Minutes of the Pediatric Advisory Committee (PAC)

The public meeting was convened from 9:00am to 5:30pm EDT, on September 19, 2023

PAC Members Present - (Voting)	**Temporary Members (Voting)**
Robert Dracker, MD, MBA, MHA, FACC (Chair) Susan S. Baker, MD, PhD Douglas Diekema, MD, MPH Charleta Guillory, MD, MPH Angela Czaja, MD, MSc, PhD Gwenyth Fischer, MD Richard Holubkov, PhD Steven Krug, MD Roberto Ortiz-Aguayo, MD, MMM Michael White, MD, PhD Patient Family Representative Gianna McMillan, DBe Consumer Representative Randi Oster, MBA **Non-Voting Members** Industry Representative Robert Nelson, MD, PhD Pediatric Health Organization Representative Jennifer Goldman, MD, MS	Jeffery Botkin, MD, MPH Francis Cole, MD Jonathan Davis, MD Jeffery Feinstein, MD, MPH Christine Gleason, MD Sarah Hoehn, MD, MBe, FAAP Washington Hill, MD Jennifer Lee Summers, MD Marc Moon, MD Mikael Petrosyan, MD, MBA Mary Munn, MD Caroline Zeiss, BVSc, PhD **Designated Federal Officer (DFO)** Marieann Brill, MBA, RAC, MT(ASCP)

U.S. Food and Drug Administration (FDA) participants

Office of Pediatric Therapeutics (OPT), Office of the Commissioner	**Office of Cardiovascular Devices, Center for Devices and Radiological Health (CDRH)**
Dionna Green, MD, FCP An Massaro, MD Elizabeth L. Durmowicz, MD	Kalkidan Molla, MS Annabelle Crusan, DVM, MS

Guest Speakers

George B. Mychaliska, MD Mike Seed MBBS, MRCPCH, FRCR Gail M. Annich, MD, MS, FRCP Josef Neu, MD	**Industry Perspective** Alan W. Flake, MD, FACS, FAAP

Dr. Durmowicz reviewed the ethical analysis for an AWT trial, identifying that neonatal subjects participating in AWT trials would be exposed to more than low risk and as such must be offered prospect of direct benefit. Dr. Durmowicz discussed that data to support prospect of direct benefit include proof-of-concept data for the AWT device, including performance data demonstrating that the device delivers the intended treatment effect, and data to support that the duration of device use is sufficient to have a measurable clinical benefit in the enrolled neonatal subject. Dr. Durmowicz discussed that if a clinical trial of an AWT is able to offer a prospect of direct benefit to a neonatal subject, the risks of the AWT trial must be justified by the anticipated benefit. She stated that the data must be adequate to determine the probability and the magnitude of the risks of the AWT device and the risks of other trial interventions and procedures, and that the relation of the anticipated benefit to the risks must be as favorable as routine clinical care for a neonatal subject of equivalent GA. In conclusion, Dr. Durmowicz provided an overview of parental permission and informed consent, and discussed the challenges related to informed consent for an AWT trial.

- **An Massaro**, Neonatology Team Leader in OPT, provided an overview of the clinical considerations for evaluating the benefits versus risks for an AWT development program. She reiterated that in order to be ethically permissible under 21 CFR 50, subpart D, a trial in neonates must offer prospect of direct benefit to the enrolled subjects. Dr. Massaro stated that the prospect of improved mortality and morbidity provided by the AWT device as well as potential device-related risks must be weighed against known mortality and morbidity associated with the current of standard of care (SOC) in the US. Dr. Massaro described current SOC in preterm infants in the US, and reviewed known morbidities related to preterm birth. She also discussed potential risks of AWT, including the risks that are unknown due to limitations of nonclinical models. She concluded by outlining requirements for a first-in-human (FIH) trial of AWT.

Clarifying questions from the Committee: *Please refer to the meeting transcript.*

Strengths and Limitations of AWT Animal Models

- **Annabelle Crusan**, Veterinary Medical Officer in the Office of Cardiovascular Devices in CDRH, gave an overview of the FDA perspective on animal study considerations for AWT devices. She began by outlining characteristics of an animal model and described how selection of appropriate and feasible animal models can support conducting a clinical study of significant risk devices under Investigational Device Exemption (IDE) applications. Dr. Crusan stated that animal studies must assess relevant endpoints, provide adequate sample size and be of sufficient duration to support further clinical studies, and acknowledged limitations in animal models as compared to human experience. Dr. Crusan explained that for AWT devices, animal studies would be needed to provide information about biological and physiological assessments including hemodynamic support, critical organ system development, and maturation. From a safety perspective, the animal studies may collect information about hemocompatibility, clinical chemistry, tissue injury and organ dysfunction. Dr. Crusan stated that the appropriate animal models can be determined through research and pilot studies that consider acceptance criteria for specific study objectives and the strengths and limitations of the animal model. Dr. Crusan

similar to humans, and the size of preterm pigs around 95 days gestation is comparable to human infants born extremely preterm. In his work, preterm pigs placed on a pumpless circuit were tachycardic and had significantly diminished umbilical blood flow and exhibited signs of heart failure within hours. The addition of a pump prolonged the period of survival but did not improve the outcome. Dr. Seed speculated that the mechanism leading to circulatory failure in their pumped circuit is related to the elevated post membrane pressures generated by the pump. Dr. Seed concluded by saying that AWT is likely to be more difficult to employ at younger gestational ages and in smaller patients due to intrinsic anatomic and physiologic constraints.

Clarifying questions from the Committee: *Please refer to the meeting transcript.*

Open Public Hearing

- **Speaker 1** gave an overview of ethical and legal implications of AWT and issues that need to be considered before deploying AWT technology. She noted that AWT/AP methods are not an extension of existing methods and are fundamentally different. For details she referenced publications submitted to the PAC through the federal docket. She highlighted the positive and negative impacts of such a technology on pregnant persons and the need to consult the pregnant person when considering AWT clinical trials. Acknowledging that the impact on pregnant persons was out of the scope of this PAC meeting, which is focused on the premature infant, Speaker 1 mentioned that the implications of the loss of a pregnancy and the grief associated with delivering a premature infant need to be considered when discussing AWT technology with potential patients. The speaker stated that deploying AWT may have a disproportionate impact on racial and ethnic minorities because most premature births in the US occur in marginalized racial and ethnic groups that lack adequate prenatal care. She stressed the importance of ensuring that more at-risk neonates are not chosen for initial study of this novel technology. Lastly, Speaker 1 highlighted the potential legal questions and protections, or lack thereof, involved in using AWT for extremely premature infants.

- **Speaker 2** urged the panel to consider the unknown health impacts of electromagnetic fields (EMF) on the extremely premature infant and on the developing organs. Speaker 2 discussed that EMF are emitted from AWT and existing NICU technologies. EMF sources include low frequency electromagnetic sources, devices used by staff, and external-to-room/hospital sources such as cell phone towers, incubators, and medical devices. Speaker 2 stated that exposure to EMF affects heart rate and decreasing EMF exposure improves outcomes. She also stated that neonates and infants are more susceptible to EMF and its effects due to thinner skull bones, higher water content of their tissues, and more active stem cells. Speaker 2 stated that an extremely premature infant exposed to EMF from birth would have more risk due to a lifetime of cumulative exposures. The Speaker made an appeal as an EMF scientist: EMF affects people adversely at much lower amounts than referenced in international guidelines; there is a regulatory gap and deficiencies for EMF exposure guidelines; and a lack of regulatory safeguards means that measures to mitigate risk from EMF exposure are important to consider prospectively.

postnatal period. Dr. Alexander stated that the fetal cardiovascular system handles a gradually increasing workload in the second and third trimester and noted the abrupt transition to neonatal circulation at birth has an impact on the EPI's developing heart. Dr. Alexander stated that prematurity also impacts myocardial structural development altering cardiomyocyte maturation.

Dr. Alexander transitioned to a discussion of extracorporeal life support (ECLS) systems. She stated that ECLS can be offered in different configurations to support the most critically ill patients with pulmonary or cardiopulmonary disease and noted that ECMO is rarely offered to patients weighing <2 kilograms due to practical limitations related to size and blood volume. She stated that ECMO circuitry is not optimized for pump flows needed for neonatal and small pediatric patients, which causes more hemolysis of the blood in the circuit. Dr. Alexander stated that the risks of ECMO include brain hemorrhage and brain infarctions among others. Dr. Alexander stated that poor ECMO outcomes are more frequent in EPIs and other small children relative to adults and alternatives to ECMO, such as AWT, could be valuable. She noted that serial cardiac monitoring will be essential during the development of AWT.

- **Josef Neu** from the University of Florida presented on gastrointestinal (GI) considerations for EPIs treated with AWT. Dr. Neu began with an overview of the macronutrients required for fetal nutrition. He then described the energy stores across the development stages for EPIs and the energy requirements for each stage of life. He stated that EPIs have a very high caloric need, similar to an elite athlete. Dr. Neu stated that it is hard to provide nutrition parenterally in EPIs in the quantities needed for optimal growth and development. He outlined the consequences of total parenteral nutrition (TPN) and lack of enteral feeding, including TPN-associated sepsis, mucosal atrophy, and immunological changes. Dr. Neu described a nonclinical study evaluating the consequences of prolonged TPN in piglets that showed adverse liver histology findings after just 7 days of TPN. Dr. Neu also presented clinical data in preterm infants showing that TPN was associated with increased intestinal permeability.

  Dr. Neu then summarized the role of amniotic fluid in fetal nutrition. He stated that the amniotic fluid is an important source of nutrients and trophic factors that impact fetal development. He stated that a relevant question is how we can mimic the nutritional and bioactive composition of naturally produced amniotic fluid in AWT. Dr. Neu concluded that some nutrition for the EPI can be provided parenterally, but how to provide adequate nutrient quantities like those obtained in utero that will provide optimal growth and development is not known.

Clarifying questions from the Committee: *Please refer to the meeting transcript.*

Ethical Considerations for a First-in-Human Trial of AWT

- **Mark Mercurio** from Yale University presented on the ethical considerations for a first-in human trial of AWT. Dr. Mercurio gave an overview of the Department of Health and Human Services (HHS) regulations that describe additional protections for children involved in research that involves greater than minimal risk (45 CFR 46.405). He stated that first-in-human trials for AWT

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The meeting concluded with the PAC's discussion on four non-voting questions. The questions for the committee are reproduced below, followed by a brief summary of the discussion, which is also available in the document entitled *Pediatric Advisory Committee 24 Hour Summary from 19 September 2023*. Please reference the meeting transcript for full details.

QUESTION #1:

Given that testing on large animal models (e.g., 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 timepoint(s) of assessment (e.g., time of transition from AWT, longer term follow-up), that may be evaluated in animal studies to understand the potential benefits and risks of AWT in the human neonate.

The panel agreed that the choice of an animal model was important to allow information from animal studies to be translated to human clinical use but recognized that there is no one perfect animal model to simulate the human condition. Some panelists expressed uncertainty about timepoints of assessments, indicating that it was unclear whether the animal studies presented during the meeting, which vary in terms of duration of AWT therapy, are sufficient to demonstrate proof-of-concept to support clinical treatment durations that may be proposed for clinical application. However, a definitive timepoint for assessments was not largely agreed upon. In addition to assessment of organ growth and maturation, panelists noted that animal studies may provide value to understand the implications of differences in nutrient sources in uterine environments compared to AWT, including differences in natural amniotic fluid compared to investigational fluids intended to mimic amniotic fluid. Panelists also indicated that adverse events, especially those that could be attributed to the device, should be evaluated in animal studies and that there may be value in using animal studies to understand and prepare for potential emergencies (e.g., device malfunctions) in clinical use.

QUESTION #2:

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?

Panelists generally agreed that global, diverse, and inclusive data sources on existing clinical experience with EPIs, including short and long-term outcomes, will be important to inform the benefit-risk assessment for enrollment considerations for a first-in-human trial of an AWT device. Panelists also noted that the use of datasets from diverse and inclusive populations may provide valuable information regarding health equity considerations for trial enrollment. The panel also discussed the need for recent data on the outcomes of 23-week gestational age infants. Given the recognition that site variation exists

appropriate reporting on device-related complications, the ability of the device to function as intended, the ability for device-related procedures to be performed safely and evaluate how well patients tolerate the procedures. When considering assessments to support enrollment of additional subjects, some panelists anticipated challenges interpreting data collected from a small number of subjects and discouraged stopping enrollment based on isolated events. This approach was suggested by several panelists due to the heterogeneity and expected adverse events in standard of care for EPIs that would further complicate decision-making based on isolated events. Panelists commented that while it will be important to collect long-term neurocognitive outcomes, that this should not serve as the basis for continuing enrollment in the FIH studies.

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Designated Federal Officer, PAC

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Chair, PAC