



FDA Briefing Document

Pediatric Advisory Committee (PAC)

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DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or recommendations that represent current FDA thinking based on available information reviewed and may not represent the final future position of the Review Division or Office. We have brought the topic of Artificial Womb Technology (AWT) to this Advisory Committee to garner the Committee's insights and opinions. The background package may not include all topics and information relevant to future regulatory decisions and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. Representatives from the general neonatology, pediatric cardiology, and bioethics academic community, as well as investigators from active AWT research programs, have also been invited to present.

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FDA Executive Summary

1. Introduction

The Food and Drug Administration (FDA) is convening the Pediatric Advisory Committee (PAC) to discuss and provide recommendations on the appropriate development plans for establishing safety and effectiveness of artificial womb technology (AWT) devices intended to treat extremely premature infants (EPIs), including regulatory and ethical considerations for first-in-human (FIH) studies.

Given the challenges in assessing the benefit-risk profile of this type of highly innovative technology, and the complexities related to the vulnerable neonatal population, FDA is convening a panel of experts for a public discussion of the available science, clinical benefit-risk assessment, and design and ethical considerations for FIH clinical trials of AWTs in children. This executive summary will include an overview of the unmet clinical need for reducing prematurity-related morbidity and mortality, a description and history of AWT, regulatory considerations for AWT clinical development programs and topics for discussion by the PAC.

The PAC discussion will be limited to the use of AWT as an alternative to current standard of care (SOC) management of EPIs in the Neonatal Intensive Care Unit (NICU). Although FDA acknowledges that there are unique considerations for enrollment of the pregnant subject in a clinical investigation exploring the use of an AWT in EPI, the intent of this PAC meeting is to focus on issues related to AWT and neonatal subjects.

2. Background

2.1 Description of disease/clinical need – Extreme prematurity

Preterm birth is associated with increased mortality and morbidity, especially for EPIs born less than 28 completed weeks gestation. Although advances in neonatal intensive care have led to improved survival in preterm infants,^{1,2} extreme prematurity continues to disproportionately contribute to neonatal mortality and long-term morbidity in childhood survivors. Adverse outcomes are most common amongst infants born less than 26 completed weeks gestation, a period termed periviable birth.³ Recent data from the National Institutes of Health (NIH) National Institute for Child Health and Human Development (NICHD) Neonatal Research Network (NRN) estimated that while approximately 70% of infants born at 24 weeks gestation and actively treated at birth survived to discharge or 1 year, the probability of survival was significantly less at lower gestational ages (GA) (i.e., 55.8% and 30% at 23 and 22 weeks GA respectively). These data are consistent with national data from the Healthcare Cost and Utilization Project's (HCUP) National Inpatient Sample (NIS) database (Figure 1).²

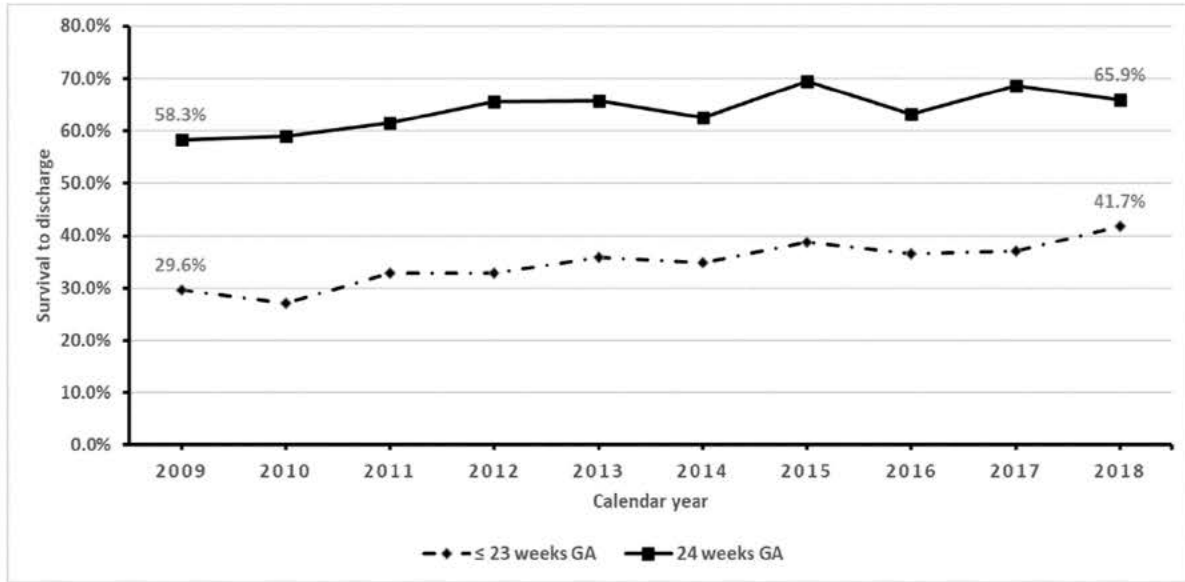


Figure 1. Source: Doshi et al, Am J Perinatol 2022 (Reference #2)

Among survivors, rates of long-term morbidity, including neurodevelopmental impairment (NDI), are high, with the majority of surviving EPIs having moderate or severe NDI* at 22 to 26 months corrected age (Figure 2).

Figure. Neurodevelopmental Impairment at 22-26 Months' Corrected Age in Children Born at 22-26 Weeks' Gestational Age During 2013-2016

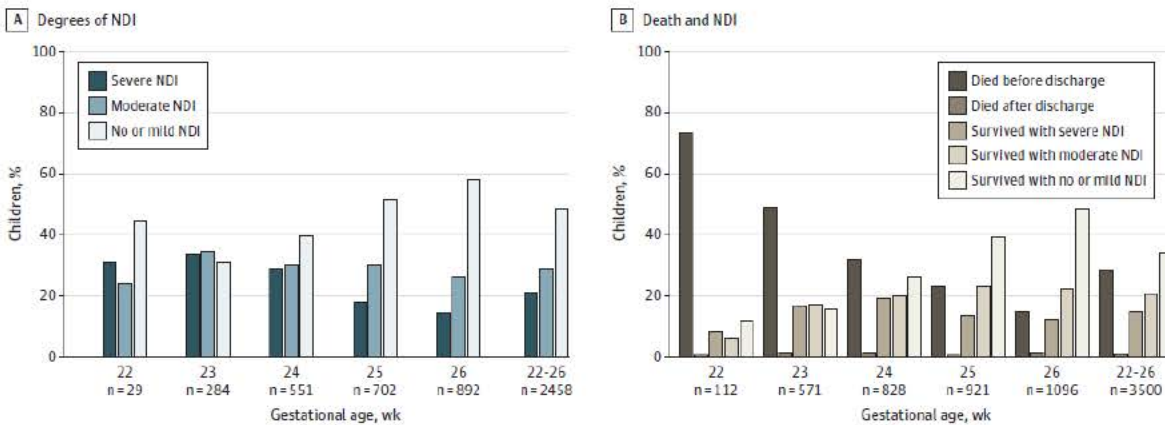


Figure 2. Source: Bell et al, JAMA 2022 (Reference #1)

*moderate NDI= Bayley-III cognitive or motor composite score of 70 to 84 or Gross Motor Function Classification Scale (GMFCS) level 2 or 3; severe NDI= Bayley-III cognitive or motor composite score <70, GMFCS level 4 or 5, bilateral blindness, or bilateral severe functional hearing impairment.

Similarly, frequency of other prematurity-related morbidities, that may span across multiple organ systems, are also inversely related to gestational age (Figure 3), which may contribute to long-term complications and increased healthcare needs in later life.

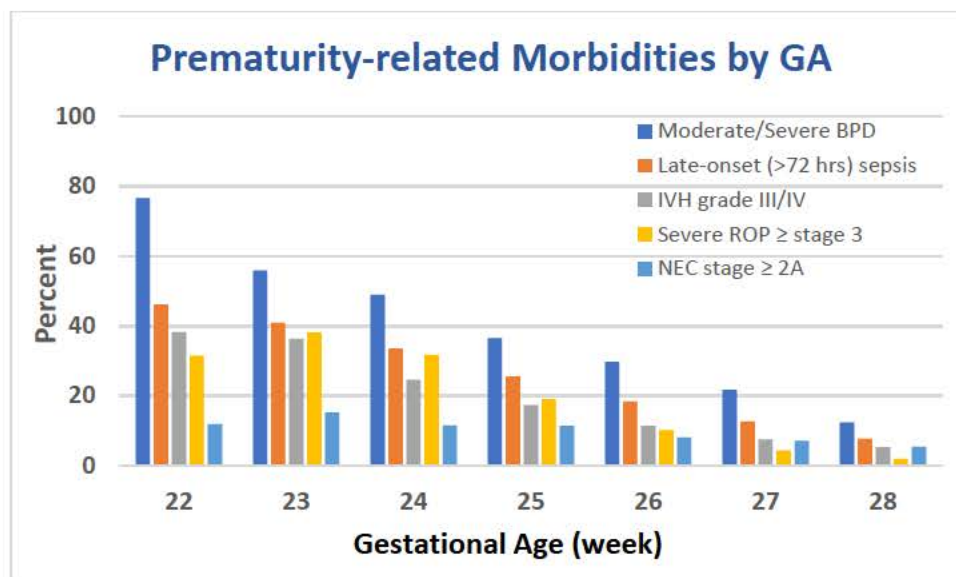


Figure 3. Source: Data adapted from Bell et. al., JAMA 2022 (Reference #1). BPD=bronchopulmonary dysplasia, severity based on Jensen et al⁴; IVH=intraventricular hemorrhage, grade based on Papile et al⁵; ROP=retinopathy of prematurity; NEC=necrotizing enterocolitis, stage based on modified Bell criteria^{6,7}

2.2 Current standard of care (SOC)

2.2.1. Delivery room management

Based on contemporary data on morbidity and mortality as discussed above, delivery room resuscitation and neonatal care are offered routinely in preterm infants born greater than 24 weeks gestation, while approaches to active treatment in periviable preterm infants are associated with more inter-center variability.⁸ Active treatment in preterm infants born at 22 to 23 completed weeks gestation is generally considered based on institutional practices and shared decision making by providers and families. Care may also be guided by recommendations of the American College of Obstetrics and Gynecology (ACOG)⁹ and American Academy of Pediatrics (AAP).¹⁰ Active delivery room management for the EPI includes routine steps of neonatal resuscitation with special attention to lung immaturity, thermoregulation, and gentle handling.¹¹

2.2.2. Transitional care and thermoregulation

Transitional care in the EPI focuses on maintaining physiological stability including avoidance of hemodynamic lability, significant variability in ventilatory gas exchange, and metabolic derangements, all of which may contribute to various prematurity-associated morbidity, as discussed further below. The vulnerability of the preterm infant to cold stress and dehydration is attributable to the relatively large surface-area-to-body-mass-ratio, thin permeable skin, minimal subcutaneous fat, and limited metabolic response to cold, necessitating care in an incubator that can provide a thermo-neutral, humidified environment.^{11,12}

2.2.3. Cardiovascular support

One of the hallmarks of transition from fetal to neonatal circulation is closure of the ductus arteriosus, which is delayed (or even fails to occur) in the preterm infant. Continued postnatal patency of the ductus leads to run-off into the pulmonary circulation and resulting left ventricular volume overload. Preterm infants can tolerate this extra volume work for variable lengths of time. Over the past decade, a trend towards less aggressive treatment of the patent ductus arteriosus (PDA) has been advocated, reserving intervention for the hemodynamically significant PDA (hsPDA). Potential consequences of a prolonged hsPDA include pulmonary overcirculation leading to lung disease, decreased systemic blood flow leading to low organ perfusion (including risk for renal, brain and intestinal injury), and cardiac compromise manifested by left atrial and ventricular dilatation and dysfunction from prolonged volume overload.¹³ Given that there are no universally accepted criteria for defining a hsPDA, thresholds for intervention (which may be pharmacologic, surgical or catheterization-based) vary but may include echocardiographic parameters and clinical signs of end-organ hypoperfusion.

Blood pressure management in the EPI is highly variable due to the absence of a validated or widely accepted definition of hypotension in the EPI population.¹⁴ Although gestational age-based normative values have been described from clinical studies,¹⁵ these studies are often confounded by clinical interventions such as vasopressor and glucocorticoid therapy. The complexity of dynamic transitional physiology and later maturational changes in the preterm infant, and the lack of widely accepted normative blood pressure ranges in the preterm infant, make the appropriate selection and timing of intervention for hypotension a challenge. Diagnosis of physiologic hypotension relies on observation of low blood pressure values and associated signs of decreased organ perfusion. However, due to the difficulty in clinically defining adequate organ perfusion, infants often receive anti-hypotensive treatment based on blood pressure values alone.^{14,15} Although avoidance of hypertension is equally challenging due to the absence of validated norms and definitions, large volume boluses and sustained hypertension are generally recognized risk factors for intraventricular hemorrhage (IVH), as further discussed below.

2.2.4. Respiratory care

EPIs are born during the canalicular stage of lung development,¹⁶ often necessitating ventilatory support that, along with other inflammatory insults, can lead to injury to the developing lung, resulting in bronchopulmonary dysplasia (BPD)⁴ and ultimately chronic pulmonary insufficiency of prematurity (CPIP).¹⁷ While variation in respiratory care management of the EPI exists across providers and institutions, general goals include maintaining alveolar recruitment with use of positive end-expiratory pressure, consideration of surfactant replacement therapy, minimizing volutrauma and/or barotrauma, and avoiding oxygen toxicity.¹⁸ Treatment of apnea of prematurity with caffeine citrate is also considered part of routine care for preterm infants in many NICUs. Despite these interventions, CPIP remains one of the most common chronic health morbidities of preterm birth,¹⁷ and there are no FDA approved therapies to prevent or treat BPD or CPIP.

2.2.5. Nutrition

The goal of nutritional support for the preterm infant is to approximate the rate of growth and composition of weight gain for a normal fetus of the same postmenstrual age, while maintaining normal concentrations of nutrients in blood and other tissues.¹⁹ General approaches include early initiation of parenteral nutrition after birth, with transition to enteral feeding as tolerated over time. While the exact plan for advancing nutritional intake varies across NICUs, evidence supports use of a standardized feeding protocol and the preferential use of human milk as important strategies to prevent risk for necrotizing enterocolitis (NEC).²⁰ While the optimal pace of enteral feeding transition is not completely established, it is generally recognized that this requires a balance between conservative approaches (where delayed introduction and slow advance of enteral feedings may be associated with lower risk for NEC) and early establishment of enteral feeds, which is associated with benefits including improved intestinal adaptation and avoidance of complications associated with prolonged parenteral nutrition use (e.g., potential metabolic derangements/deficiencies, catheter-associated infections, parenteral nutrition associated liver disease).²¹

2.2.6. Neuroprotective and developmental care

The high risk for NDI in the EPI stems from vulnerability to acute hemorrhagic and/or ischemic injury as well as potential developmental brain injury resulting from nutritional deficiencies, environmental stressors, and other injurious exposures in the ex-utero environment. Risk for neurologic injury is attributed to anatomic (e.g., presence of the germinal matrix, immature vascular integrity), physiologic (e.g., immature/dysfunctional cerebral autoregulation) and cellular (e.g., selective vulnerability of pre-oligodendrocyte) factors that are unique to the preterm developing brain.²² Neurologic care in the EPI focuses on neuroprotective strategies and developmental care aimed to avoid known risk factors for injury and may include provisions for minimal handling to avoid stress, midline head positioning to optimize cerebral hemodynamics, avoidance of bolus volume or sodium bicarbonate infusions, minimizing lability in pCO₂ and blood pressure, and avoiding acute changes in intrathoracic pressure.²³ Optimizing sound and light exposures and encouraging parental involvement (including skin-to-skin care when feasible) are other important aspects of developmental care in the NICU. As clinical recognition of past or ongoing evolving brain injury is difficult, routine surveillance by neuroimaging (i.e., serial cranial ultrasound and, in some centers, term-equivalent MRI) is used to identify lesions and counsel families about potential long-term neurodevelopmental impact. While management of IVH-associated post hemorrhagic hydrocephalus may require neurosurgical intervention,²⁴ therapeutic interventions in the NICU for recognized brain injury are limited and largely focus on rehabilitative therapies (e.g., physical, occupational, and/or speech therapy) and referral for ongoing early intervention and neurodevelopmental follow-up after NICU discharge.

2.2.7. Other care considerations in the EPI

In addition to the multiple body systems discussed above, other special considerations for postnatal care in the EPI include active surveillance and anticipatory management of suspected systemic infection given the high risk for early and late-onset sepsis in the preterm infant.²⁵ Close observation and attention to fluid management and avoidance of nephrotoxic medications is needed in the setting of acute kidney injury (AKI), which is frequently observed in infants requiring intensive care and is further compounded by incomplete nephrogenesis and impaired functional renal maturity in the EPI.²⁶ Finally,

exposure of the developing eye to relatively high-oxygen tension in the ex-utero environment is associated with retinopathy of prematurity. Management includes surveillance by serial eye exams and intervention by retinal ablation (i.e., cryo- or laser photocoagulation therapy), intraocular administration of anti-vascular endothelial factor therapies, or other surgical interventions (e.g., scleral buckle, vitrectomy) for advanced stage retinopathy of prematurity (ROP).²⁷

2.3. Rationale for AWT

While increased understanding of the various complications of preterm birth have led to advances in NICU care and improved outcomes, high rates of death and long-term morbidity continue to be observed in the EPI, particularly in the lowest periviable gestational ages. Adverse outcomes are attributed to both extreme organ immaturity that cannot be adequately supported with modern NICU treatments and the added unintended iatrogenic injurious consequences of life-sustaining interventions. For example, while lung immaturity necessitates supportive care with positive-pressure ventilation to allow time for lung growth and maturation, ventilator-induced lung injury often occurs at a faster rate than growth and repair, leading to BPD and later CPIP. Despite best practices by care providers to maintain physiological stability in the ex-utero NICU environment, periodic hemodynamic lability, intermittent hypoxia or hyperoxia, and infectious/inflammatory complications cannot be avoided. Artificial womb technology (AWT) is a proposed therapeutic strategy that aims to bridge the period between extreme preterm birth and later gestation to allow for organ maturation in a system that mimics the womb environment and provides artificial placental (AP) support for nutrition and gas exchange. (N.B. While AWT and AP terminology is used inconsistently in the literature,²⁸⁻³⁰ for the purposes of this background package, AWT refers to a system which includes an extrauterine environment comprised of a simulated womb with artificial amniotic fluid whereas AP refers to the component of the system that provides extracorporeal circulation and oxygenation for medication and nutrient delivery, as well as gas exchange). AWT aims to avoid iatrogenic ventilator injury, provide stable gas exchange and hemodynamics, and provide an environment to promote organ maturation that may offer advantages over current NICU care for the EPI.

3. History and Description of AWT

3.1. Overview

The interest in applying extracorporeal membrane oxygenation (ECMO) to treat respiratory failure and serve as a system to provide AP support in the EPI began over 50 years ago with initial challenges including umbilical vessel spasm, circulatory failure, sepsis, thromboembolism and cannula-related problems.³¹ With these challenges, AWT research slowed in light of advances in neonatal care including improvements in mechanical ventilation equipment and strategies, the advent of surfactant therapy and the implementation of antenatal corticosteroid therapy. Over the past few decades, however, concern that innovations in care and associated improvements in outcomes for the EPI may have plateaued led to renewed interest in AWT development. While several different approaches have been investigated in various animal models,^{31,32} concepts common across AWT systems include maintenance of fetal circulation/physiology, extracorporeal circulation for oxygenation and delivery of parenteral therapies, non-injurious approach to lung management, and an extrauterine environment for growth and development.

3.1.1. Fetal circulation/physiology

An important component of AWT is the maintenance of fetal circulation (Figure 4) which involves circulatory shunts including the ductus venosus (allowing blood flow return from the placenta to traverse the liver), ductus arteriosus (connecting the pulmonary artery to the aorta), and foramen ovale (connecting the right and left atria). Patency of these shunts in utero is maintained by low partial pressure of oxygen, blood flow across the vessels and circulating prostaglandins. After birth, the rapid decrease in pulmonary vascular resistance and increase in oxygen tension initiate ductal closures and the shift in atrial pressures lead to closure of the foramen ovale.³³ In order to maintain fetal physiology, AWT systems incorporate low-resistance oxygenators to mimic placental hemodynamics, aim for target saturations that mimic intrauterine values (Figure 5), and provide continuous infusion of prostaglandin E1 to maintain patency of fetal circulatory shunts.³²

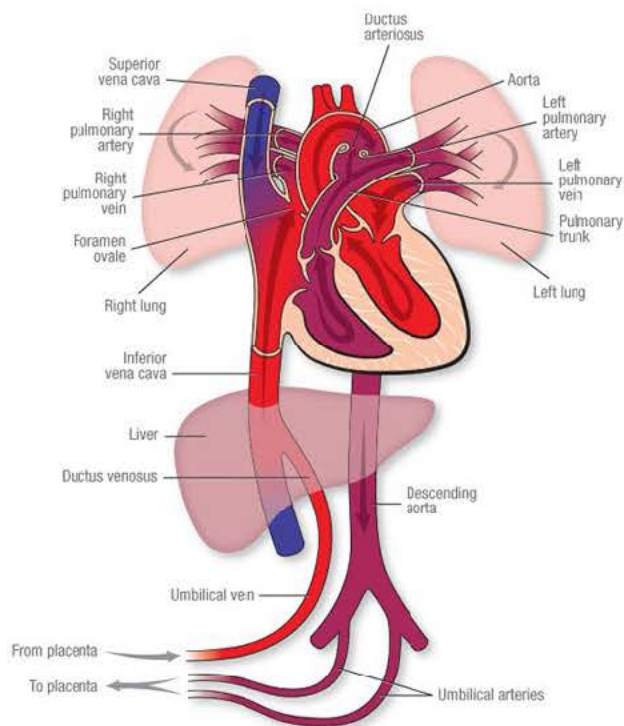


Figure 4. Source: American Heart Association; [Fetal Circulation | American Heart Association](#)

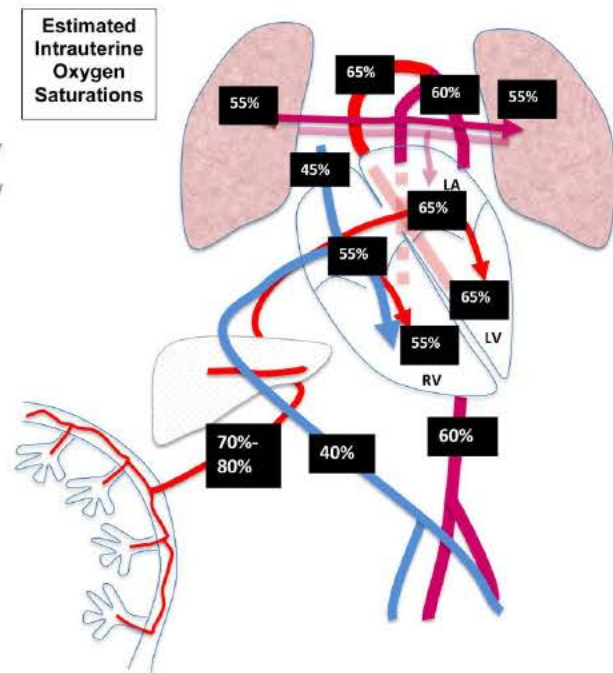


Figure 5. Source: from Morton et. al., 2016 (Reference #33)

3.1.2. Extracorporeal circulation/oxygenation

Establishing and maintaining extracorporeal circulatory support requires vascular access (both for venous drainage and for return of AP-oxygenated blood) and a circuit that can maintain flow with either an external pump or with a “pumpless” configuration that relies on cardiac-driven flow. Vascular access configurations include umbilical vein (UV) and umbilical artery (UA) or UV/jugular vein (JV) or carotid artery/JV cannulations (Figure 6). While avoidance of cervical cannulation may have advantages of preserving important vessels and minimizing potential embolic events to the brain, a challenge with

umbilical vascular access is vasospasm. Use of short umbilical cannulas and papaverine to prevent vasospasm has been described as an approach to maintain umbilical cannulation.³¹ While there is ongoing work to develop circuits with surface-based anticoagulation systems that can eliminate the need for systemic anticoagulation,³² current AP/AWT systems use systemic heparin to prevent risk for thrombotic events. However, the flow rates, reduced surface area, and priming volumes of the AP/AWT circuits may be associated with lower heparinization needs compared to standard neonatal ECMO circuits.

Graphical representation of extracorporeal circuit configurations of published AP/AWT models

- | | | |
|---|--|--|
| A) AP: VV (venovenous)
UV/JV cannulation with
pump and oxygenator | B) AWT: VA (venoarterial)
UA/UV cannulation
with dual oxygenator | C) AWT: VA (venoarterial)
UA/UV cannulation
with single oxygenator |
|---|--|--|

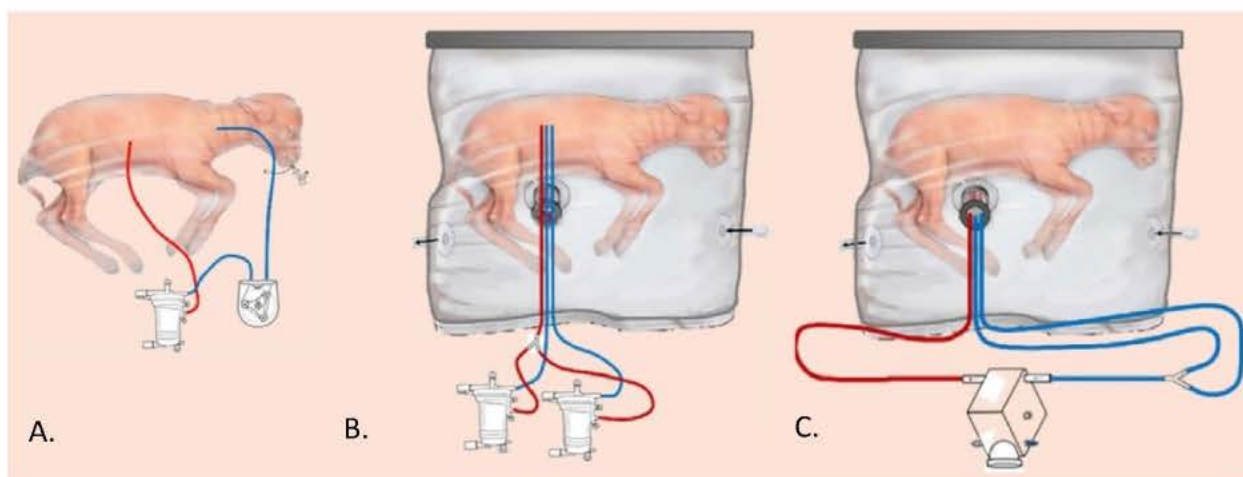


Figure 6. Source: De Bie et al, *Prenatal Diag* 2021 (Reference #31); reprinted in Spencer et al; *Sem Fet Neonat Med* 2022 (Reference #32)

3.1.3. Lung management

Maintenance of fluid-filled lungs is a fundamental aspect of AP/AWT support that enables maintenance of fetal circulation by delaying transitional physiology induced by lung aeration after birth. Presence of fluid in the airways may also stimulate lung development³¹ while eliminating the need for positive-pressure ventilation and its associated complications. Two proposed approaches have been described to maintain fluid-filled lungs. These include complete submersion in artificial amniotic fluid within an AWT environment and endotracheal intubation with instillation of perfluorocarbons (PFCs) during support with an AP system.³² Early concerns regarding infection risk with the complete fluid submersion approach were addressed with transition to a strategy comprised of a closed, sterile environment, use of continuous fluid exchange, and close surveillance for signs and symptoms of infection with a low threshold for treatment with antimicrobials.³¹ While the PFC based approach requires endotracheal intubation and does not offer the insulation from sound and other environmental insults provided by the AWT system, it may allow for more routine access to the baby for provider care and parental bonding.

3.1.4. Extrauterine environment for growth and development

As described above, AP and AWT systems differ in the specialized environment provided to protect and support organ growth and development. While an AP system alone allows for care in a standard NICU incubator, the AWT system maintains the patient in a fluid-filled soft enclosure. Nutritional support is provided via total parenteral nutrition for the duration of AP/AWT support, with a goal of delivering 70-80 kcal/kg/day,³¹ as the estimated caloric goal for growth is expected to be lower than the preterm infant undergoing SOC in the NICU environment. The overarching goal of AP/AWT systems is to provide stable cardiorespiratory support, as lability in perfusion and gas exchange are two of the primary mechanisms for injury to the preterm brain and other organ systems.

3.2. Summary of select published approaches investigated in nonclinical studies

3.2.1. AP in a 130-135 day preterm lamb model

The University of Michigan AP model uses a pump-assisted VV circuit with JV/UV cannulation and a fluid-filled endotracheal tube instead of fluid immersion. The average survival duration of (118 to 130 days GA) preterm lambs in the Michigan model is 17 days.³⁴⁻³⁹ The model requires vasopressors to stabilize hemodynamics, corticosteroids for lung maturation, supraphysiological partial oxygen pressures to ensure adequate oxygenation, and reports inconsistent maintenance of ductal patency despite infusion of prostaglandins.³⁶⁻³⁸ The Michigan AP model has reported positive results on the development and function of different organ systems including lung maturation,^{37,40} cerebral maturation,⁴¹ and gastrointestinal tract.^{38,39} However, assessment of cardiac function remains unreported. Furthermore, clinical translation questions remain regarding whether this model (i.e., preterm lambs at 130-135d, weight range 2.5-5.1 kg) will replicate the same results in a model that correlates to human EPIs at 22-24 weeks gestation which has a lower gestation equivalent in fetal lambs (i.e., <95d). An important distinction of this model is that it is designed for postnatal rescue therapy for refractory respiratory failure after standard resuscitation, whereas the following AWT models describe an approach that transfers the fetal lamb directly from the uterus to AWT support.

3.2.2. AWT in a 112-115 day and 95-day preterm lamb model

The Ex-Vivo Uterine Environment (EVE) was developed in collaboration by Tohoku University in Japan and the University of Western Australia in Australia. This model uses a pumpless AV circuit with parallel two hollow-fiber membrane oxygenators, external circuit flow regulators, and a closed, low-volume container with continuous sterilization of recirculating amniotic fluid. The average duration of preterm lamb survival in the EVE model is 7 days.⁴²⁻⁴⁵ The model requires vasopressors to stabilize hemodynamics, administration of prophylactic antibiotics to reduce the risk of bacteremia and corticosteroids to stimulate lung maturation, suppress inflammatory responses and prevent hypotension.^{42,43,46} Studies examining the brain showed evidence of white matter injury (WMI) due to systemic hypoperfusion or acute embolic events.^{43,45} The EVE model was also studied in fetal lambs of 95 days GA weighing 0.6 to 0.7 kg. In this study, seven lambs were sustained on the circuit for 5 days with stable hemodynamics, oxygenation, growth, and cardiac function. Assessment of the lungs and brains were unremarkable in all except one animal, which showed evidence of WMI after experiencing a 5-minute flow interruption due to accidental catheter occlusion.⁴⁶ In a more recent study, EVE was

studied in 95-day fetal lambs compromised by lipopolysaccharide induced intrauterine inflammation.⁴⁷ Eight of the ten animals in this study survived for 5 days on EVE; three had evidence of WMI on histology and five required dexamethasone to manage refractory hypotension.

3.2.3. AWT in a 105-117 day preterm lamb model

The EXTEND AWT model was developed by a team from the Children's Hospital of Philadelphia (CHOP). This model uses a pumpless AV circuit in which preterm lambs are submersed in a closed, sterile fluid environment with continuous exchange of synthetic amniotic fluid. The duration of preterm lamb (aged 105 to 117 days' GA) survival in the CHOP model was demonstrated up to 28 days.⁴⁸ The model does not require the use of vasopressors or corticosteroids to maintain stable hemodynamics and prevent hypotension. Additionally, the EXTEND model does not require external flow regulators to deliver oxygen and maintain circuit flow. The EXTEND investigators have reported positive results on the growth and organ maturation of preterm lambs including lung development,⁴⁸ pulmonary function, metabolic health,⁴⁹ cardiac function,^{50,51} and cerebral maturation.^{48,52} However, specific assessment of kidney and liver are still unreported. Notably, the lambs used in the published EXTEND nonclinical experiments were equivalent to EPIs from a lung development perspective (i.e., 23-34 wk GA human lung development equivalent) but were considerably larger (1.0-2.0 kg) than periviable EPIs (median birthweight range ~0.54-0.56 kg)⁵³ and more mature from a cerebral development perspective (i.e., >30 wk GA human brain development perspective).^{54,55}

3.2.4. AWT in a ~95-day preterm miniature pig model

The University of Toronto studied the feasibility of an AWT model to support preterm miniature pigs (98±4 days gestation) using a pumpless circuit and an oxygenator connected to the fetal circulation by the umbilical vessels, while nurturing the fetus in an artificial uterine environment consisting of a "Biobag" to allow for submersion in artificial amniotic fluid with periodic exchange.^{28,56} The preterm miniature pig model was selected, according to the investigators, because of the similarity to the human umbilical cord anatomy. The average survival duration of preterm miniature pigs in the Toronto model is 684±790 minutes. Although the study showed that AWT support of preterm miniature pigs is feasible, the investigation ended due to cardiovascular deterioration and hemodynamic instability in all preterm miniature pigs which was attributed to subphysiologic circuit flows. During the transition from maternal/uterine circulation to the AWT environment, vasopressors, antibiotics and anticoagulants were used. The weight of the preterm miniature pigs was 743±350 g which is comparable to human fetuses at 26 weeks.⁵⁷ In a more recent study that included a small pump added to the initial AP model, survival of preterm pigs increased to 46.4 ± 46.8 hours. However, despite the addition of the pump, slower but consistent declines in UV flow with tachycardia and hypertension resulted in circulatory deterioration.⁵⁷

3.3. Clinical considerations for development of AWT systems

3.3.1. Nonclinical proof-of-concept (POC) for effectiveness - Demonstration of organ growth, development and protection

The goal of AWT is to provide a bridge from extreme preterm birth to later gestation within a physiologic environment that mimics the womb in order to reduce prematurity-associated morbidity associated with standard NICU care. Nonclinical studies should address the feasibility of cannulation in vessels of size relevant to the human EPI and the ability to maintain adequate extracorporeal circuit flow

to support end organ perfusion and oxygenation. POC to support a prospect of direct clinical benefit to a human subject exposed to AWT should be demonstrated by evidence of organ growth and gestational age-based maturation across organ systems in nonclinical studies. For example, lung growth should be evidenced not only by increased size and weight but also histological maturation from the canalicular to saccular stage of lung development.¹⁶ Lung growth and development in the AWT system should be improved compared to animals exposed to SOC mechanical ventilation. Similarly, animal models should demonstrate normal brain development with regards to regional growth, cortical, and microstructural maturation. Given the concern for injuries such as intraventricular hemorrhage and WMI that are specific to vulnerabilities associated with preterm birth, selected animal models should demonstrate analogous maturation of the germinal matrix and oligodendrocyte lineage to have clinical relevance to the preterm human infant. Normal growth and protection from injury should be demonstrated across organ systems including the heart, kidney, liver, integumentary and gastrointestinal system.

3.3.2. Nonclinical safety – Mitigation of device-specific risks

Nonclinical studies should address device-specific risks including impact of maintaining fetal physiology and extracorporeal circulation on the developing heart, ability to mitigate infection risk by active surveillance and treatment, and the risks of AWT-related procedures and interventions including medications (e.g., anticoagulants, prostaglandin E1, artificial amniotic fluid, medications to prevent umbilical vessel spasm) that are not SOC for EPIs. While the scientific rationale of AWT is based on support in a physiologic state that mimics fetal physiology in the womb, the use of an extracorporeal circuit and prolonged prostaglandin exposure may have impact on the developing heart, as some preclinical studies have demonstrated both transient⁵¹ and more severe cardiac dysfunction²⁸ in published AWT/AP models. Particular attention to the risk of systemic anticoagulation is important given that high risk for bleeding complications, including intraventricular hemorrhage, have been reported in preterm infants treated with ECMO as rescue therapy for respiratory failure. Although recent literature supports advances in ECMO and anticoagulation management have led to lower incidence of intracranial hemorrhage in neonates, rates of hemorrhage continue to be higher in preterm infants (21%) compared to term neonates (7%).^{58,59} Whether immediate transition to AWT after birth and hemodynamic stability during support offer protection against intracranial hemorrhage that outweighs added risk from systemic anticoagulation should be considered. While artificial amniotic fluid may serve as an external physical buffer and provide internal distending pressure to promote lung and intestinal growth in AWT, additional considerations include biocompatibility and whether this simulated fluid functions analogously to amniotic fluid, which has a complex composition including growth and nutritional factors. While EPIs are routinely exposed to parenteral nutrition (PN) during the transition to enteral feeding, AWT will require prolonged total PN (i.e., for the duration of AWT support) and delay of enteral feeding initiation compared to SOC where enteral feeding is typically initiated as soon as possible after birth to promote intestinal adaptation and to avoid PN-associated risks.¹⁹⁻²¹

3.3.3. Nonclinical Animal Model Considerations

Animal studies guided by good laboratory practice, including those that are used to study AWT devices, can help determine if the device will work as intended and can be used to evaluate device safety and performance to support initiation of human trials. 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 applicable human physiology and pathology. A comprehensive understanding of the benefits and limitations of different models is necessary to allow for a rigorous evaluation of medical devices that generate high quality data with true bearing on the endpoint being evaluated. To optimize the data generated by animal studies requires knowledge of the biology of specific species and whether a given model can be used to closely simulate the clinical condition. In specific studies, there are animal model limitations that include anatomic, physiologic, and developmental differences between an animal model species and humans. For instance, organ system development and disease states cannot be modeled in a single species to help predict outcomes in humans, and therefore, the selection of an adequate animal model(s) to generate data to answer specific question or evaluate potential experimental outcomes may involve several species to provide a more comprehensive evaluation of anticipated risks. For in vivo evaluations of ECMO devices indicated for adults, the domestic sheep (*Ovis aries*) animal model is often utilized as the body and blood vessel sizes for cannulation are comparable with adult humans, the species' docile nature allows for handling and monitoring, and there are available historical data to evaluate blood responses to shear stress and blood-contacting materials commonly used in ECMO circuits. For AWT studies and toxicity assessments in preterm animals, there is a history of fetal lamb use reported in the literature (as described above in section 3.2). Determining the most feasible and useful animal model for AWT is challenging because maturation of multiple organ systems is affected throughout the duration of exposure to the device. The susceptibility to toxicity depends on the organ's stage of maturation. Embryonic and fetal development across different species is not uniform for different organ systems and differ between animals and humans. For example, the fetal lamb is larger than the human infant at the equivalent stages of lung development, the fetal lamb's shorter umbilical cord is comprised of two arteries and two veins compared to two arteries and one vein in human, and the growth rate of a fetal lamb is approximately twice the rate of human fetal growth. Such intraspecies differences impact the translatability of critical aspects of organ development during exposure to the device. For example, how fetal lamb and other large animal models such as fetal piglets compare to EPIs can create challenges when differentiating between observed adverse effects resulting from device use and those that may be attributed to a study design limitation. These differences should be carefully considered in the conduct of a robust and rigorous animal study.

For the in vivo safety evaluation of AWT, FDA is considering the advantages and limitations of the use of fetal non-human primate (NHP) models. The olive baboon (*Papio anubis*) infant has the largest body birth weight compared to other common NHP models such as Rhesus macaque (*Macaca mulatta*) and Cynomolgus macaque (*Macaca fascicularis*). However, the preterm baboon fetus, equivalent to canalicular stage of human lung development, is less than 500 g, which is a limitation for cannulation; the smaller left ventricle of the fetal heart will not be able to overcome ECMO circuit resistance; and the circuit volume will be 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 to inform cardio-pulmonary outcomes and due to anatomical (size) differences at equivalent stage of lung development with respect to EPI, may logistically preclude application of the therapy. Therefore, to ensure the relevance of the model and the utility of data generated, NHP models selected should address such differences and how they may impact the data and conclusions drawn from such studies. If the endpoints will be impacted in a manner that precludes an accurate evaluation of either safety or efficacy, an alternate model(s) should be selected.

3.3.4. Considerations for First-in-Human (FIH) studies

FIH studies for AWT may be designed in the context of regulatory considerations for early feasibility studies of innovative devices and must be designed in accordance with the ethical regulations governing safeguards for protection of children in research (see subsection 4.2). Key components of study design include a robust plan for safety monitoring and adverse event reporting, pre-established individual and study stopping rules, oversight by an independent Data and Safety Monitoring Board (DSMB), endpoints to evaluate for a clinically meaningful treatment effect, and an effective informed consent process.

4. Regulatory Background for Device Development

4.1. Center for Devices and Radiological Health's (CDRH) Early Feasibility Study (EFS) Program

CDRH's EFS Program is a voluntary program which facilitates conduct of early-stage clinical device studies in the US to increase access for patients to potentially beneficial technologies and to support device innovation. EFS concepts are described in the FDA guidance document titled, [Investigational Device Exemptions \(IDEs\) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human \(FIH\) Studies](#).

As with all clinical studies of investigational devices, an early feasibility study must comply with 21 CFR part 812, which outlines the requirement for IDEs and comply with other relevant FDA regulations. For example, early feasibility studies that enroll children must also comply with 21 CFR 50, subpart D, the Additional Safeguards for Children in Clinical Investigations.

Traditional feasibility studies typically focus on obtaining clinical safety and effectiveness information on a final or near final device design or capturing outcomes data to guide pivotal study design. In contrast, EFSs are performed to gain initial insights into proof of concept, basic safety, therapeutic parameters, human factors, and patient characteristics that may impact device performance. Initial clinical experience obtained from an EFS can guide device modifications, optimize operator techniques, refine the intended use population, inform non-clinical test plans, and help plan future clinical studies. These outcomes, which are integral to the device development process, are intended to improve device performance and clinical results.

As outlined in the guidance document, an EFS is defined as a small clinical study evaluating a device that may be early in development and often before the design has been finalized. An EFS is often the study needed to study a novel device when information to advance device development cannot be practically obtained with additional non-clinical assessments, additional non-clinical assessments are not expected to be valuable, or when non-clinical tests are unavailable.

For EFS IDEs, animal studies may be conducted to support study approval when an animal model is needed to further assess basic safety or device functionality beyond the information provided from non-animal testing. Typically, animal models do not fully encompass human disease conditions such that for EFS, they focus on a limited range of safety and proof-of-concept objectives. Animal studies that do not

meet criteria for Good Laboratory Practice (GLP) can be used to support EFS IDE approval as long as any deviations from GLP are identified and justified and do not compromise the validity of the study results.

A key EFS principle is that some nonclinical testing may be deferred, supported by an appropriate justification, until the device design has been finalized for use in a larger study. In reviewing EFS IDE submissions, FDA considers the target disease condition (e.g., whether it is life-limiting or life-threatening), limitations of and risks associated with alternative treatments (the standard of care), and patient/guardian tolerance for risk and perspective on benefits. Since EFS can be associated with greater uncertainty regarding benefits and risks, clinical protocols should contain enhanced risk mitigation strategies to increase patient safety. Examples of risk mitigations may include:

- Study sites with the expertise and resources to manage adverse events and provide appropriate alternative therapies
- Highly qualified investigators with special training to conduct the EFS
- Follow-up assessments at frequent intervals to monitor subject safety and device performance, often more frequently vs. a traditional feasibility or pivotal study
- Timely reporting of serious adverse events to FDA (e.g., after each occurrence rather than only in a periodic progress report)
- A pre-specified plan for periodic patient outcome assessments and reporting to FDA prior to enrollment of additional patients (e.g., as frequently as after each use for a particularly novel high-risk device).

The [EFS Program](#) provides a mechanism for innovators to work directly with sponsors, FDA review teams, and clinicians to collaborate early so they can increase the efficiency of device development.

Considering the novelty of the AWT systems, the high mortality and morbidity rates associated with EPIs, and the challenges in developing nonclinical animal models that are representative of the clinical use conditions, FDA will consider relevant EFS principles in the clinical evaluation of the AWT devices.

4.2. Ethical considerations – Subpart D

The Additional Safeguards for Children regulations (21 CFR 50, subpart D) must be considered when a child will be enrolled in a clinical investigation. These regulations specify limits for the level of risk to which children may be exposed in a clinical investigation. Unless the risks of an investigational device are limited to minimal risk^a (21 CFR 50.51), or no more than a minor increase over minimal risk^b (21 CFR 50.53), the use of the investigational device in a child must offer a prospect of direct clinical benefit to the child, the risk must be justified by the anticipated benefit, and the anticipated benefit-risk profile must be at least as favorable as that presented by accepted alternative treatments (21 CFR 50.52), unless the protocol is referred by an IRB for review by a federal panel and allowed to proceed in

^a Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (21 CFR 56.102(i)). The standard of minimal risk should be interpreted as those risks encountered in the daily life of normal, average, healthy children living in safe environments and indexed to the experiences of children of the same age and developmental stage as the subject population.

^b Minor increase over minimal risk should be understood to mean a slight increase over minimal risk that poses no significant threat to the child's overall health or well-being. Any potential harms with the intervention or procedure should be expected to be transient and reversible and the probability for severe pain, discomfort, or harm should be extremely small or nonexistent.

accordance with 21 CFR 50.54.^c In addition, because a clinical investigation may include multiple research-related interventions or procedures, a “component analysis” should be conducted for each research-related intervention or procedure to evaluate its potential benefits and risks. Subpart D also requires that adequate provisions be made to obtain the permission of the parent(s) or guardian(s) (21 CFR 50.55).

The risks associated with an AWT in EPIs in a clinical investigation would be considered more than a “minor increase over minimal risk” (21 CFR 50.53) and therefore use of an AWT must offer a prospect of direct benefit to the individual subject (21 CFR 50.52). The prospect of direct benefit is assessed based on (1) POC data from nonclinical or clinical studies, (2) data to support that the device design and device performance characteristics are likely to have the intended treatment effect, and (3) evidence that the duration of the use of the device is sufficient to have an impact on a meaningful clinical outcome. Data to support prospect of direct benefit should support that the use of the AWT is likely to increase survival or reduce critical morbidities for the enrolled infant.

If data are adequate to support prospect of direct benefit for a clinical investigation of an AWT in EPIs, inherent to subpart D is that the prospect of direct benefit to the child must justify the risks, and that the relation of the anticipated benefit to the risk must be at least as favorable as that presented by SOC. As such, before a FIH clinical investigation of an AWT can proceed, adequate data must be available to support that the risks and benefits of the AWT device are at least as favorable as SOC. The survival and morbidity rates of EPIs receiving current SOC should be considered carefully to ensure the benefit-risk assessment of the AWT in the selected EPI study population is anticipated to be at least as favorable as SOC.

In addition, the risks and anticipated benefits of the procedures and interventions included in the protocol must be evaluated individually and collectively to ensure the research risks do not exceed the allowable thresholds. A research protocol often includes multiple research-related interventions or procedures, some that offer prospect of direct benefit and some that do not. Any intervention or procedure conducted solely for research purposes and not needed for clinical management or routine clinical care should be evaluated separately to determine whether it offers prospect of direct benefit to the enrolled child (known as a “component analysis” of risk). If a specific intervention or procedure does not offer prospect of direct benefit, the risk of the intervention or procedure should be limited to a minor increase over minimal risk, and meet the other conditions outlined under 21 CFR 50.53 unless the protocol is referred for review, as per 21 CFR 50.54.

If a child is to be enrolled in a clinical investigation, the parent(s) or guardian(s) must provide permission (21 CFR 50.55). The parental/guardian permission form must address the required elements of consent, as well as appropriate additional elements to allow the parent(s) or guardian(s) to make an informed decision. Parents or guardians should be given the opportunity to ask questions when considering

^c Under 21 CFR 50.54, if a clinical investigation is not approvable by an IRB under 21 CFR 50.51, 50.52, or 50.53 and the IRB determines the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, the IRB can refer the protocol for the clinical investigation to the FDA for review by a federal panel. After consultation with a panel of experts, the FDA Commissioner determines whether the protocol can proceed under 50.51, 50.52 or 50.53, or whether the protocol can proceed under 50.54.

participation in the clinical investigation and continue to be provided information as the investigation progresses and as the situation requires.^d Challenges in the informed consent process for enrollment of an infant in an AWT trial may include the parent also being the pregnant person, and as such, also a research subject, therapeutic misconception,^e the parent or guardian's perceived pressure to consent to experimental procedures, and the emotional circumstances under which informed consent may be obtained.

For additional information about the Additional Safeguards for Children (21 CFR 50, subpart D), see the [Ethical Considerations for Clinical Investigations of Medical Products Involving Children](#), Draft Guidance, September 2022.

5. Summary and Discussion Topics for the PAC

The goal of an artificial womb technology (AWT) 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 NICU standard of care (SOC), in infants born extremely premature.

In consideration of the information provided during the meeting on AWT, the PAC will be asked to opine on the following topics:

1. Considering the strengths and limitations of available large animal models, discuss what types of nonclinical data would be needed to inform the proof of concept (POC) for prospect of direct benefit and safety for use of AWT in human subjects.
2. Considering knowledge gaps that may not be answered by nonclinical studies, discuss what types of existing clinical data (i.e., from natural history of EPIs or other conditions/procedures) may be leveraged to help inform the benefit-risk determination of AWT.
3. If the totality of the data is adequate to support first in human (FIH) studies of AWT, discuss recommendations for design of a FIH clinical trial to optimize patient safety (i.e., risk mitigation strategies).
4. Discuss considerations and challenges in obtaining effective informed consent in an AWT trial.

^d For additional information on the informed consent process, see draft guidance for IRBs, clinical investigators, and sponsors [Informed Consent Information Sheet \(July 2014\)](#).

^e Therapeutic misconception is when individuals incorrectly presume that the experiment in which they are participating (or agreeing their preterm infant should participate in) is medical treatment.

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