Ethical Considerations for a First-in-Human Trial of Artificial Womb Technology

Food and Drug Administration hearing
Pediatric Advisory Committee
9/19/2023

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Yale SCHOOL OF MEDICINE

A brief overview of some of the ethical considerations…

1. Relevant ethical principles and guidelines
2. Patient/subject eligibility criteria
3. Terminology and moral status
3. Specific recommendations, and questions to be answered

Mercurio MR. *Pediatr Res*. 2018

Werner KM, Mercurio MR. *Semin Perinatol*. 2022

Dual laudable goals and possibly competing interests: Which way should the balance tip?

Vulnerable populations and the risk of exploitation

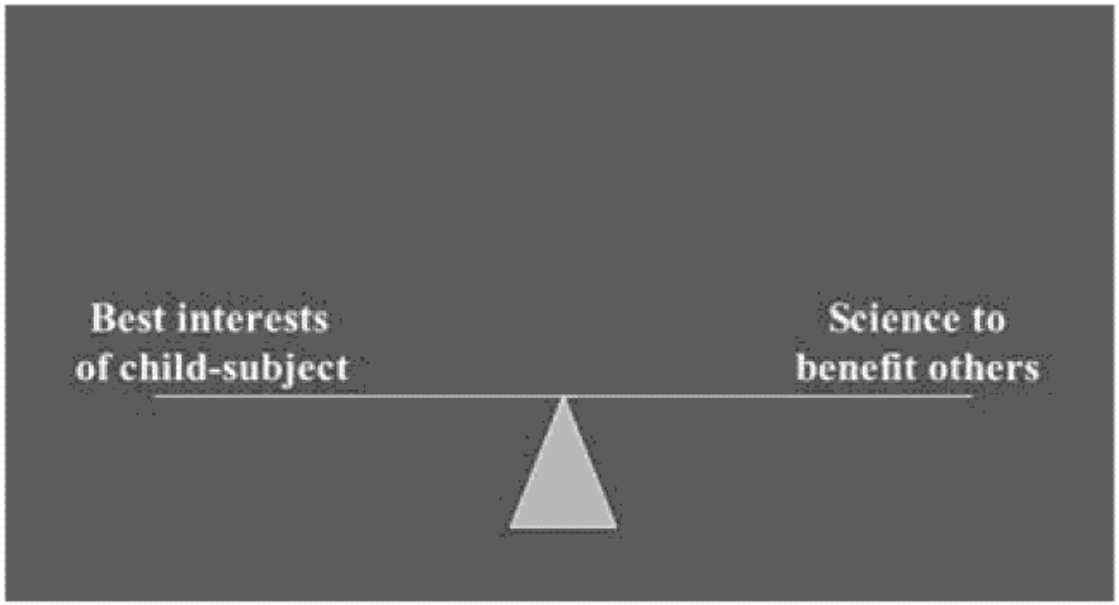

Image from
Kodish, E. Ethics and Research with Children. Oxford University Press 2005. p. 23

Which way should the balance tip?

"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."

Kodish, E. Ethics and Research with Children. Oxford University Press 2005. p. 22

HHS: 45 CFR 46 "Common Rule" (revised 2018):
Additional Protections for Children as Subjects in Research

§ 46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

HHS will conduct or fund research …only if the IRB finds that:

- (a) The risk is justified by the anticipated benefit to the subjects;
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- (c) Adequate provisions are made for soliciting the permission of parents or guardians

– US Dept of Health and Human Services, Office for Human Research Protection. Subpart D — Additional Protections for Children Involved as Subjects in Research. https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/common-rule-subpart-d/index.html accessed 9/15/2023

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Two research subjects

- Protocol could involve Cesarean delivery in a setting where it otherwise would not have been clinically indicated
- Risks to pregnant patient
- Risks to future pregnancies/newborns

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Ethical Considerations Regarding Artificial Womb Technology for the Fetonate

	Domain Name	Estimated Age	Prenatal Development Stage	Rationale for Upper Age Limit	Current Medical Support	Current Experimental Support
DOMAIN I	Fertilization & Implantation	0 to 2 weeks (CA)	Zygote implants in uterus and becomes embryo	Limit set by regulation	In vitro fertilization	Embryo culture up to gastrulation
DOMAIN II	Embryological & Early Fetal Development	2 weeks (CA) to 21 weeks (EGA)	Embryological organogenesis followed by fetal development and growth	Infants born before 22 weeks EGA are generally considered to be non-viable	Non-existent	Non-existent
DOMAIN III	Peri-Viability	22 to 25 weeks (EGA)	Fetal Growth and Maturation	Infants born at 25 weeks EGA have survival rates > 80% and active resuscitation is advocated	Neonatal resuscitation, MV, NIV, surfactant, steroids, ECMO, TPN	AWT Liquid ventilation
DOMAIN IV	Vulnerable Prematurity	26 to 34 weeks (EGA)	Fetal Growth and Maturation	Infants born after 34 weeks EGA have less risk of infant respiratory distress syndrome	Neonatal resuscitation, MV, NIV, surfactant, steroids, ECMO, TPN	Optimization of existing supportive technology

*

gray zone, zone of parental discretion

Figure 1. Four domains of prenatal development and corresponding current medical support and experimental support.
Legend: EGA, estimated gestational age; CA, conceptional age; MV, mechanical ventilation; NIV, Noninvasive ventilation; ECMO, Extracorporeal membrane oxygenation; TPN, Total Parenteral Nutrition; AWT, artificial womb technology.

- De Bie et al. *Amer J of Bioethics* 2023

Ethical permissibility, Domain III and parental choice

- The zone of ethical permissibility determined by prognosis, feasibility, and relevant rights
  - Mercurio and Cummings. *JPerinatol* 2020
- The "zone of parental discretion" (L. Gillam), aka "the gray zone"
- Thresholds often described in terms of gestational age

JAMA | Original Investigation

Mortality, In-Hospital Morbidity, Care Practices, and 2-Year Outcomes for Extremely Preterm Infants in the US, 2013-2018

Bell et al. NICHD Neonatal Research Network. *JAMA* 2022;327(3): 248-264

Table 2. Survival of Infants Born at 22-28 Weeks' Gestational Age in 2013-2018 for All Infants a

	No./total (%), by gestational age, in weeks			
	2013-2018			
Survival	22	23	24	25
All infants				
No.	550	1083	1398	1604
Survived >12 h	159 (28.9)	856 (79.0)	1298 (92.8)	1546 (96.4)
Survived to discharge or 1 y[c]	60/549 (10.9)	535/1083 (49.4)	972/1391 (69.9)	1266/1599 (79.2)
Discharged home	56/549 (10.2)	520/1083 (48.0)	948/1391 (68.2)	1245/1599 (77.9)
Remained in hospital at 1 y	4/549 (0.7)	15/1083 (1.4)	24/1391 (1.7)	21/1599 (1.3)

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Remained in hospital at 1 y	4/549 (0.7)	15/1083 (1.4)	24/1391 (1.7)	21/1599 (1.3)
Infants actively treated at birth[d]				
No.	201	958	1369	1589
Survived >12 h	159 (79.1)	856 (89.4)	1298 (94.8)	1546 (97.3)
Survived to discharge or 1 y[c]	60/200 (30.0)	535/958 (55.8)	972/1362 (71.4)	1266/1584 (79.9)
Discharged home	56/200 (28.0)	520/958 (54.3)	948/1362 (69.6)	1245/1584 (78.6)
Remained in hospital at 1 y	4/200 (2.0)	15/958 (1.6)	24/1362 (1.8)	21/1584 (1.3)

Canadian Neonatal Network 2010-2017 (all 30 tertiary NICUs)

Infants admitted to NICU not moribund **(active Rx)**

GA (n)	Survival
• 22 wk (85)	32 %
• 23 wk (679)	50%
• 24 wk (1504)	69%

Shah et al. *J Pediatr* 2020

22 wk: survival at 3 years

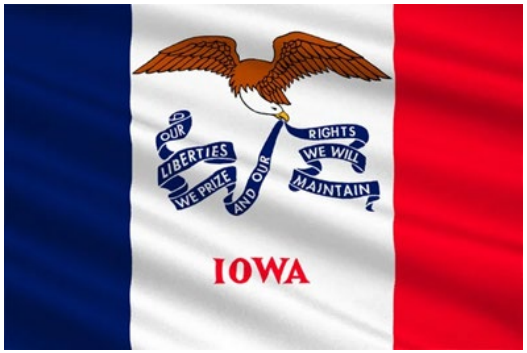
- Neonatal Research Network, Japan
- 52 tertiary centers, 2008-2012
- Survival = 46% overall (125/271)
- Survival = 51% of those admitted to NICU (125/245)

- Kono et al. *BMJ Pediatrics Open* 2018

Survival to discharge:

University of Iowa 2006-2015 birth cohort * Attempted resuscitation**

GA at birth	Survival to DC
22 wks	64% (14/20)
23 wks	82% (41/50)
24 wks	89% (70/79)



*Specific protocols, high antenatal steroid use, special tiny baby teams

**No resuscitation attempted in: 2 pts at 22 wks, 2 pts at 23 wks, 0 at 24 wks

- Watkins et al. *JPeds* 2020

Nagano Children's Hospital

- Nagano Children's Hospital, Japan
- Single center, inborn 2011-2018

Gest age	Survival (live born)	Survival (adm NICU)
22 wks	81% (13/16)	93% (13/14)
23 wks	93% (25/27)	93% (25/27)

- Yanagisawa et al. *Am J Perinatol* 2022

What current survival data should be used for determination of relative risk?

- The center where the AWT is to be trialed?
- US overall data (NRN data?)
- The centers with the best outcomes?
- Should we emulate centers with best outcomes before trying AWT?

Gestational age alone is a poor proxy for survival

- Intensive care for extreme prematurity – moving beyond gestational age.
  - Tyson and NICHD NRN. *NEJM* 2008

- NICHD outcomes estimator: GA, Wt, sex, antenatal steroids, plurality
  - Rysavy and NICHD NRN. *NEJM* 2015

… a better proxy for prognosis than GA alone

Outcomes with conventional therapy

NICHD Neonatal Research Network (24 centers)
2006-2012 birth cohort

	Likelihood of Survival with Active Resuscitation
22 wk male 500 gm Singleton, no antenatal steroids	15%
22 wk female 500 gm Singleton, received ANS	37%
23 wk female 650 gm Singleton, received ANS	60%

NICHD Extremely Preterm Birth Outcomes Tool
https://www.nichd.nih.gov/research/supported/EPBO acc 9/15/2023

Disability prevention with AWT

- Outcome is not only about survival
- Pulmonary morbidity and potential for prevention
- Neurodevelopmental impairment and potential for prevention
  - Short and long-term evidence
  - e.g., intraventricular hemorrhage diagnosed by ultrasound at 7 days vs cognitive function assessed at 7 years

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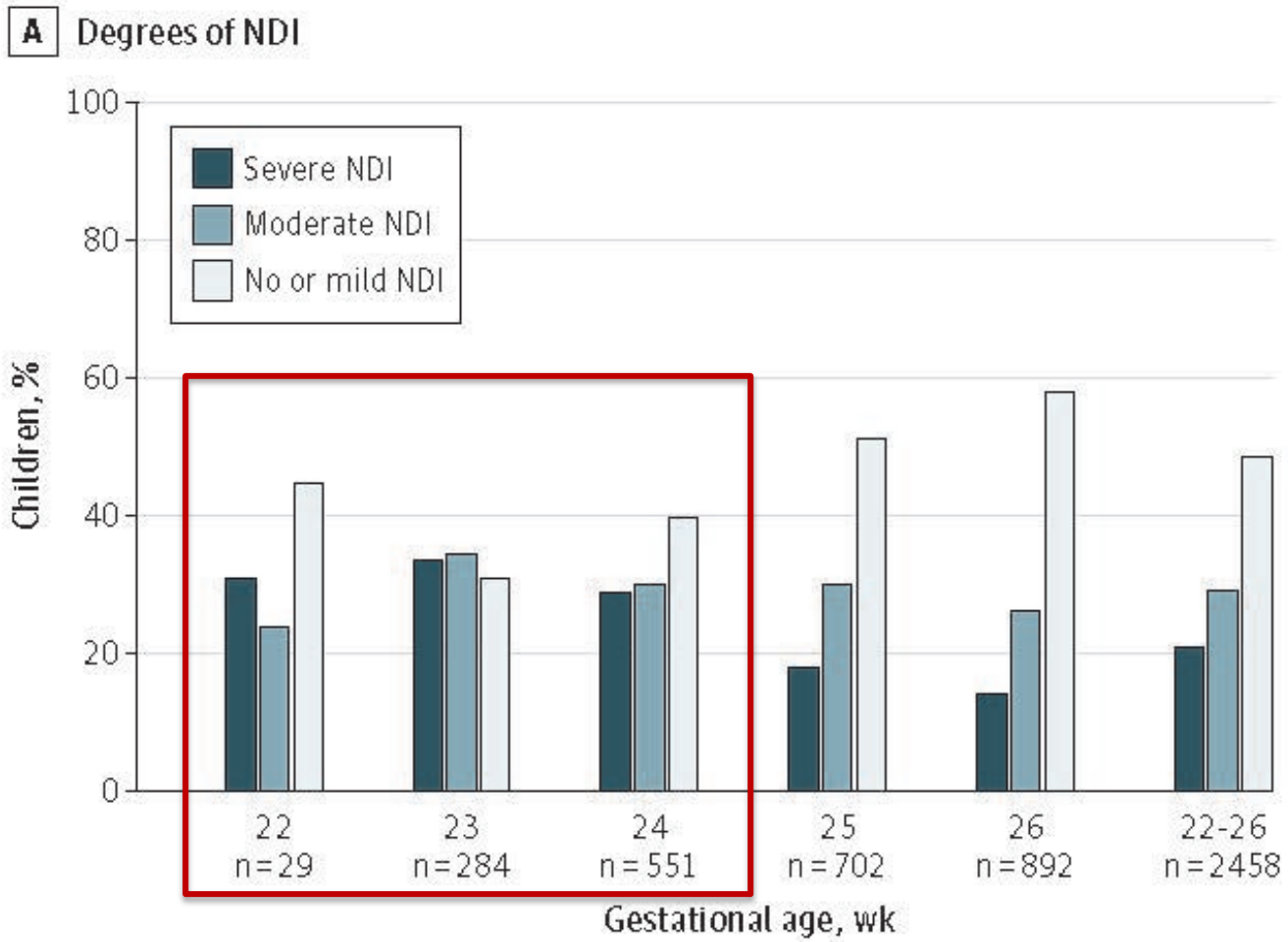
Neurodevelopment impairment: Cognitive, CP, vision, hearing



22 wk: outcomes at 3 years

- Neonatal Research Network, Japan
- 52 tertiary centers, 2008-2012
- Survival = 46% overall (125/271)
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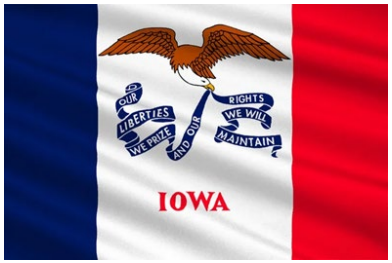
- **22 wks: NDI = 46%**

- Kono et al. *BMJ Pediatrics Open* 2018

Disability among survivors

University of Iowa 2006-2015 birth cohort

GA at birth	No/Mild NDI among survivors (18 -22 months)
22 wks	55% (6/11)
23 wks	68% (23/34)
24 wks	79% (42/53)



- Watkins et al. *JPeds* 2020

Risk of decisions based on early NDI outcomes

Developmental Follow-up of 200 VLBW newborns

Moderate to severe cognitive impairment

(MDI < 70 / MPC < 70):

20 months: 39%

8 years: 16%

- Hack et al. *Pediatrics* 2005

But… a risk of later manifestations of other disorders

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Parental permission/consent…

- Permission/consent often the setting of preterm labor, often in the setting of fear, exhaustion, urgency, and pain

- Aside from mode of delivery (pregnant patient gives sole consent), there are commonly two decision-makers for the newborn, for clinical and research participation. *Must both agree to the use of AWT?*

- *Whose permission is needed to withdraw*

What's in a name?

- **Words Matter**

- *What should we call the individual on AWT?*
- Fetus? Neonate?
- Gestateling? - Romanis. *J Med Ethics* 2018
- Fetal neonate? Fetonate? - DeBie. *Am J Bioeth* 2023
- *Will this depend on gestational age (domain)?*

- **Moral Status**

- How much an individual's interests should count
  - Mary Ann Warren. Moral Status. 1997

- *Legal, cultural, and ethical considerations*

Pushing back the gestational age threshold?

?

*

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- De Bie et al. *Amer J of Bioethics* 2023

Lowering the threshold for attempted resuscitation: an ethical justification for refusal? (Domain II)

Two-Year Neurodevelopmental Outcome of an Infant Born at 21 Weeks' 4 Days' Gestation

Kaashif A. Ahmad, MD, MSc,[a,b] Charlotte S. Frey, MS, MPAS, PA-C,[a,c] Mario A. Fierro, MD,[a,c] Alexander B. Kenton, MD,[a] Frank X. Placencia, MD[d,e]

PEDIATRICS Volume 140, number 6, December 2017:e20170103

- BW 410 gm: 21 weeks, 4 days by LMP, 21 weeks 2 days by 9 wk US
- Prolonged mech vent, BPD, ROP
- Discharged at 39+ weeks on nasal cannula O2
- 24- month follow-up: cognitive, motor, language Bayley III scores normal for 20 months corrected age.

- Though lowering the GA threshold is not the intention of AWT at present, a parent will eventually ask, and we should be prepared with an ethically defensible answer.

Ethical Challenges in first in human trials of artificial placenta and artificial womb

- ***Recommendations:***

- **Collaborative informed consent**: research surgeon, neonatologist, MFM

- **Collaborative study design** between investigators, surgeons, neonatologists, MFM, bioethicists

- **Planning/discussion among stakeholders**: IRB, community stakeholders, parent representatives involved in discussion

- Kukora et al. *Journal of Perinatology* 2023

  - *A humble suggestion: a national conference on the ethics of AWT to include representatives from all of the above*

Ethical Challenges in first in human trials of artificial placenta and artificial womb

- ***Recommendations:***

- Initial enrollment of very high risk (e.g., < 20% predicted survival)

- Gradually increase to include infants with a better prognosis (e.g., 20-50% survival) as a comparative effectiveness trial to conventional therapy, evaluating outcomes like survival and long-term neurodevelopment.

  - Kukora et al. *Journal of Perinatology* 2023

Fundamental questions:

– *What are the appropriate thresholds??*

– *What level of anticipated disability is considered worth the risk of AWT?*

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Thank you