U.S. FOOD & DRUG ADMINISTRATION

Clinical Considerations for Evaluating Benefit Versus Risk for Artificial Womb Technology Development Programs

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Pediatric Advisory Committee – September 19, 2023

21 CFR 50 Subpart D – Additional Safeguards for Children in Clinical Investigations

Section 50.52: Clinical investigations involving *greater than minimal risk* but presenting *prospect of direct benefit* to individual subjects

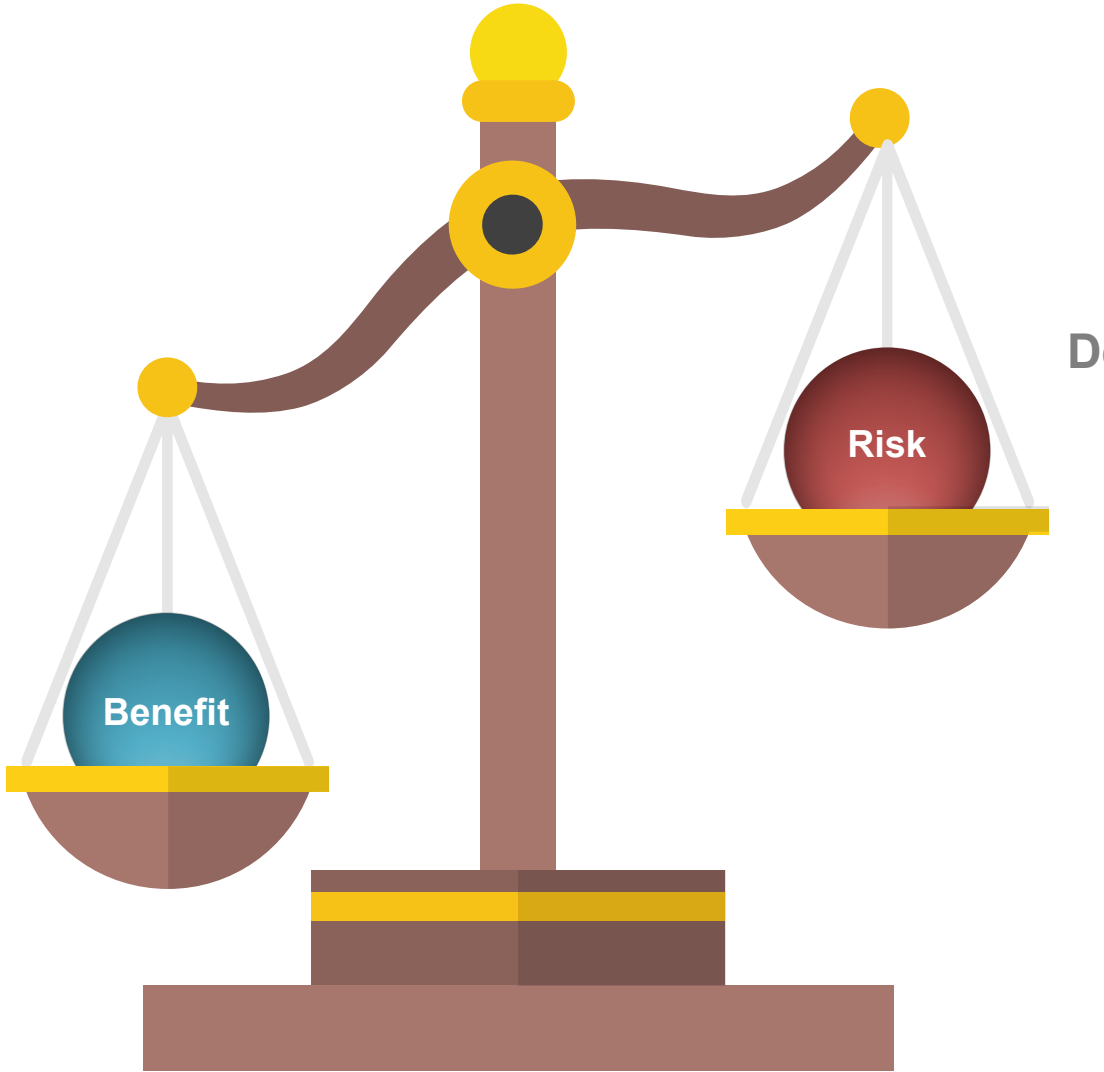
(a) The ***risk is justified*** by the ***anticipated benefit*** to the subjects;

(b) The relation of the anticipated benefit to the risk is ***at least as favorable to the subjects as that presented by available alternative approaches***; and

(c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians

Benefit versus Risk – Required for Marketing Authorization

Improved mortality & morbidity



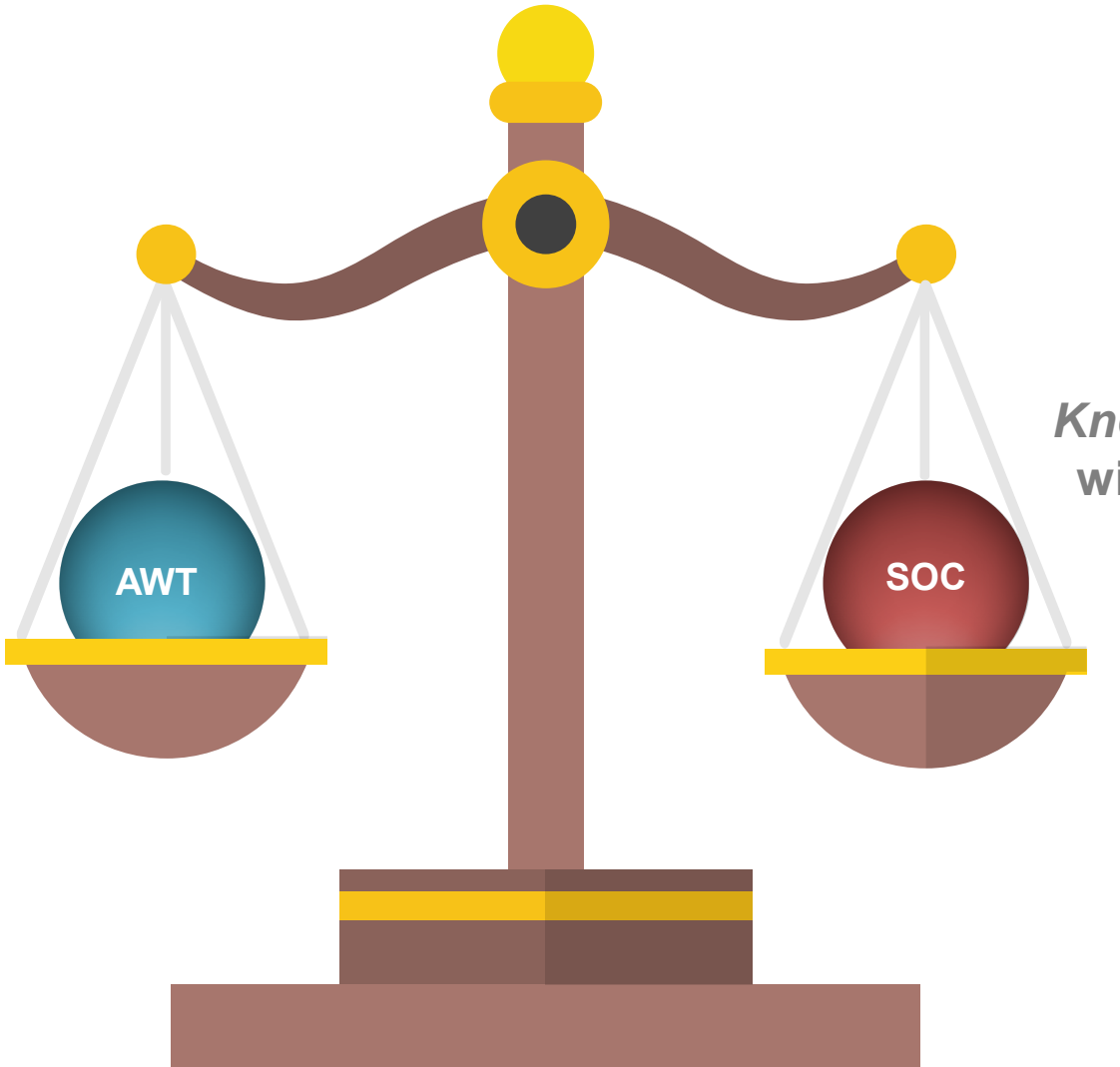
Device-related risks

Benefit versus Risk - Required for investigation in children

Prospect of improved mortality & morbidity

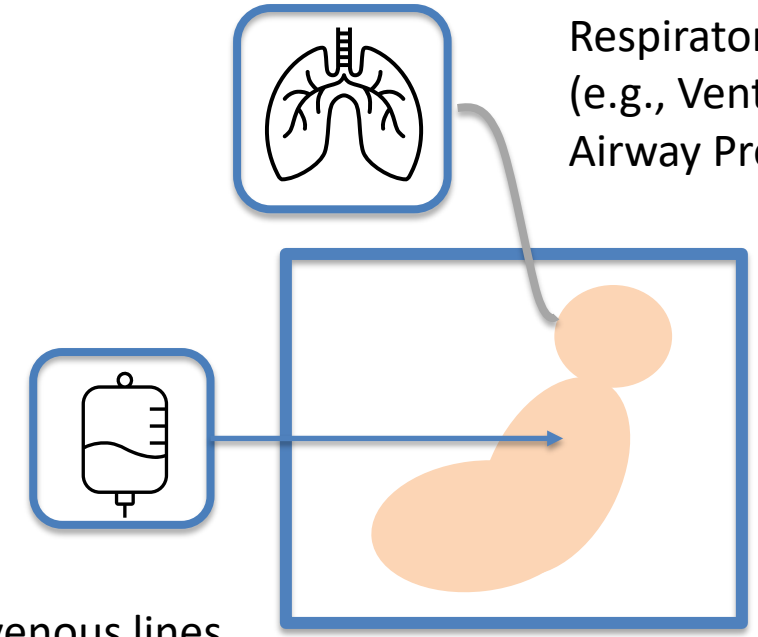
VS

Potential device-related risks



Known mortality & morbidity with standard of care (SOC)

CURRENT STANDARD OF CARE

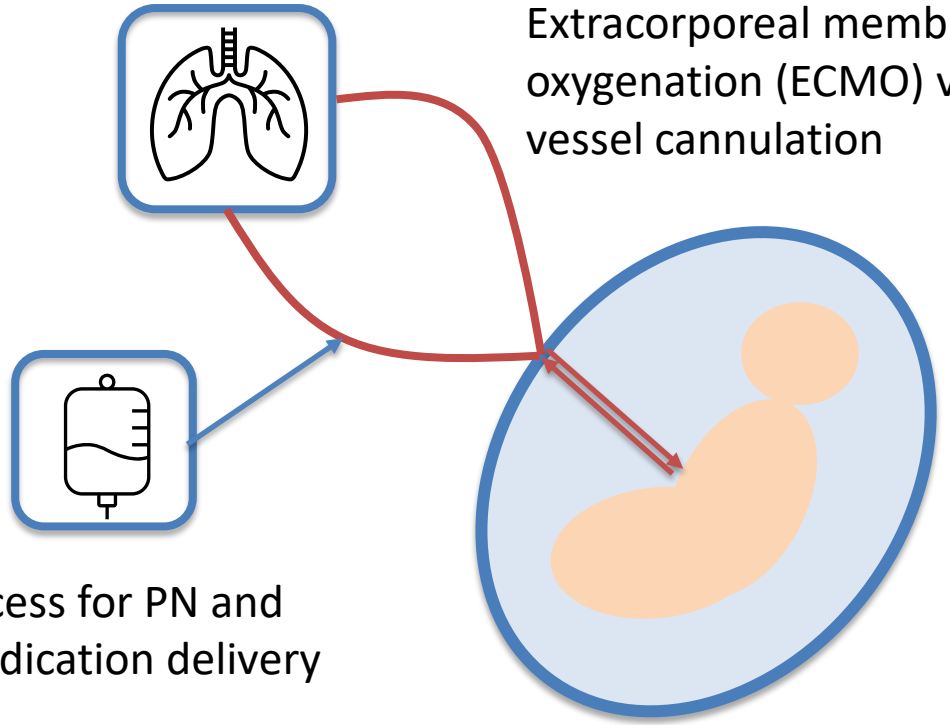


Respiratory support devices (e.g., Ventilator, Positive Airway Pressure)

Intravenous lines
- Parenteral nutrition (PN)
- Medications

Incubator

ARTIFICIAL WOMB TECHNOLOGY



Extracorporeal membrane oxygenation (ECMO) via vessel cannulation

Access for PN and medication delivery

Simulated womb environment with maintenance of fluid-filled lungs

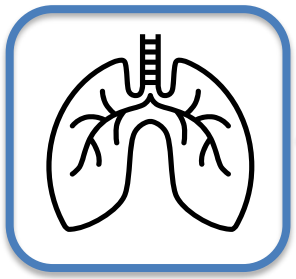
CURRENT STANDARD OF CARE

Known morbidities

may be contributed to by iatrogenic insults

→ **Mortality**

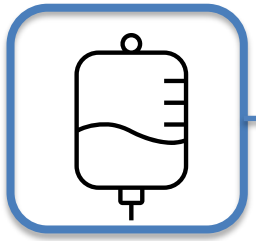
- *Central Line Associated Blood Stream Infection (CLABSI)*
- *Parenteral nutrition-associated liver disease (PNALD)*

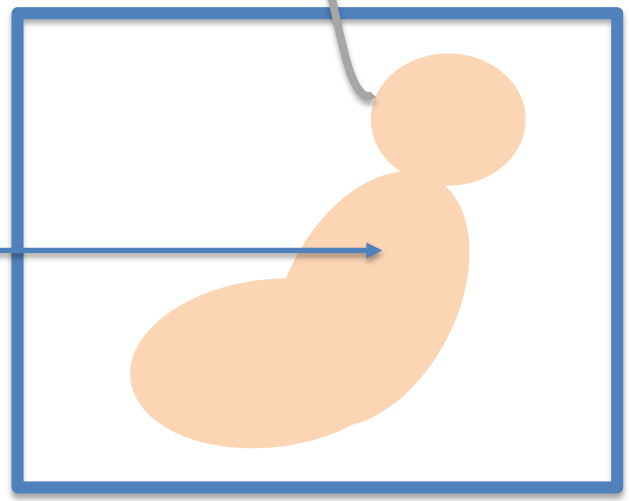


- *Ventilator-induced lung injury*
- *Oxygen toxicity*
- *Ventilator-associated pneumonia*

Bronchopulmonary Dysplasia (BPD)
Retinopathy of prematurity (ROP)

Necrotizing Enterocolitis (NEC)
SEPSIS



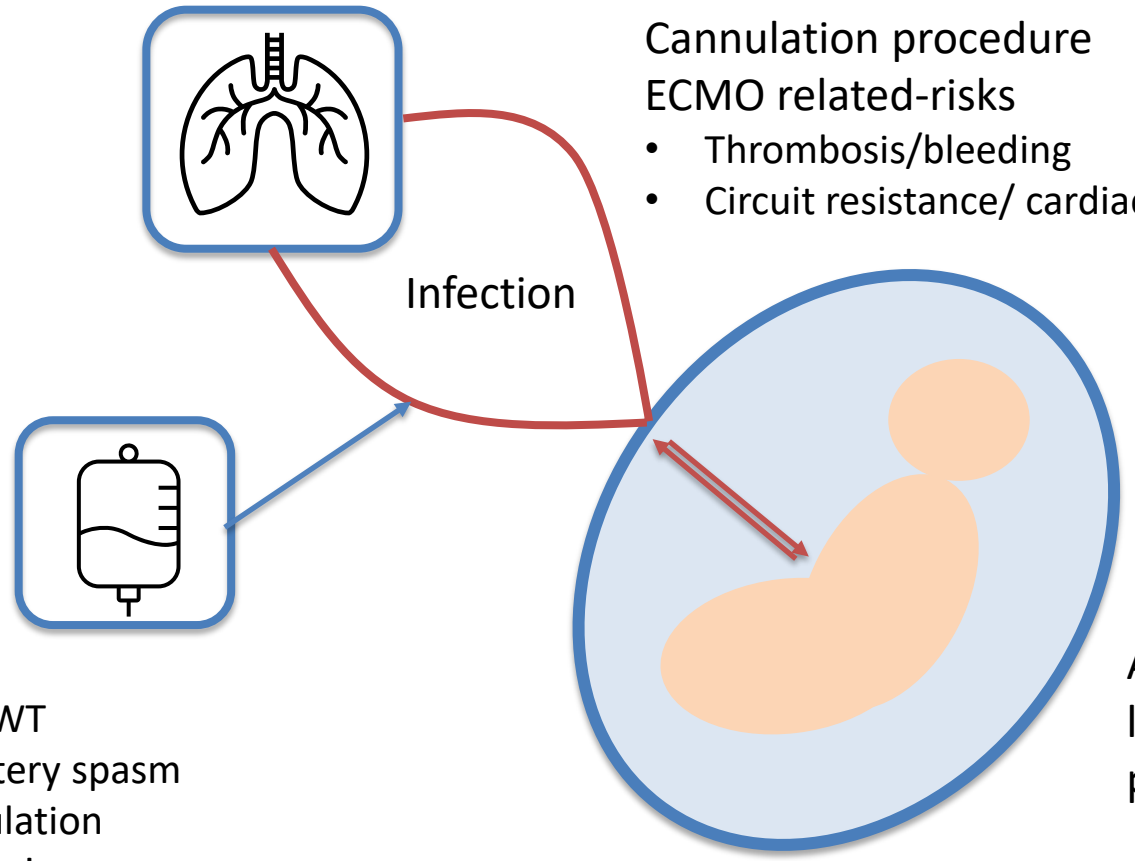


Intraventricular hemorrhage (IVH)
Periventricular leukomalacia (PVL)
Neurodevelopmental Impairment (NDI)

- *Inadequate metabolic & physiologic support*
- *Noxious exposures from the NICU environment and concomitant medications*

ARTIFICIAL WOMB TECHNOLOGY

Potential device related risks



Cannulation procedure

ECMO related-risks

- Thrombosis/bleeding
- Circuit resistance/ cardiac afterload

Concomitant medications

- Paralytic for transition to AWT
- Treatments for umbilical artery spasm
- PGE1 to maintain fetal circulation

Prolonged TPN/ delayed feeds

Artificial amniotic fluid or lung instillation of perfluorocarbons

REQUIREMENTS FOR A FIH TRIAL OF AWT

SUPPORT FOR PROSPECT OF DIRECT BENEFIT

- *Ventilator-induced lung injury*
- *Oxygen toxicity*
- *Ventilator-associated pneumonia*

BPD
ROP

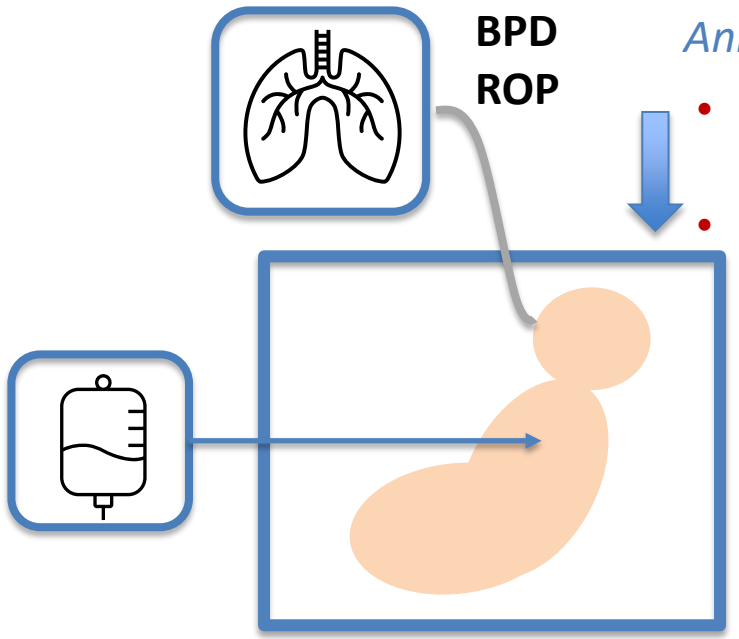
Animal models

- *Inadequate metabolic & physiologic support*
- *Noxious exposures*

IVH/PVL
NDI

- *PNALD*
- *CLABSI*

NEC
SEPSIS



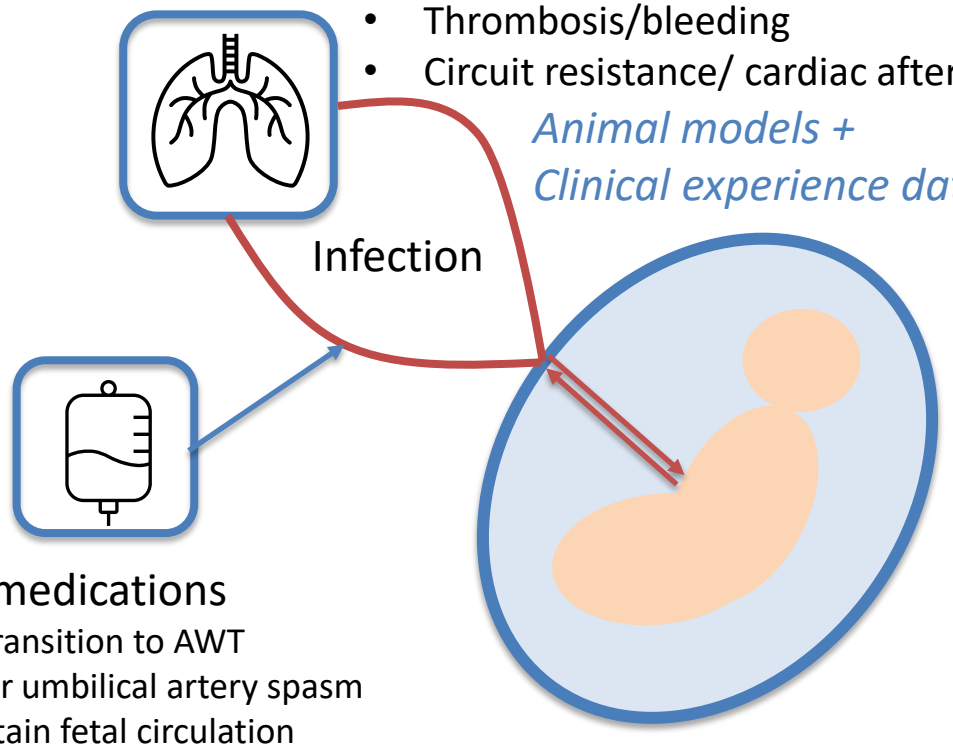
SAFETY/ ADEQUATE RISK MITIGATION

Cannulation procedure
ECMO related-risks

- Thrombosis/bleeding
- Circuit resistance/ cardiac afterload

Animal models + Clinical experience data

Infection



Concomitant medications

- Paralytic for transition to AWT
- Treatments for umbilical artery spasm
- PGE1 to maintain fetal circulation

Prolonged TPN/ delayed feeds

Artificial amniotic fluid/PFC

Animal models + Clinical experience data

Benefit versus Risk - Required for investigation in children

Improved mortality & morbidity

- Death
- Bronchopulmonary dysplasia (BPD)
- Intraventricular hemorrhage (IVH)
- Periventricular leukomalacia (PVL)
- Necrotizing enterocolitis (NEC)
- Retinopathy of prematurity (ROP)
- Sepsis
- Neurodevelopmental impairment (NDI)

Device-related risks

- Cannulation procedure
- ECMO related-risks
  - Thrombosis/bleeding
  - Circuit resistance/ cardiac afterload
- Artificial amniotic fluid
- Concomitant medications
  - Paralytic for transition to AWT
  - PGE1 to maintain fetal circulation
  - Treatments for umbilical vessel spasm
- Prolonged TPN/ delayed feeds

FDA Presentations

- Background on Artificial Womb Technologies (AWTs)
  Kal Molla, MS
- FDA's Regulatory Safeguards for Children Involved in Clinical Trials: Considerations for Artificial Womb Technologies
  Elizabeth L. Durmowicz, MD
- Clinical Considerations for Evaluating Benefit Versus Risk for Artificial Womb Technology Development Programs
  An N. Massaro, MD

Clarifying Questions

- Animal Model Considerations for AWT
  Annabelle Crusan DVM, MS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