology. I suspect by this point in the day, others have discussed this already, but bronchopulmonary dysplasia, the chronic lung disease that these extremely preterm newborns experience from the combination of a very immature lung exposed to positive pressure ventilation, as well as an oxygen-rich environment, the free radical toxicity. All of these things combined have led to a lot of kids having long-term problems. Some having difficulty getting off a ventilator and some having long-term pulmonary problems.

The other big category, perhaps that looms even larger for neonatologists and for pediatricians and for all these kids and families, is the neurodevelopmental impairment that we see in kids born at borderline viability. And there appears to be a potential for prevention of this morbidity as well. Mind you, there's short and long-term evidence, and it's going to be difficult in the short-term to know the more important things. For example, we can see at seven days of age, one can diagnose intraventricular hemorrhage at seven days by ultrasound. But really what I

think matters more to most families, to most patients is going to be not so much what is seen structurally, but what actually ends up being seen functionally. And sometimes it will take years to get a good handle on what the cognitive function might be like in one of these kids. So, it's going to take a long time to understand the impact on neurodevelopmental impairment from this new technology. However, the potential obviously is there.

If we take a look at what the impairment is now with current technology. Again, these are data from the Neonatal Research Network. And on the Y axis, you see children from the percent of kids from 0 to 100%. On the X axis, we see the bars representing different gestational ages, 22, 23, and 24. And if we just look inside the red box, we see that the darkest line represents those with severe neurodevelopmental impairment. And we're focusing primarily on cognitive impairment, cerebral palsy, visual impairment, and hearing impairment. We see the middle line there is for moderate impairment, and the light line is for no or mild impairment. And again, the numbers you see at 22 weeks are relatively low, even though this is multi-center information. But we see that roughly, it's about a third, a third, and a third, severe, moderate, and no or mild. We see that about a third of these kids are going to have no or mild neurodevelopmental impairment at the lowest gestational ages. If we look at the Japanese neonatal network, again, larger numbers, their overall survival was 46%. The degree of neurodevelopmental impairment was also 46% among the survivors.

If we look at the data from Iowa, that's the US center that had such a good success with survival, here we see that among those who survived, no or mild neurodevelopmental impairment was found among survivors in about half the kids are going to have no or mild neurodevelopmental impairment at 22 weeks. By 23 weeks, about two-thirds of those kids are going to have no or mild neurodevelopmental impairment. So, while there's a sense that the vast

majority of these kids born at the borderline gestational age are left with profound or severe impairment, that's really not what the data show. And importantly, there's a risk of making decisions or making assumptions based on follow-up that's too soon. And this is a system of data very briefly from Maureen Hack now going back almost a generation. But she showed that if we look at some very low birth weight kids at 20 months, and we found that 39% of them had moderate to severe cognitive impairment. But looking at those same kids at 8 years, it was 16% with moderate to severe cognitive impairment. And this has been repeated in many places in other countries. And what it shows is that if you look at them over a longer period of time, you find that, in fact, those early estimates of severe impairment were probably pessimistic. But there's also a risk, of course, in looking just early on, there's a risk of manifestations that might appear later that weren't apparent early on. Such things as autism, for example, learning disabilities, behavioral issues, and others.

Now, the third component of the HHS recommendations. All of which I think have had good ethical foundations. This third component is an important one - adequate provisions are made for soliciting the permission of parents or guardians. So, think about this for just a moment. We say permission when we refer to someone giving permission. One gives permission for treatment or research for their child. One gives consent for research or treatment for oneself. But this is occurring in the setting of preterm labor, which is often a setting of fear, of exhaustions, of urgency, and pain. This is how often clinical decisions are made surrounding borderline viability, unfortunately, makes things far more difficult. And aside from the mode of delivery where the pregnant patient gives sole consent, there are commonly two decisionmakers for the newborn for clinical and research participation. So the question is, must both of these parents agree to the use

of artificial womb technology? And looking down the road a little bit, whose permission would be required to withdraw from the study, to withdraw that technology?

Another ethical consideration is about words and when we say what's in a name, what should we call the individual on artificial womb technology? Is it a fetus? Is it a neonate? There are characteristics of a fetus in that the fetal physiology is maintained to a great extent, and yet the individual is no longer inside the uterus. So, some would say that's a neonate. New terms, such as gestateling from Romanis has been suggested. The folks in Philadelphia, the De Bie et al., who suggested a term fetal neonate or fetonate and which term we choose, I think, will have implications. There are legal and ethical understandings about fetuses, and there are those about neonates. There are none really thus far about fetonates. And will the terminology we use depend upon the gestational age or domain? We're talking now primarily about that domain of 22, 23, 24 weeks. That area, that zone of parental discretion. But we have to understand that we're in a culture, we're in a situation where there's not agreement about the moral status of fetuses. The moral status of neonates. Even preterm neonates versus older neonates. And moral status is a relatively obscure term, which clinicians really don't want to hear about generally, but that it's worth considering here. It really is. It refers to, according to the philosopher, Mary Anne Warren, how much an individual's interests should count. So we have to think, is the moral status of a ten-week fetus, 15-week fetus, 20-week fetus versus a 25-week preterm baby? Do these differ? Do the rights differ? And obviously there's a tremendous amount of disagreement within our culture. But these are things we have to think about before the first individual is placed on this technology, which is, what is the moral status of this person? Is it more like that of a fetus? Or more like that of a newborn, or is it something in between, as perhaps the use of a new terminology might suggest? I would say for now, I would suggest that if this patient or this

research subject is in our newborn intensive care unit and is no longer in the uterus, I would prefer we not use a new term, but refer to this as a neonatal patient as, for example, when we have patients who are on ECMO. Which indeed is a partial throwback, if you will, to fetal physiology. We refer to them as neonatal patients on ECMO and not as a different word. And I would say that I would suggest we refer to these patients as neonatal patients who are on artificial womb technology, but that may change. That's a matter of opinion, obviously. And that may change depending on what gestational age we're eventually working with.

Now we've been talking about domain three, but the question is what about domain two? Now, domain two, because it's got a broad span right from two weeks to 21 weeks and the very early gestational ages. I really agree with those who think there's not much to be in by discussing that at length at this point, because that technology is so far off in the future, that's not really what we need to be considering here today. But for those born just prior to 22 weeks were considered, it says here to be non-viable and treatment is non existent, I offer for your consideration one case presentation of a child who was born at 21 weeks and in fact survived and did well and there have been anecdotal reports. So it is not impossible for a child to be born under 22 weeks and survive.

It is not the intention, as I understand it from what I've read, I've been told, those who created this technology, it's not the intention to lower the gestational age threshold at this point in time. But I think we have to say that at some point we may be approached by a parent who asks, can we use this technology for my child? And we need to be prepared with an ethically defensible answer before that question is asked in the clinical setting. I think it can be pretty clear with a research protocol that one can set very specific parameters. But at some point, even if it's

not the intention to move that threshold for gestational age, at some point that question is going to be asked and we need to be thinking about how we're going to answer it and why.

There's a very nice review article on the ethical challenges written by Kukora et al. which makes some specific recommendations, which I think sound very good. Collaborative informed consent by the individuals you see there including maternal fetal medicine specialists as relates to the cesarean section and the risks of the pregnant patient, collaborative study design, planning and discussion among stakeholders all before the first patient is placed on artificial womb technology. This all makes good sense to me, and I would add a humble suggestion. I think a national conference on the ethics of artificial womb technology to include representatives from all the groups listed above and perhaps others would be an excellent idea. They also recommend initial enrollment of only the very high-risk patients, and they suggest a threshold, for example, of less than 20% predicted survival. And then a gradual increase to include infants with a better prognosis, for example, 20 to 50% survival as comparative effect in this trial to conventional therapy. Evaluating outcomes like survival and long-term neurodevelopment. And the fundamental questions, I think, related to this are these the right thresholds? And what are the appropriate thresholds we should be using? And what level of anticipated disability is considered worth the risk of artificial womb technology? Particularly when it is a brand-new technology in the human setting. I've included some selected references for the recordings for those who are interested.

I think this is a very promising technology. And while I think we have to approach it with caution and with eyes wide open, and with an open and thorough discussion of the ethical issues, I think we should move forward with those discussions. And I look forward to that conversation today. Thank you so much for the invitation.

Clarifying Questions

Dr. Dracker: Thank you very much, Dr. Mecurio. We're going to take a break at 3:20 so we can have a ten-minute rest period before we start the questions. I'd like to remind all of you that the chat option should only be used for AV issues. We have to maintain transparency and comments about any of the aspects we're discussing should be available to the public. With that, I'd like to take questions for Dr. Mercurio, which will continue until 3:20. Thank you. Whoever had a question first, please go right ahead.

Dr. Cole: Hi, this is Sessions Cole from Washington University. Dr. Mercurio, is the issue of the threshold informed at all by differences in pregnancy duration that are genetic ancestry-based?

Dr. Mercurio: Hi, it's Mark Mercurio. Pregnancy duration, that's ancestry-based. I'm not certain I understand the question.

Dr. Cole: Black women have shorter gestations than European-descent women.

Dr. Mercurio: I would say that it's not immediately obvious to me that would determine which children, I should say, which pregnancies would be eligible for this study. I think it should be based on what the comparative risks are as they put for the currently available treatment as compared to the anticipated outcomes for the technology in question.

Dr. Cole: But some would say that an African-descent fetus is five to seven days more mature at 22 weeks or 23 weeks than a European-descent fetus.

Dr. Mercurio: I hear what you're saying. So, for each individual, and one thing I tried to show was, and Susan Hintz knows this stuff, I'm sure, better than I do, the one thing I tried to show was that for a given gestational age, there's a wide variability. And I mentioned about those factors, the weight, the gestational age, but also the sex and the presence of steroids, et cetera.

But there are other things as well. And that could include ethnicity. It could include other factors as well. I don't have those data to look at a specific child and say, this child has X percent chance of survival with conventional therapy. As you saw, that chance varies tremendously depending on the center, but, and I think ancestry may have something to do with that as well. But in terms of trying to quantify it, the best tool for an individual pregnancy right now that I'm aware of is that extremely preterm outcomes tool that the Neonatal Research Network has put online for us.

Dr. Cole: Thank you—

Dr. Mercurio: Even that's not meant to make a prediction about a specific child, but it gives us an idea of the likelihood of survival.

Dr. Hintz: Yeah, because Dr. Mercurio mentioned my name, maybe I will just say I do want to just underscore what he said. That tool really is not an individual tool, it's not an individual patient tool. We also very strongly recommend that it's used only for survival. And I would say again, and I'm sure Dr. Mercurio would agree that survival is not the only outcome that families feel is important. So, I think I'll just respond in that way to Dr. Mercurio's comments.

Dr. Mercurio: And I think we're in complete agreement on that, Susan, that obviously that disability is important aspect of outcomes that families want to consider as well. I think one of the hard questions is to what degree that should be considered and what level of disability is such that would justify use of this new technology or anticipated disability. Those are hard questions, but I think what you said is right on the money.

Dr. Dracker: Alright. Thank you. Randi Oster, you are next, but I want to remind the committee members that I will take your questions in the order where we receive them. And again, please state your name and affiliation. Thank you.

Ms. Oster: So, this is Randi Oster, I'm the consumer representative. Dr. Mercurio, I just wanted you to comment on the endpoint that we need to really be focusing on. And I look at your first chart where you had the balance between what's best for the child and what's best for science. I want to just say, I think in that balance we also have to look at the parents. But the reason I want to focus on endpoint is, I think, that when we look at the AWT, the output of measurement is survival. But when we look at the family, the output is quality of life. And therefore, I'd like you to help us understand how we pull those two measurements together, specifically looking at the Common Rule and what are the adequate provisions that we would need for permission and included in that your thoughts on financial support for how you go forward with this.

Dr. Mercurio: I think, trying to get to what some of the spirit of what you're saying in terms of what's important, I think that the survival is important as is the potential disability. But the very first part of your question. Could you repeat? I'm sorry, Randi, could you repeat the very first aspect of your question again.

Ms. Oster: So, the first part of my question, first of all, is to make sure that we include the parents in with the child as we're balancing this for science and then to understand what is that endpoint? Because the endpoint is different. Let's say for the AWT piece of equipment, which is the baby survived versus looking at it from a quality of life.

Dr. Mercurio: Oh yeah, thank you. No, that's very important. I appreciate it. No, I should say that I believe those who are advocating, who have created and are advocating for artificial womb technology, would say that it's not just about improving the likelihood of survival. That is one potential advantage to artificial womb technology, to be sure. But they would argue, and I think that we heard some good presentations this morning, that in fact, because we avoid fluctuations

in blood pressure, because we avoid exposures to positive pressure ventilation, that we not just improve survival, but in fact, reduce the likelihood of disability. Of course, this remains to be proven, but so part of the outcome that they seek for this technology that we seek for this technology is not just about survival. It's about reduction in the level of disability. How that translates, by the way, to quality of life is really a separate question and a complicated one in terms of how people with certain disabilities view the quality of their own life, which we don't have time or I probably don't have the expertise to get into. But I think that this technology is not just about survival. So, if we're trying to figure out if this technology worked, we're going to have to see what percentage of those kids looked good at two years, but as Dr. Hintz pointed out nicely, that's really only to be looking at these kids. We want to know how they're doing when they're eight years old too, and perhaps older than that as well. So, we're not going to really know the outcome of this technology for years after it's first used. Just as we don't really know the outcome of conventional management until years after it's used. Because it takes a long time for a lot of these disabilities to manifest themselves or the level of disability to manifest itself.

Ms. Oster: Thank you.

Dr. Dracker: Thank you. Dr. Botkin, my Alexa says you have two minutes.

Dr. Botkin: Hi, Jeff Botkin, University of Utah. Thanks, Mark, for the excellent presentation. You touched on this a little bit, but I'm interested in your thoughts on the appropriate engagement of fathers. Now, the regulations, I don't think require more than one parent for a prospect of direct benefit intervention, but seems to me to be a mistake if you aren't fully engaging the father in some capacity. I don't know whether that means a formal consent process or not, but I'd be interested in your thoughts on the appropriate way to engage fathers in this enterprise.

Dr. Mercurio: I would hate to give you a short and ill-considered response to that, Jeff, but I would say this much. I think we can at least start with the way we do it with conventional therapy now, which is to say that, how we try very much when we're in that gray zone, that zone of ethical permissibility at 22 or 23 weeks, for example. We work very hard to get the parents on the same page in terms of whether we should attempt aggressive care or not. And I think it's going to be the same here that I think that if there are two parents involved that we want very much to have them both on the same page. And I would approach this the same way I would approach what we do now with putting a child at 22 weeks on high-frequency ventilation. I don't know that this has to be so much different. But one of the questions I think is going to be very interesting is if we can do this for up to four weeks. If we're two weeks into it, and one parent says, I want you to open up that bag and take that baby out or whatever terminology they use for the individual inside, they say I want you to take that baby out. And the other parent says absolutely not leave that baby in there. I think that someone needs to have figured out exactly what we're going to do in that setting where the parents disagree on whether it should be continued. Because obviously there are theoretical advantages to continuing. It's important to note, and I know Dr. Botkin, that you're well aware of this, that while we talk about 22, 23, 24 weeks as being an area where parents are given a lot of choice, that choice really doesn't last forever. Because over the course of days, and certainly, over the course of the first few weeks, the likelihood of survival goes up dramatically. And as such, where we might give parents a lot of options in the first few days, three weeks into this, it's not immediately clear that they should have the same options. So, all of this has to be sorted out very carefully. And of course, people cannot be, should not be coerced into participating in a clinical trial. But exactly what both

parents' role would be in a decision to withdraw from this in the middle of a course, is something that should be thought about ahead of time.

Dr. Cole: Great, thanks.

Dr. Dracker: Dr. Mercurio, thank you very much for an excellent presentation and your insight and excellent answer to the questions. We will take a break. We'll resume again at 3:30 sharp. Thank you.

Questions to the Committee & Discussion

Dr. Dracker: Welcome back after the short break. I apologize for the brevity of it. I'd like to make a statement, which is not necessarily scripted, but we're entering into the questions to the committee, and to that end we need to encourage all members to participate in the discussion. And should solicit the views of all members so that any comment, insight, or concern that could influence a voter's conclusion on the matter at issue is heard and considered. All of us count and this is an important aspect of the meeting.

Question One

Dr. Dracker: Question one, I should say, the goal of an artificial womb technology device clinical development program is to obtain evidence to support the safety and effectiveness of the use of such technology to support normal growth and organ maturation while reducing high rates of prematurity associated morbidities observed with current neonatal intensive care practices and standards of care in extremely premature infants. In consideration of the information provided today on AWT, please discuss the following question.

Question one. Given the testing on large animal models, lamb, piglet, non-human primate has limitations related to between species differences in anatomy and physiology, which may prevent direct representation of the use of AWT devices in the human neonate, please

discuss key safety and proof of principle endpoints, including time points of assessment, such as the time of transition from AWT, longer term follow-up, and maybe evaluated in animal studies to understand the potential benefits and risks of AWT in the human neonate. Are there any questions or comments on the wording of the question? Please speak freely if you have any questions with the phrasing. If there are no questions or comments concerning the wording of question one, we will now proceed with the question and open the question for discussion. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel. If there is no further discussion on this question, we will now proceed to the next question. Given the limitations—

Dr. Green: Dr. Dracker. I'm sorry to interrupt, but I think there are some hands raised.

Dr. Dracker: I did not see them. I apologize for that. Thank you. I cannot see the list of people. Marieann, can you provide me the list, please?

Ms. Brill: Dr. Krug has his hand raised. Okay, please go ahead.

Dr. Krug: Hey, good afternoon. This is Steve Krug. I'm a panel member and I'm a faculty member at the Feinberg School of Medicine. I'm not a neonatologist, however, I care for a lot of a lot of children who've survived prematurity and I offer one observation. First of all, the presentations today have been outstanding. But the scope of complications that we need to consider is actually, I think, broader than what was actually presented. And again, I think the presenters were focusing on the things that are the most common and/or the most potentially severe. It's incredibly clear to me that survival is not the endpoint. And that survival isn't necessarily what's most important to families. And one of the difficult issues we're going to have here, which is certainly going to, I think, add a fair amount of time to trial to then expansion to

practice, is that there is going to need to be some fairly extensive follow up on these infants for quite some time. Certainly for me to be then able to say, you know what, this is the same, or maybe it's better. Thank you.

Dr. Dracker: Alright. Dr. Guillory.

Dr. Guillory: Charleta Guillory, Baylor College of Medicine professor in pediatrics, neonatologist. There are two things that really hit me here in terms of long-term follow up. The thing that comes to mind, we know that prematurity is higher in African-Americans. We know that the extreme premature infants are also higher. And we know that this gap has been there for almost a decade unchanged. So, as we move forward with these babies as they survive, and we've already talked about two-year outcomes and five- and seven-year outcomes. And when we follow our babies, one of the things we really have to discuss is the financial issues and the resources to support these children. And so, I'm just concerned that as we care for these babies that they will not get the resources and help that they need to really have any benefit of affecting the social determinants of health and the outcomes that we've already so nicely mentioned in the previous discussions. And that's one thing.

The other thing I'm concerned about is the presentation for consent forms. How do we make sure that the people who are getting the consents are not in any way adding pressure, are coercing them? And I really see that we really need to have a better system that it's not the people who are doing the procedure necessarily getting the consent forms. And we do need a group or a different type of approach because that's another thing that is not really brought up that you see all the time. Thank you.

Dr. Dracker: Thank you. I'd like to remind the members that we are primarily discussing the current issue of animal models for this technology. And we are not really describing or

responding to the issue of adult-applied technology. So we want to stay focused on the presentations that were given earlier today. Dr. White, you had a question.

Dr. White: I had concerns looking at the different models that it seems the model that's closest to the human fetus in size is the piglet. The lamb model is much larger and more easily accessible, and there's been some pretty good success it looks like with the lamb model. But when we move to the piglet, we see some significant problems with perfusion and maintaining adequate perfusion. It's very difficult to understand the differences that might be present because the two different techniques are very different as well. So we don't know if the problems with the piglet and the difficulties and perfusion in that smaller creature are related to the technique or if it's related to the basic problems that we're going to encounter with a smaller subject to begin with. So, I feel a bit uncomfortable saying, oh let's just go straight to a human who is the size of the piglet based on the lamb model, which is a much larger animal and much more successful, but also admittedly easier to manage because of the size of the equipment that we have to use. I just have that concern and I don't know how to address it properly other than to raise that as an issue.

Dr. Dracker: Would anyone else like to address his concerns?

Dr. Flake: Yes, I would like to. This is Dr. Flake from the Children's Hospital of Philadelphia. So, we presented data in two lamb models. One was much bigger than the human infant, and the earlier gestation model was very close, actually, in many of the individual lambs to being the size of an extreme premature infant. There's also a study from Australia using comparable technology that was just very recently published with two weeks survival for lambs that were 650 grams in size. So, as I said previously, I don't think it’s size that's the limitation. If you can match circuit specifications to the individuals’ own cardiovascular requirements and

ability to auto regulate, then size isn't the issue. You can survive on an AV pumpless circuit through nine months or eight months of gestation. The difference between the pig and the sheep goes beyond simple size. The pig model is a near-term model, which makes it physiologically quite different than the mid-gestational animal models. And that's one of the limitations of the pig is that if you're going to try to run a three or four-week experiment on the pig, you're going to go well beyond term, even a two-week experiment. So that limits the value of the pig for long-term information, and it's the term developmental status of the pig limits it for any sort of developmental studies. So, those are my comments, I think. Can we support pigs for longer than we have? I think we can. There's no reason to think that we couldn't. We get physiologic, but I'm not supposed to discuss the pig model today, so I'll stop. But it's not a size issue is what I'm trying to say. And I don't think the pig is the optimal model to try to demonstrate long-term artificial womb support in because of its near term status at the size it is equivalent to a human patient.

Dr. Dracker: Thank you. Dr. Flake—

Dr. White: Dan—

Dr. Dracker: I'm sorry.

Dr. White: I'm sorry. If I can continue just for a moment. You've answered some of the questions. I think some of the questions go into the discussion we ought to have tomorrow. I don't recall a large number of animals that have been maintained for weeks that are the size of a human fetus. And it seems to me that it's important that we be able to say with certainty, we can do this for four weeks comfortably if we're going to go to the point of asking people to give their permission to work with their infant. Shorter times than that may not reap much of a benefit. Is that a correct assumption?

Dr. Flake: I think there's a benefit for every week of additional gestation that you achieve. You can go through the numbers and look at the benefit, so I think if you were to run two or three weeks, you would still potentially have significant benefit, both in terms of mortality and our primary focus, which is morbidities. You're right, we would like to go four weeks in every infant. We may be able to go longer than four weeks in human infants. Again, the sheep is a challenging model in that respect because of its very rapid growth and high blood flow requirements. So, I would answer to that, yes, four weeks would be great. But I don't think four weeks is absolutely necessary to provide benefit to the patient.

Dr. White: Okay. Thank you.

Dr. Dracker: For the members, I'd like to clarify that this is the advisory committee deliberation. This is not a question and answer session. This is a time when only the advisory committee should be discussing their concerns as it relates to the questions I pose. So, I know it's difficult not to ask questions of the experts and the presenters, but this should be amongst the members of the advisory committee only. Randi, you had a question or a comment?

Ms. Oster: Yeah, I'm going to lead with my comment and because I think it's important at this time as consumer representative to talk about the public. And I just want to start here to say, in light of this last summer of Barbie and the Oppenheimer movie, the public embrace the questions of what does it mean to be human and our responsibility for thinking through the impact of our technological expanses. The extend womb combines both. The endpoint for measurement needs to clearly be defined based on the baby and the parents for quality of life. And I want us to be thinking that way. I'll be saying more later, but I think it's important that we understand that the public knows we can't go backwards. So, the decisions we make for domain

three will also start to translate into what we were told were domain two and I'll use that as my open for now.

Dr. Dracker: Thank you. Dr. Zeiss, did you have a comment?

Dr. Zeiss: Hi. Yes, I have a comment related to the neuropathology. I do believe that the evidence has been presented. I feel comfortable that the experiments as done provide adequate support for normal neurologic development in the lamb, even in the younger lambs. I don't think that much more can be done to enhance that point. That said, even the younger lambs, they're at a stage of development which is more advanced than a 23-week old human, where you would have a lot of neurogenesis and vascular development. And that increase in cerebral blood flow with vascular fragility, I think is very susceptible to hemodynamic abnormalities that could result in the artificial womb, and I think that if we look at the lamb and the pig experiments, I also keep going back to this difference. Why could we not replicate in the pig, what we see in the lamb? Given the pig is more developed, we should be able to have these animals at least survive to term without the hemodynamic difficulties, without being able to really assess the neuropathology, I don't believe we have an animal model we can do that in. We are left with relying on maintaining absolute hemodynamic stability to protect the brain. So, I think that perhaps tomorrow we should open a discussion on how that could be achieved in not one animal model, but two.

Dr. Dracker: Thank you very much. Next on the list was Dr. Gleason.

Dr. Gleason: Yes, hi, Christine Gleason, University of Washington, neonatologist. In addressing this particular question about additional things or what we should be considering in additional animal studies in order to understand potential benefits and risks of this. I think, and I've been concerned ever since I heard about this, about nutrition. And Dr. Neu gave a lot of very important issues with how we can actually try and replicate the intrauterine environment in terms of growth

and nutrition in an intrauterine way. And I think that more is needed in animal studies to understand that and understand what we may be missing and what we may actually be able to do. For example, with these commercial amniotic fluid preparations and things that can give better growth, bigger is not necessarily better. And be able to look at things more carefully like the liver and the kidney at comparable stages of development, in addition to the intestinal tract. What happens to the microbiome in this setting after all those weeks with TPN and swallowing of the sterile amniotic fluid? So that's one thing that I think could benefit from additional animal studies.

And then the second thing is I didn't hear a lot about I guess what we would call, certainly in these animal studies but for sure in the human studies, adverse effects like in emergencies and what happens when the oxygenator fails or something happens to the bio bag and the fluid. There are all sorts of things, basically troubleshooting, and then if this, then this. If this, then that. It seems to me that in safety of this, there needs to be more, and probably there is. I'm sure with all those years of doing this, and lambs, piglets, and so forth in these animal models, there have been all sorts of things that have been learned that troubleshoot various catastrophes and emergencies and things that happen. But as much as that can be done in an animal model, just the technical things, before it's actually a first-in-human study. I think that's another area that could benefit from additional animal experiments going forward.

Dr. Dracker: Thank you, Dr. Gleason. Dr. Hoehn?

Dr. Hoehn: Thank you, Sarah Hoehn University of Chicago. I just wanted to comment on this specific question about what we should be doing as an endpoint looking at the animal models. We heard from the different experts that a 24 weeker born today has a 71% overall survival and a 24% risk of hemorrhage, which is still a very reasonable survival. And as someone who takes

care of a lot of children with complex medical needs and a lot of ex-premature infants that are long-term dependent upon technology, I don't think we can ignore survival as an outcome in and of itself. And so, I just think if we're going to compare what we think to this standard of care, we can't only look at quality of life. Yes, quality of life matters. It's very important, but we can't compromise if we have a 71% survival with standard of care at 24 weeks. So I just wanted to comment on that specific endpoint. I don't think we can ignore mortality.

Dr. Dracker: Thank you. I need to mention to all of you that discussion should be focused today and today only tomorrow will be a very different time for discussion. Thank you. Dr. Hill, you had a question or a comment?

Dr. Hill: Yes, I had a comment and Dr. Gleason summarized it probably better than I. From what I've heard today, I'm not clear on where we are with the various animal models. And are we at a point where we need to do more? Or we're there so that we can now move forward with clinical trials. And the other concern from what I've heard today has to do with safety. What happened when they were unable to cannulate or things of that sort? So, those were my two concerns. Where are we on this journey from an animal standpoint and from what I heard, we still are not certainly at the end. Those were my comments.

Dr. Dracker: Thank you. Dr. Fischer, did you have something to discuss?

Dr. Fischer: Yes, thank you. This is Gwen Fischer from the University of Minnesota regarding discussion question one, which primarily focuses on what the FDA should consider for animal studies for these devices. I think that while not perfect, one comparison and one starting-off point for the FDA can be the approval for the Berlin Heart, which happened more than a decade ago, but is one of the only FDA-approved devices that is similar to this in terms of how the technology functions. The second being the Jarvik device and the other PumpKIN devices,

which also underwent very significant animal trials. In essence, while this is a very different patient population, the technology itself is very similar to ECMO. And so, I feel that these studies that were required of those devices are a good jumping off point. Particularly, the ones looking at stroke and bleeding rate they also did survival at 30 days, I believe. And then other secondary endpoints, like infectious rates, pump failure, and other things that the FDA required those two groups to look at in their animal studies. Thank you.

Dr. Dracker: Thank you. And finally, Dr. Nelson.

Dr. Nelson: Yeah, let me just ask a question first. As the industry representative, I don't see anything other than the public briefing document. So, I have a couple of comments around the complexity of the choice of population to go into relative to duration and technical issues and the like. And so, I'm happy to save that to a later question, since it's not directly on the animal model, if that's appropriate, but I honestly don't know what the questions are going to look like, because all I saw was the topics in the briefing document.

Dr. Green: Dr. Nelson, if you could focus on the question at hand, which is discussion question one regarding the animal models for the time being. Thank you.

Dr. Nelson: Okay, then I'll delay my comment until a later question.

Dr. Dracker: Alright. Thank you, Doc. Alright. Marieann, if there are no further questions, I assume we move on to the next question. Is that correct?

Ms. Brill: I believe Dr. Gleason had her hand raised a while ago or not.

Dr. Dracker: Oh, I'm sorry. I did not see that. Dr. Gleason go right ahead.

Dr. Gleason: Yeah. Hi, just a follow up because I was thinking again about troubleshooting and what happens if and so forth. And it really, I know there are a lot of reasons why non-human primates are not the right size and so forth for cannulation and so forth. But I did just wonder if

the NICU care models, there have been, preemie, non-human primate studies done EPO studies, things like that, the umbilical cord, they're in incubators, they're on ventilators and so forth, I just wonder if consideration could be made in terms of safety in some of these other trial runs that are more similar. In terms of not necessarily in development or lung maturation and brain and so forth, but just caring for them and they're much more like human infants, preemie infants. So, I just wonder if that couldn't be considered in addition to all these other things that we just talked about with animal models, that the non-human primate really might just be worth considering for safety and just trial runs, really, that are closer to what it will be like in the first-in-human studies.

Dr. Dracker: Alright, and that is part of our second question that we will discuss. Marieann, should we summarize the discussion for question one at this point?

Ms. Brill: Yes, please.

Dr. Dracker: Okay. So, what I've heard from all the members is that number one, there is a concern with following the long-term consequences of using this technology. And number two, from what I've heard, making sure that we are using the appropriate animal model and assessing it fully before we undertake human studies. Does the committee agree that is a short summary of what your concerns were? Dr. Fischer, did you want to add something or mention something too or no?

Dr. Fischer: No, I agree to that.

Dr. Dracker: Okay. Thank you. Michael, do you have any comments?

Dr. White: Michael White. Yeah, I think that's a reasonable assessment. Sorry.

Dr. Dracker: That's alright. Marieann, are you satisfied with that or Dr. Nelson? I saw your name come up. Do you have a question or comment as well?

Dr. Nelson: Yeah, I just want to underline the duration issues. I think those have been discussed. That basically the animal models need to be of sufficient duration to be able to provide a transition from, let's say, early viability to a time at which you've achieved the clinical improvement that you hope to achieve. So I think that duration is very important. We've heard differing durations in the different animal models, but I just want to underline duration.

Question Two

Dr. Dracker: Okay, thank you. Any other comments from the committee? Alright, Marieann, should we move on? Thank you. This is question two. Given the limitations of the animal models and the clinical experience data discussed, what additional, if any, existing clinical experience data may be leveraged to help inform the benefit-risk assessment of enrollment in a first-in-human trial of an AWT? Marieann, if you can give me a list of hands up so I know who is first. Thank you. Dr. Nelson, did it before—

Dr. Nelson: No, thanks. I think this is where I can make the comment I was thinking about. When I looked at the NICHD data, one could see a bit of a plateau from 22 to 23 to 24 weeks and then a not insignificant or fairly significant improvement in morbidity and mortality at 25 weeks. So one could make an argument based on that. We've talked a lot about threshold, but one could argue that where you want to get to on the assumption that there's ongoing organ development during the course of the application of the AWT that, in fact, you want to get to at least 25 weeks. And so, that sort of sets a duration and it sets a threshold that if you can only achieve two weeks, you've got to start at 23. If you might do three weeks, you start at 22. And if you've basically decided that you're not going to put a fetus who is otherwise not viable onto this technology, that pretty much tells you your window, if you will, of where you want to be. Now, if you can get to 26, great. But I would argue if all you can do is get from 22 to 23, that's not much

of an impact. Or 22 to 24 from the neonatal outcome data, at least from the clinical perspective, if you want to at least match what it means to be in utero from 22 to 25 weeks, you want to basically accomplish that same thing. It's not just comparing, and this is a question, what the outcome would be from a neonatal perspective, but also, you know what you might achieve by remaining in utero for another three weeks. I think that would be the ideal to be able to match what happens at 25 or 26 weeks because you've been able to mimic the in utero environment for at least two or three weeks. Dr. White said four weeks. I think that's probably a bit overly optimistic. If that's achieved, that's great. But I say at least two or three weeks.

Dr. Dracker: So, Dr. Nelson I just want to understand, your suggestion is that we have adequate data in utero and ex utero at 25, 26 weeks. And to look at the data for those infants to use as a comparator for when you have these children under this technology trying to achieve that same gestational age. Is that correct?

Dr. Nelson: Yeah, and I guess there's an ambiguity there. In other words, do you hold the technology to the same standard of what would happen if you were born at 23 weeks versus do you hold it to the standard of what would happen if you remained in utero up to 25 weeks?

Dr. Dracker: I understand.

Dr. Nelson: And I'm not going to answer that question, but I think there's a bit of an ambiguity there. At a minimum, you'd want it to be at least equal to what would have happened with standard of care if you were born at 23 weeks. But ideally, I think this is what the investigators hope to achieve, is that you would have the same outcome as if you were born at 25 weeks.

Dr. Dracker: Okay, understood. Thank you. Dr. White.

Dr. White: I think what Dr. Nelson had to say is a reasonable summary of what I was trying to get at, which is we need to decide what is considered a reasonable expectation for

improvement and where we want that outcome to be. I don't want to get into the information in the discussion that we're going to have tomorrow, but I think we need to have adequate data in an animal model that we can reliably get to whatever goal that's going to be. I think four weeks is a reasonable expectation, but that's me, no one has to agree with that. So, I think I'm in agreement with what Dr. Nelson has to say. I also want to make just one quick comment about the Berlin Heart and how that was approved. In the Berlin Heart, the choice was death versus ECMO or death versus the Berlin Heart, which is a very different circumstance than what we're discussing here. So it'd be hard to use that same decision tree in what we're discussing today. Thank you.

Dr. Dracker: Thank you. Dr. Fischer.

Dr. Fischer: Yes, this is Gwen Fischer from the University of Minnesota. Thank you, Dr. White. In reference to the Berlin Heart data, I agree, but was thinking more that some of the animal model data that was required for that might be a good jumping off point and probably more relevant to what was required of the Jarvik device, which was much more recent and is comparing to an FDA-approved therapy.

Regarding question two, my thoughts on this are very much similar to the first commenter that I think what we need to look at is the data from the 21, 22-weeker assessment and that it would be great if we could get some more recent data on a 30-day mortality and also mortality and morbidity to NICU discharge.

Dr. Dracker: Thank you. Randi Oster.

Ms. Oster: This is Randi Oster, the consumer representative and the question of how do you help inform the benefit-risk assessment of enrollment in the first-in-human trial goes back to the requirement of the 21 CFR 50 subpart D, which is what is known about mortality and morbidity.

And therefore, I would advise the FDA that the unknowns that we have discussed today have to be very clear, laid out as a benefit-risk for anyone considering this.

Dr. Dracker: Thank you very much. Dr. Davis.

Dr. Davis: Thanks very much. John Davis from Tufts in Boston. I think with respect to this question we've had, Susan did a very nice job of presenting some of the neonatal research network data, which is very important data. But I'd also suggest that there are other opportunities for FDA to work with other data sets. Because I think you really do want real world data to look at how these children are doing in general. Not just in a limited number of academic centers which are high-functioning in a sense, but potentially looking at a data set, like the pediatrics for the next that Danny Benjamin and others have leveraged to look at a variety of clinical data. I think that would be worthwhile. FDA has funded the international neonatal consortium. Where I'm one of the directors, we have over 400,000 babies in that data set from Japan, Europe, Canada, the US. And I would also think looking at the short-term complications of those babies being born potentially at 23 or 24 weeks. Again, using real world data to look at the backdrop. And I think that also can help establish what the risks are of a variety of different morbidities and mortality for the different gestational ages. So, while I think the NRN data is very compelling and very important, I'd also suggest that FDA leverage other data sources to help inform the benefit-risk assessment where you can see in other hospitals outside the NRN in different countries, different places, really what the various morbidities and mortalities are.

Dr. Dracker: Thank you, Dr. Davis. Dr. Holubkov.

Dr. Holubkov: Dr. Davis just more eloquently said what was I going to comment on as a biostatistician. Great presentations today, because we saw the numbers for these 22, 23, 24 weeks are very small. So, I was going to suggest the same thing. Harness more cohorts, harness more

recent data, can some sort of global report or summary report meta analysis be done, perhaps identifying with the numbers available. Possibly rough, possibly more refined. Again, predictors of favorable outcomes, let's say at hospital discharge. So again, what additional data can be leveraged? Recent data on cohorts around the world as much as available as Dr. Davis, of course, just said. Thank you.

Dr. Dracker: Thank you very much. Are there any other questions or comments on the wording of question two? Dr. Botkin had a comment. I'm sorry.

Dr. Botkin: Yeah, thanks. I'll jump in there. I think one of the things we haven't talked much about, or I didn't see in the reading materials was about clinical training of staff to run this technology, and it seemed as though in a number of the animal models, adverse events were oftentimes associated with the operator error. And so, I would want to see some information about the plans for training clinical staff and no doubt there's going to be a team of people who have different roles and responsibilities. So how is it that they can adequately rehearse their responsibilities, know what their jobs are, know what monitor, et cetera? And no doubt there'll be a learning curve on this, but once you get into real babies, the learning curve has to be as short as possible. So again, I'd be interested in knowing and perhaps from other experiences with new technologies. How do you get staff up to speed such that they're ready for that first baby that arrives?

Dr. Dracker: Thank you. Dr. Cole, I'm sorry I interrupted you. Go right ahead.

Dr. Cole: Sessions Cole from Washington University in St. Louis. I'm a neonatologist. One other suggestion for the FDA to inform benefit-risk assessment would be a diverse and inclusive assessment of parental perception of benefit versus risk. We haven't heard a great deal about parental input and what the spectrum of perception of benefit is for parents. Thank you.

Dr. Dracker: Thank you, sir. Are there any other comments? Dr. Nelson.

Dr. Nelson: Yeah, given Dr. Cole's suggestion, given the comments that Dr. Hill and Dr. Guillory have given about equity I just wanted to call people's attention to a recent report, I had no involvement in it, of the National Academy of Medicine toward equitable innovation in health and medicine. And I have to commend the sponsors of applications and IDEs in this field to just take a look at that and see what they can do to incorporate the approaches to equity in their innovative approaches. So, I think that would go a long way towards addressing some of the issues that have been raised by Dr. Hill and by Dr. Guillory and also by Dr. Cole in his last comment. Thanks.

Dr. Dracker: Thank you, Skip. Anyone else? Alright. I will try to summarize this. It sounds like in response to question to the committee feels that we have to make sure that we have proper comparators, not only utilizing external data from large data sets from throughout the world, but also looking at outcomes as compared to the two to three to four-week period that a child may be on this technology and as how it compares to the data from gestational age of 25, 26-week neonates. And also, when we are considering the benefit-risk assessments we need to make sure that the parents are fully aware of the technology and understand what they're being asked to participate in. But also make sure that it is inclusive of all infants, regardless of race, creed, color, and background. And make sure the informed consent, a process, I think, is adequate for the parents of these infants. Does the committee agree with that overall synopsis?

Dr. White: Yes.

Dr. Dracker: Thank you.

Speaker not identifiable: Yes.

Dr. Dracker: Thank you very much. Marieann, should we proceed to the next question?

Ms. Brill: Yes, please.

Question Three

Dr. Dracker: Thank you. Question three. What challenges do you anticipate in obtaining effective informed consent for an AWT clinical trial? Please discuss potential strategies to address any anticipated challenges. Dr. Holubkov, do you have a question or comment? Marieann, is that my current list of—

Ms. Brill: McMillan first?

Dr. Dracker: I'm sorry.

Dr. Holubkov: I apologize if my hand was up. I did not have it up.

Dr. Dracker: That's alright. So, who is the first to raise their hand? Jump right in until I get—

Ms. Brill: Gigi McMillan.

Dr. Dracker: Thank you.

Ms. McMillan: Hi, I'm Gigi McMillan from Loyola Marymount University and I'm the PAC patient Family Representative. So, previously consent challenges that were mentioned were that the mother is also a subject and what about therapeutic misconception and what about investigator bias and what about the parent emotional state? So, I've actually been personally in a similar consent scenario when my young child was faced with a life-threatening malignant brain tumor. And my husband and I had to choose between standard of care that would significantly undermine our son's quality of life or enroll in a research study that offered the potential for a much higher long-term quality of life. But if it didn't work, we would delay the embarking onto the standard of care regime, and perhaps this would impact his prognosis. So, I want to share that despite the horrific options that were in front of us and our emotional distress, we were able to come to a reasoned decision. And the key components to our consent process were complete

information in understandable language with relevant visuals, multiple opportunities to ask questions, access to an objective third party for private discussion while we were trying to come to our decision, and ongoing emotional support after the decision was made. I'm sure there are other strategies that would also benefit this particular situation, but at least these four that I've mentioned seem reasonable and fairly available for this indication. I just don't want us to assume that because the issues are complex and that the parents are distressed. That they cannot make a well-considered decision.

Dr. Dracker: Thank you. Dr Cole.

Dr. Cole: Yes, thank you. I'm Sessions Cole, neonatologist from Washington University in St. Louis. I think while an informed consent process focused on a high-risk patient is certainly a strategy that is in use, another part of the consent process might be to consider going to a high-risk center and providing educational materials in the first trimester for high-risk women so that they have an opportunity to be aware of this possibility should their pregnancy encounter the problem of inevitable delivery at 23 weeks. In addition, I believe that the Children's Hospital of Philadelphia group has a community advisory group and leveraging that community advisory group to help bring the specifics of this clinical trial to the community's perception, I think, would also be helpful. The bottom line is anything, I think, we could do to inform and educate before the inevitability of a 22-week delivery. I think we should try to pursue. Thank you.

Dr. Dracker: Thank you very much. Dr. Hoehn.

Dr. Hoehn: Thank you. Sarah Hoehn, University of Chicago. To me, what I was thinking when we were talking about how important it is that we have equity and inclusion around innovation, was how in some ways this is really similar to resuscitation research in terms of people have to make decisions very quickly. And we think we have to be careful because, in

general, people who seek out really aggressive fetal interventions are people who have a lot of access to health literacy. And it's not necessarily equally available to everybody, but some things that have been successful in other environments are doing focus groups. And you could do focus groups where you have a big variability in representation, both racial groups, ethnic groups, education groups. And have discussions in different focus groups in different communities, which would be a way to get some feedback on it prior to trying to get consent when someone's having preterm labor. So, that's all I wanted to mention, just the similarities to resuscitation research and how I think it's really important that we think about either focus groups or how to get education and feedback from people in various racial and ethnic groups.

Dr. Dracker: Thank you, Dr. Fischer.

Dr. Fischer: Gwen Fischer from the University of Minnesota responding to discussion question three. I would just strongly agree with the patient advocate and the others who've spoken before me about the need for patient involvement both at the recruitment and consent part of the process. But also, the trial design process as I think that we have seen historically that highly invasive trials in pediatrics are very difficult to recruit for. One specific barrier that we may face at some point is the need for designing a randomized control trial, and that, in particular, has been very difficult to recruit for in pediatrics.

And then lastly, I do think given the comments from some of our experts today regarding practice standard differences between sites, may be an issue. As an example, when a family getting this opportunity here versus resuscitation at another hospital versus comfort care at a third hospital. So, we just need to make sure that's addressed early on in the clinical trial design process.

Dr. Dracker: Thank you. Dr. Botkin.

Dr. Botkin: Thank you, Jeff Botkin, University of Utah. Actually, as McMillan really summarized my thoughts on this, so I'll just emphasize. I think the use of visuals and animation in this context is going to be very helpful for folks. A consent form that was part of our reading is this sort of typical 20-page dense document that is largely worthless. So, we do need more creative and innovative ways to help people understand what the nature of this choice is. So, that was it. Thanks.

Dr. Dracker: Thank you, Dr. Krug.

Dr. Krug: Thanks. This is Steve Krug from the Feinberg School of Medicine in Chicago. Kudos to the advisory committee members who made a much more eloquent discussion regarding the challenges faced in terms of assuring that the consent process is an equitable one that reflects disparities and also reflects perception of research. And the excellent points made about whenever feasible, as in with a high-risk pregnancy, perhaps of having this discussion as a possibility prior to the actual event where we're now asking a parent to make an urgent decision. I think the other potential challenge here is that the intentions of the study will be misrepresented in places like social media. And I think that if we are going to be successful in enrolling patients, and I presume this is not going to be happening at every single hospital in the country, because there are only a few places that probably have the skill to do this. That needs to be considered as well because that has certainly had a substantial impact on substantially more routine healthcare practices that in theory have demonstrable value, yet we can't convince parents to do them. Thank you.

Dr. Dracker: Thank you. Randi Oster, you had a comment?

Ms. Oster: Yes. When we have been talking today about informed consent, we need to be looking at the adverse events. We specifically talked about equipment that doesn't work or

training that wasn't done properly. And, therefore, the liability and in the informed consent, it should be very clear the liability that these institutions are taking as they're doing this clinical trial at how compensation will be for those parents.

Dr. Dracker: Thank you. Dr. Guillory.

Dr. Guillory: Charleta Guillory, Baylor College of Medicine, Texas Children's Hospital. The main challenge, I think, or a major challenge is going to be distrust and how when you mention words like clinical trial or research those are words that will be seen as, how can I say this? Oppressive, in a way. One of the things that I see, and that's what we do with our ECMO consents, is to have someone that provides patient support, patient advocate. Many times we do have to make sure language barriers are addressed as well. So, we have people that are there, language interpreters, and we have all different language interpreters available. But the way I think to get at this is always through education, especially you know many of the mothers who are going to have repeat high-risk babies or high-risk premature babies. So to make sure that the education is done before you get to that point. So, I think doing it prior to delivery is important and making sure that they are well-informed. Even before this is done. You can start that process early. Thank you.

Dr. Dracker: Thank you very much. Dr. Hill.

Dr. Hill: Dr. Guillory stole my thunder as did some of the other eloquent participants. When I see challenges, someone brought up some of the real health benefits that we have been trying to get our patients to agree to and it's been an issue and a problem and still is.

The second point is potential strategies and, I'm sorry, I forgot the speaker's name. They do have a community group at the University of Pennsylvania. They just presented at the National Medical Association meeting and it has been very successful and I would urge the FDA

to find a way to involve the community in answering the question, how do we develop strategies to address the challenges? And lastly, yes, as a maternal fetal medicine specialist, some of these mothers are going to have had a previous 22-weeker and discussing it with them ahead of time, not in the heat of the moment in labor and delivery would be very beneficial. Those my comments and thank you.

Dr. Dracker: Thank you very much. Dr. Gleason.

Dr. Gleason: Hi, Christine Gleason, University of Washington. I have two comments. The first is that I've been looking at the discussion question and just reflecting on what's meant by effective informed consent. So, what are we thinking? How would we define effective? Effective for whom? For what? And so forth. So, it just strikes me as it's something we should reflect on. What do we mean? What's the outcome going to be that makes us decide this was effective informed consent? And I think we would all agree that it would be terrific if parents could be fully-informed and fully comprehend what we're asking for their participation and the participation of their neonate. But I think all of us who know that this is extremely challenging in this situation and in many others, as people have already mentioned in pediatric clinical trials. So, I think one of the things that's particularly challenging for this and in trying to fully inform, as best we can, parents is that you have two things you have to inform them about.

One is basically about the standard of care. What is at 22, 23, 24 weeks? What are the outcomes? What are their choices? If aggressive resuscitation or not, this is the kind of conversations we have. And it's very difficult to fully inform as others have already mentioned in this very emotionally-charged, fearful crisis setting. So, there's that. And then there’s we have something else that we're trialing that may be effective, that may make it better for your baby, et cetera. So, you have to try to explain the one, which is difficult for all of us that have been, doing

this for years. And then try to put on that, what would this investigational device be like? So, I think that the things that have been mentioned about trying to do as much education including videos with avatars and so forth to try and inform people. Even in the moment, people with lived experience, parent advocacy groups and things like that, who can talk about extreme prematurity and then what this new device might provide and what the risks and benefits are. So, I think those potential strategies and doing as much as you can ahead of time before someone's in active labor less than four centimeters, but still, it's just going to be very difficult to try and bring that all to the fore in those hours, or maybe you'd have a day or two to try and really get fully-informed consent. So, those are my comments.

Dr. Dracker: Thank you very much. Dr. Gleason. Dr. Feinstein.

Dr. Feinstein: Hi, Jeff Feinstein, Stanford Children's Health. I think we've talked about a number of different issues here and a number of different challenges, both for the families and for the providers and for the researchers. And we talked about the concept of effective informed consent. One of the things that came up in one of the earlier presentations is we don't actually even have a standardized nomenclature for what the babies are going to be termed. So, if you think about all of the logistical pieces in this and trying to make sure that all of the different families and all of the different centers get some version of similar information, similar approaches, similar promises, if you will, the concept of a centralized IRB may be quite effective here. The concept of potentially convening some version of an expert panel to determine what some of the nomenclature may be. And for this particular space, which is brand new, the fact that somebody is going to be first in with their clinical trial. Again, do we let them set the rules that the nomenclature set the endpoints, or should this be a more global discussion? So, the first-in and everyone subsequent is all using similar approaches such that people who are hearing about this

again, whether as a clinician or as a researcher or as a patient and family at least have some semblance of similar experiences.

Dr. Dracker: Thank you very much. Are there any other comments or questions? Alright. I will do my best—

Dr. White: Yes—

Dr. Dracker: I'm sorry.

Dr. White: Dr. Dracker.

Dr. Dracker: Yes.

Dr. White: I did have some comments. If you don't mind.

Dr. Dracker: No. Go right ahead.

Dr. White: So, I agree with Dr. Cole. Anything we can do to get to these families before anything happens or before they're hit in the face by the fact that their baby has to be delivered is going to help. I don't know that it will cure everything. I think there's a misconception here too, that we're talking about multiple centers. I think it's absolutely necessary that a first-in-human trial be performed at one center with consistently good neonatal intensive care. So that support is available for those that don't make it on to whatever this process is going to be. So, I think first of all, we should make sure that this happens. Each of the new technologies as they progress needs to be done in one center first. The MOMS trial is a good example. That didn't happen at one center. But they had a consortium and everyone agreed that it would take place at three places across the country. So they could get enough information before proceeding to anything more. So, I think we start with one center for each of these things, make sure that we're comfortable that center has the technology that is likely to be successful as others become

available, open another center, and let them try it. But all this needs to start out with the most expertise that's available. I guess that's enough for me to say, thank you.

Dr. Dracker: Okay, please remember to ask if you have questions regarding the wording of the question, please let us know. Dr. Fischer. Did you raise your hand for question as well or comment?

Dr. Fischer: Yes, I just wanted to follow up on what Dr. White was just saying, agreeing that the likely scenario here is a first-in-human trial at a large center that has capability to offer resuscitation as a secondary option to families. But I think as the trials expand into more of a multi-trial, we'll need to think about justice for patients who do not immediately have access to this. And what are we going to do if a family requests being moved to a center where this is offered. Scenarios like that, I do think will come up. So just something to consider when we're doing trial design. Thank you.

Dr. Dracker: You're welcome. And thank you for your comment. I want to remind everyone that the focus of this is with regards to the informed consent for an AWT clinical trial in the first-in-infant. And from what I've heard from everyone, number one, it sounds like we need to consider having an at-risk group where we would draw from for the person-in-trial. So, identify risk factors for a pregnant woman at this gestational age and that we have an effective means of communicating the risks and benefits of this device trial. So that the parents understand fully what the risks of doing this are and what the risks are of not participating in this trial. First-in is going to be significant and, as many of you said, it really should occur at a site expert at applying this technology. Dr. White, did you have another question or no? Or comment? I guess not. So, are there any other questions or comments regarding the wording of question three.

Ms. Oster: This is just Randi Oster. Just in your summary, I want you to add in that there is liability and there are adverse events. And what is the responsibility of the institutions and the manufacturer for the family.

Dr. Dracker: Right. And that's a critical issue for the informed consent process.

Ms. Oster: Yes.

Dr. Dracker: Alright, Marieann, are you satisfied with the discussion at this point to proceed? So again, I think the important aspects of the informed consent process is that they be inclusive and have optimal clarity in explaining to the prospective parents what the risks and benefits are. And that the first-in event occurs at a clinically competent center who's familiar with the technology. Alright. So, if there's no further discussion, we will now proceed to the next question. Thank you very much.

Dr. Hill: How many questions are there?

Dr. Dracker: There's 15 questions. I'm just kidding. Just kidding. This is the last one.

Dr. Hill: Thank you. I didn't mean to interrupt.

Question Four

Dr. Dracker: It's fine. The fourth question is to discuss the critical aspects of safety monitoring in an AWT first-in-human trial. What adverse events of special interest should be monitored in an AWT trial to assess subject safety and, B, FDA anticipates that a first-in-trial would initially enroll and treat a single subject at a time when considering enrollment of additional subjects. What safety endpoints, including time points of assessment should be considered before enrolling a subsequent subject. Please consider that and please raise your hand if you have comments or questions about that. Dr. Nelson.

Dr. Nelson: Yeah, this is a very difficult question. I agree with the idea that you wanna initially enroll and treat a single subject at the time, but then the question is what endpoints are you using to make a decision to enroll the subsequent subject? If you think about it, if you're enrolling someone between 22 to 24 weeks and you go for three or four weeks, you're transitioning into standard neonatal care from AWT at, let's say, 25 to 27 weeks. But then you have another 13 weeks to hit the time when you're probably going to be discharged and you have another two years to when you're going to get any kind of a reasonable neurocognitive assessment , let's say using a Bayley . You might get something early say three or four months post-adjusted age using an ages and stages questionnaire. But if you wait for that amount of time, you'll basically be talking about six subjects enrolled over ten years, which is obviously not a reasonable outcome. So, I think the challenge is going to be to identify what would be surrogate measures. So one, I might say, is IVH, intraventricular hemorrhage, but the challenge there is going to be these are patients who will indeed suffer an intraventricular hemorrhage and how are you going to draw any sort of reasonable assessment to allow the technology to continue. Let's say if there is a grade two or grade three bleed when the odds are you could have had a grade two or grade three bleed in this same population, independent of the technology. So, I guess what I'm saying is I don't have an easy answer to this other than to say you need to come up with some short-term measures, because otherwise this technology would be in development for the next 15 years before there's any meaningful data.

Dr. Dracker: Dr. Nelson, you have a lot of experience with this. To me, this question is very complicated and covers multiple points that I'm not sure should all be put together in one.

Dr. Nelson: I guess my comment is that in neonatology we all know that if you really want to know the outcome, it's going to take years. But that's not possible here. And so, if you're

enrolling one at a time, you just need to identify some short-term safety endpoints that need to be looked at to then make a decision about continuing. And the difficulty is that this is a population who's going to, in fact, suffer some of those same morbidities independent of the AWT technologies. So, you know if the first patient has let's say a grade two bleed. What do you do? A little bit further down the line, but this is maybe where some of the clinical data really needs to be developed, what that baseline is. But one case, you wouldn't want that to kill the technology. And so, this is this is going to be a very tough decision.

Dr. Dracker: Right. Alright. Thank you. Dr. Fischer

Dr. Fischer: Gwen Fischer, University of Minnesota. I totally agree with Dr. Nelson on that point. And one potential option is to do a side-by-side comparison of age, weight, whatever scoring system you're going to use to compare and then use sort of an adaptive trial design of which I'm definitely not an expert. But seeing this as being able to have a very flexible trial design, understanding how expensive this is going to be. And then secondly, will just add that personally, I think neurocognitive, long-term neurocognitive assessment should be a post-market trial understanding that otherwise it's going to be very difficult to get this device out to pediatric access.

Dr. Dracker: Thank you. Dr. Hoehn.

Dr. Hoehn: Sarah Hoehn, University of Chicago. This is similar to what Dr. Nelson and Dr. Fischer said, but it is really hard because you have got to have short-term safety endpoints. And obviously the big things you want to look at are mortality, bleeding, there are going to be risks of bleeding, there's risks of clots, infection, and growth. You saw a lot of the data and the animal data about how they continue to grow. But I think there would also be things looking at the side effects such as bleeding, but also looking at whether or not in real humans do the babies actually

grow because if they're not growing, obviously then they're not going to continue to mature. So that would be some of the more immediate safety endpoints you could look at. And I think it's really hard because it almost needs to be set up as a non-inferiority trial, that it's not worse than the standard of care, but the only way to approve it is under this prospect of direct benefit, which is really hard because what people are trying to do is prove that it's not worse than the standard of care. But it's hard to reconcile the non-inferiority with this prospect of direct benefit in the absence of no human data. And I do think it would have to be really important that there is a very robust DSMB that's looking at all the data in real time, probably on a weekly basis, just so everyone's aware of any of the potential initial short-term complications.

Dr. Dracker: Thank you. Dr. Davis.

Dr. Davis: Thanks very much. John Davis from Tufts in Boston. I think you really need to focus, first, is going to be need for a lot of discussion on inclusion criteria. What specific types of patients are going to be enrolled in this trial? And that's something we can get into more tomorrow. But I think with respect to the adverse events, I would like to know, not eventually do you get BPD or do you get an IVH or do you get those things? And certainly we're going to look at those, but you're dealing with very small numbers of patients initially. And I think those are going to be hard to sort out of what I would focus on during the experimental period. And I think what's important is to say, how did the equipment function? Were you able to maintain temperature control? Like Chris Gleason said earlier, did the bag leak? Did the oxygenator respond appropriately? Was there evidence of liver toxicity, abnormal liver function while the TPN was going in. Was there cardiovascular instability because we've heard, maybe the fetal heart was not able to maintain blood flow through the circuit and things of that nature. So, I would really suggest focusing on how does this equipment operate, and how do the patients able

to easily get cannulated. Are they able to go into the bag? What types of medications did you have to do? Because I would argue that if you have to heavily sedate a fetus for three weeks with opioids or benzodiazepines that maybe that isn't as advantageous, because that may be harmful. So, I think you're really going to have to look at all these types of things to see how these fetonates from Mark's talk tolerate the procedure and whether there's any associated short term toxicities and not necessarily focus on the longer term outcomes, not with a small number of patients. And I really do agree with Skip that, you know, for you to pick one patient and say that there was a complication. Obviously, you'd have to have stopping rules for this trial, like any other trial, but I would be hesitant to say, based on a leak in the bag or that one particular baby didn't tolerate from a cardiovascular standpoint and needed more support than what was anticipated. I wouldn't say that would be enough reason for me to say, okay, fine, let's stop it. Especially because we know that there's so much heterogeneity in preterm babies and how they respond as we've talked about. I think there's lots more we could talk about with this, but I would really focus it down on the equipment, the performance, and the tolerability of being engaged with this equipment for the fetus over that time period. Thank you.

Dr. Dracker: Thank you, Dr. Davis. Dr. Baker.

Dr. Baker: I'm Susan Baker from the University of Buffalo. I'm not a neonatologist so I feel that I'm at a particular disadvantage, but I have done many trials for pharmaceutical companies and so on throughout the years. And what I'm struggling to understand here is what would be an adverse event? Given the complexity and the heterogeneity of these little ones, is an adverse event only something that could be ascribed to malfunction of the equipment? Or is it an intraventricular hemorrhage or something like that? So, I think I would really need to know a little bit about how an adverse event is defined and what would be reported.

And following up on that, I think others have sort of alluded to this, but I'd like to hit it fairly head on. When there is an adverse event and it can be ascribed to the equipment or the drug that's being tested, there is liability. And in most of the informed consents that I've participated in, somebody takes on responsibility for the financial problems that occur down the track. For example, if a surgical procedure would need to be performed or if there was some other monitoring that had to go on after a drug was discontinued. With these very complicated babies, how do the investigators know, what they can ascribe to being an adverse event? And in that instance, who takes the financial liability for caring for those babies? I think this is very complicated and it's very difficult for me as a non-neonatologist to really understand how that would all play out. Thank you.

Dr. Dracker: Thank you. Dr. Gleason.

Dr. Gleason: I think Dr. Baker brought up a very interesting perspective. Having an adverse event that is clearly, in some instances, going to be related to the system, a malfunction and so forth, meaning that the patient either has to come off of it or suffers something even more significant than just being born at 23 weeks gestation and what kind of liability that would present and who would take care of it. I think that's a very important question to consider and certainly reflects how complex this doing any kind of clinical trial in extremely preterm infants who have so many adverse events in their lives in their early days is very difficult. Because almost everything that happens, it's an adverse event and it's very hard to separate out.

Although in this case, knowing things that are related to the AWT system, I think might be easier to sort out at least in those first couple of weeks when they're on the system, mechanical failures, things of that nature. So, I agree with all the comments that have been said about the adverse events of special interest that should be monitored. Certainly, those should be

primarily in those weeks or days that they're on the system. Those are of special interest in this because we're going to have to be very careful about the things that directly relate to the system and how it operates or doesn't operate properly.

The other comment that I would have is just thinking about this population, and it's been mentioned now several times, too, that one of the things that we hope is a direct benefit is an improvement in mortality. Even though progress has been made, this is a high-mortality relative to farther along in gestation of population. And so, death is an adverse event for sure. And so, what should we be looking at? Some of these babies, maybe even the first-in-human subject is going to be successfully cannulated, go on the system, and so forth, and then die. And it may not be related to the system at all. And so, there's plenty of data that shows that most babies, these extremely preterm babies when they die, it's usually within the first week. Sometimes there's been data that it's within the first 12 to 24 hours. So I think we need to consider that when we think about adverse events and looking at that first patient and then each subsequent patient knowing that unless this is a miracle therapy. And that their patients are going to die because there's a high mortality at this very early gestation for all sorts of reasons. So, those are my comments.

Dr. Dracker: Thank you, Dr. Gleason. Dr. Farb from the FDA would like to respond to Dr. Baker's question. Dr. Farb, are you there?

Dr. Farb: Yes. Thanks, Andrew Farb, FDA. I think the last three comments really get to the heart of this question and really address exactly what we're looking for from the panel. And that is early feasibility studies cast a wide net for information gathering starting with proof of principle, and then when getting to the adverse events, we're looking for all of those. All the important ones that affect the outcome and get to the safety of an effectiveness of this device.

And then, but what we've heard the last two comments in particular is the interpretation of those events and attribution of those events to what might be directly related to the device functionality and what could go wrong. And how the sponsors in developing the device have been able to develop their device to address potential failure modes and whether that's successful in the actual first application of the device. And then what may be events that may or may not be attributable to the treatment related to the device, but may reflect the natural history of treating these very premature infants. So, I want to thank the panel for those comments.

Dr. Dracker: Thank you, Dr. Farb. Dr. Munn, you had a comment or question?

Dr. Munn: Yes. Hey, this is Mary Munn. Maternal fetal medicine at University of South Alabama. And I would just like to advocate for the consideration of maternal complications as one of the adverse events that is monitored. We keep talking about the babies and the neonates, but let's not forget the mothers in all of this. I envision that this is going to require cesarean deliveries with classical incisions for very preterm babies. And that's a significantly morbid procedure for a mother. So, again, I would advocate for monitoring the risk of bleeding and transfusion, hysterectomy in the mothers.

Dr. Dracker: Dr. Munn, I would assume then with your suggestion that the informed consent process should also include those aspects of care.

Dr. Munn: Absolutely.

Dr. Dracker: Great. Thank you. Randi Oster, you had a comment?

Ms. Oster: Yes, I wanted to just frame this that this is a new frontier and we are developing a technology that literally will have a big impact on society. And therefore, when we are looking at what we can do to consider enrollment for additional subjects, I would like to go back to Dr. Mercurio's suggestion that there is a conference on the ethics of what we are doing here. So that

when you're enrolling additional subjects one at a time, they understand the impact that they could have in this new frontier and really have had the input of the conference people to also have thought this through before we keep going one person at a time to just develop a technology.

Dr. Dracker: Thank you. Dr. Cole, your comments.

Dr. Cole: Sessions Cole from Washington University in St. Louis and a neonatologist. In terms of trying to compartmentalize the set of judgment points for considering enrollment of additional subjects, I think we've heard that, and based on the animal work to date, there are clearly some anticipatable adverse events associated with the circuit and infection, cardiovascular instability, failure to grow. I think those would be in one compartment.

A second compartment would be the known complications of extremely preterm birth and that data safety monitoring board would have to make a call as to whether or not a grade two intraventricular hemorrhage is really a consequence of, for example, if a grade two or three intraventricular hemorrhage occurred four weeks into the run, that would be a little bit different than it occurred, within 24 hours of delivery, or 48 hours of delivery. So, I think that there's a second compartment of considerations that have to do with the morbidities associated with extreme preterm birth. In terms of the endpoints and time points, while I certainly acknowledge that the NICHD network has looked at children out two years, three years as a break point in terms of assessment, as Dr. Hintz indicated, that assessment doesn't give the final answer. And I would say, given what we know now about the impact of fetal programming on adult outcomes that there's going to need to be a commitment to follow these patients for a long time. Thank you very much.

Dr. Dracker: Thank you, Dr. Cole. Dr. Krug.

Dr. Krug: Again, this has been a great conversation. But to the question, something else to consider. This morning we heard from the folks who've been studying this, and again, very impressive work. One of the implied potential safety features of this approach would be the ability to, in theory, seamlessly transition the patient from the AWT to traditional neonatal therapeutic support in a neonatal intensive care unit. The need to obviously transition the baby perhaps not in a planned way, but in a reactive way, I think, is certainly a potential safety event. But, I think that we need to look at the quality of that resuscitation effort. Or define some measures for the resuscitation efforts that occur, because those efforts may have an impact on patient outcome. And I think if we are offering that up to the population as a sort of available backup we should try and deliver on the promise. Thanks.

Dr. Dracker: Thank you, Dr. Diekema.

Dr. Diekema: Yeah, first I want to just point out that a lot of the concerns people are raising here actually also relate to our third question on informed consent. The importance of really being clear in the consent form, for example, that this is experimental, it's not a therapy and doing everything possible to not overemphasize potential benefits. But the other thing I want to raise, and I'm not sure exactly where this fits, although I do think it fits here, is as Dr. Mercurio pointed out, probably all of the babies that would initially be eligible for this trial fall into that zone of parental discretion. In other words, these are babies where a parent would be allowed to choose to do comfort care and there's a part of me that worries that is altered and the willingness to do that is altered once you put these babies on AWT. But the flip side of that is also that with at least some of the more basic endpoints like mortality, for example. Parents who get three or four days into AWT therapy and do decide that they've had enough that this may not be what they want for their baby after having watched it will then withdraw or ask to have that technology withdrawn.

And that impacts the endpoints to some degree. And so, not only does that need to be tracked in some important way when you look at endpoints, but I also worry that maybe the freedom of parents to make those decisions might be altered.

Dr. Dracker: Thank you.

Ms. Oster: I just want to just say that's one of the reasons we need the ethical conference that Dr. Mercurio talked about.

Dr. Dracker: I wanted to mention that when a child is undergoing this therapy, the assessment of the child is probably going to be different than what the typical assessment would be of a child born at 22, 23 weeks gestation as far as you know on a ventilator receiving hyperal. Watching the bowels, watching the lungs things like that. But in this device, I think it's going to have different safety issues and different points that we'll have to be cognitive of to assess if the trial is experiencing an adverse event and then I think as mentioned by Dr. Diekema is that the issue of a parent seeing their child within a bag for two to four weeks and hooked up in multiple ways could be emotionally very traumatic to the parents. Obviously different than seeing a child in an isolate being supported. So, I think these are all issues that first-in-human is going to be a very significant event for everyone, both the physicians and providers involved and also for the parents, obviously, and the child. Are there any other comments? Okay, Michael.

Dr. White: This is Michael White in New Orleans. It seems to me that we've looked at least three, maybe four different techniques for providing what we're trying to do. And I think that all of these have their relative merits. And we're talking about long-term assessments, and I think the initial trials need to focus on some pretty straightforward endpoints. And I think we start with, can this therapy be instituted safely? That's the first thing we have to be able to say. Yes, we can do this and yes, we can do it safely. So the first goal has to be, can we get the subject onto this

device and make it work? And the second has to be, what is our endpoint once we get them on that device? Do we go to a specific time point? And can we reach that time point? And if we can't reach that time point, can we safely transition them to set standard of care?

And once we get to those things, then we start talking about, okay, can we establish particular goals for how this baby should progress once they are put on standard of care therapy? Time to extubation, other things of that nature that we can assess in a newborn. Because as you say, developmental stuff, that's going to be, sometime after college, at least in my mind, in my experience with my own kids. So, I think we just have to come up with a framework for we're going to try this device, let's do this in a systematic way, starting with, can we put the subject on the device and can we get them off of that safely? There are going to be all kinds of things that happen in between. They're going to be the same sorts of things that are going to happen to other babies of a similar age. I think you look at these in terms of what is expected for a baby of this age. And is this something that we see out of context? Or, how do I say this properly, not expected in an infant of this age? And if we start seeing it happen more frequently than what is a standard estimate of how often this should happen in infants of this age, then we have to think about, okay, is this something that is due to the device and we have to stop it. And that's probably all I should say, we're going to be looking at some of this stuff tomorrow with the information that's proprietary. And I don't want to get into that. Does that help?

Dr. Dracker: It does. Thank you, Michael.

Dr. White: Thank you.

Dr. Dracker: Any other comments from the committee. Alright. So, I'm trying to figure out—

Ms. Brill: Sorry, Dr. Gleason. I just saw her hand raised.

Dr. Dracker: Okay.

Dr. Gleason: I just wanted to say that. I think you started the discussion, I'm sorry, I've got this something in my eyes, by saying that this was such a complex question that maybe it should be divided into two and I agree with that. So the adverse events and then the endpoints, safety endpoints, and the time points and so forth. I think they could they could easily be better if you divided it into two questions. I'm just agreeing with you.

Dr. Dracker: Thank you, Dr. Gleason. And that's what really hit me is that, number one, the people developing these technologies are familiar with what adverse events might occur. Not only based upon the animal model, but also with their experience in human beings and neonates. And then once we have that first-in data, then we know what we can watch for. What safety endpoints have to be developed as we go forward and utilize other infants in these studies. But the first-in is going to be critically assessed, both short-term and long-term, and that the point that you are satisfied with the tolerance of the technology and the outcome of the technology will determine when you start enrolling additional subjects. Does the panel agree with that assessment? But I do agree that I think these two questions should be separated out.

Dr. Gleason: Agreed.

Dr. Dracker: Dr. White, is that you again? Dr. Gleason, did you have a comment or a question or no?

Dr. Gleason: No. Sorry.

Dr. Dracker: Okay. Dr. Hill.

Dr. Hill: Washington Hill Health MFM from Sarasota, as the other MFM on this call, I want to echo what Dr. Munn said in regards to making sure that we look at adverse effects in the mother. In terms not only of a cesarian, but in an infection, length of stay in the hospital, but also the psychological outcome that this mother may have in addition to having a premature infant. Those

were my comments. But let's not forget to look at closely the outcome and the effects on the mom. Thank you.

Dr. Dracker: Thank you, Dr. Hill. Marieann, do you have any other questions or anything else we need to assess at this point?

Ms. Brill: I believe no other questions and I do not see any hands raised. I'm so sorry, Dr. Guillory.

Dr. Guillory: I'm sorry. Charleta Guillory, Texas Children's Hospital, Baylor College of Medicine. I know the very first patient will be extremely scrutinized and everything, all information, both short-term and long-term, I'm sure will be collected. But I think as one of the doctors mentioned earlier, I'm having a problem with seeing the length of time it's going to take this infant to get onto the machine in the first place. And I guess I shouldn't be asking a question, but I can see a role for an exit procedure having the baby still connected. I'm not sure how that would work, because you need to get to the umbilical artery and vein, but we do use exit procedures for some of those things. So, I was just wondering if that was even an option here. And I guess not because you need the placenta and the umbilical cord. So probably not. Anyway, that will be an important adverse effect, how long does that take to get the infant onto the procedure.

Adjournment

Dr. Dracker: Thank you. I think we can then close the meeting. I would like to personally thank everyone. You are a wonderful committee and I think this is an exemplary assessment of a new technology that I think we want to see possibly employed for the betterment of premature infants. So, thank you and I look forward to our discussion tomorrow.

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