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FDA's Regulatory Safeguards for Children Involved in Clinical Trials: Considerations for Artificial Womb Technologies

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Outline

- FDA's Additional Safeguards for Children in Clinical Investigations
- Ethical Considerations for a Trial of an Artificial Womb Technology (AWT)
    - Analysis of Prospect of Direct Clinical Benefit
    - Analysis of Risk
    - Informed Consent/Parental Permission

Research Involving Children

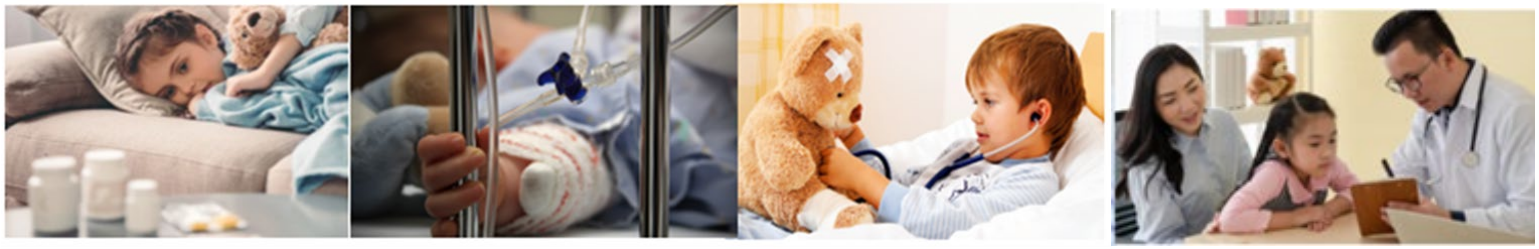
Children are vulnerable and require additional safeguards

Pediatric research is necessary to safeguard and improve the health and well-being of children

Department of Health Education and Welfare, Research Involving Children: Report and Recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1978)

Clinical Investigations In Children

- Clinical investigations in children are essential:
  - to obtain data on the safety and effectiveness of medical products (e.g., drugs, biological products, medical devices) in children
  - to protect children from the risks associated with exposure to unsafe or ineffective medical products
- Children are a vulnerable population who cannot consent for themselves and therefore are afforded additional safeguards when participating in research
- Safeguards are an essential requirement for the initiation and conduct of pediatric clinical investigations as part of a medical product development program



FDA's Regulatory Safeguards for Children: Basic Ethical Framework

Ensure Necessity

Children should only be enrolled in a clinical trial if the scientific and/or public health objective(s) cannot be met through enrolling subjects who can consent personally, and the objective(s) are important for the health and welfare of children

Limit Risks

Absent a prospect of direct clinical benefit, the risks to which children are exposed must be "low"

For children, there is a limit to the risk that knowledge alone can justify, and risks should be minimized

Prevent Disadvantage

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

Obtain Permission

Children should have a suitable proxy to provide permission for them to enroll in a clinical trial

Department of Health Education and Welfare, Research Involving Children: Report and Recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1978)

Overview: FDA's Regulations for Children[a]

- A clinical investigation involving children[b]
  - Must be restricted to "low" risk (i.e., restricted to "minimal" risk or a "minor increase over minimal risk") absent a potential for direct benefit to the enrolled child

  OR

  - Must present risks that are justified by the "prospect of direct benefit" to the child; the balance of which is at least as favorable as any available alternatives

  AND

  - Must have adequate provisions for soliciting parental permission and child assent (as appropriate)

[a]The Additional Safeguards for Children in Clinical Investigations (21 CFR 50, Subpart D)
[b] Unless rereferred by an institutional review board (IRB) for review by a federal panel

FDA's Regulatory Safeguards for Children
21 CFR 50, subpart D

§ 50.51

Clinical investigations not involving greater than minimal risk

§ 50.52

Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects and the risks are justified by the anticipated benefit

§ 50.53

Clinical investigations involving greater than minimal risk (but limited to minor increase over minimal risk), no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition

§ 50.54

Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children

§ 50.55 Requirements for permission by parents or guardians and for assent by children

Greater Than Minimal Risk but Prospect of Direct Benefit[a]

- A benefit is “direct” if it:
  - Accrues to the individual subject enrolled in the clinical trial
  - “Benefit” is often modified by “clinical” to indicate that the benefit relates to the health of the enrolled subject
- Prospect of direct benefit is based on data that support proof of concept and that use of the intervention (e.g., drug dosing, device design, trial duration) as specified in the protocol will result in a clinically meaningful treatment effect
- For clinical investigations involving greater than minimal risk[b] but presenting the prospect of direct benefit to individual subjects:
  - the risks must be justified by the anticipated benefit and
  - the risk/benefit must be as favorable as available alternatives

[a]50.52; [b]Minimal risk is a risk normally encountered in the daily lives, or in the routine medical or psychological examination, of healthy children

Parent/Guardian Permission

- Before a child may be enrolled in a clinical investigation, the permission of the child's parent(s) or guardian(s) must be granted and obtained in accordance with regulations that govern obtaining informed consent[a]
- Informed consent:
  - Is a process
  - Should include the opportunity to ask questions and consider participation
  - Should continue to provide information as a trial progresses and the situation requires[b]
- The parental permission form must contain adequate information to allow the parent(s) or guardian(s) to make an informed decision[b]

[a] Permission must be obtained in compliance with 21 CFR 50 Subpart B, 21 CFR 50.3(r) and 21 CFR 50.55

[b] Informed Consent: Guidance for IRBs, Clinical Investigators, and Sponsors, August 2023

Ethical Considerations for AWT Trials

Ethical Analysis of an AWT Trial

- An AWT trial would expose neonatal subjects to more than a "low" risk[a]

  Therefore:[b]

  1. Enrollment of a neonate in an AWT trial must offer a prospect of direct clinical benefit to each subject, AND
  2. The risks of the AWT trial must be justified by the anticipated benefit to the subject, AND
  3. The relation of the anticipated benefit(s) to the risk(s) must be as favorable as that offered by clinical standard of care, AND
  4. Parental permission must be granted[c]

- The anticipated risks and benefits of each research-related intervention and procedure in an AWT trial should be evaluated individually and collectively to ensure the research risks do not exceed the allowable risk thresholds

[a]21 CFR 50.53; [b]Unless the protocol is referred by an IRB for review by a federal panel and allowed to proceed in accordance with 21 CFR 50.54; [c] 21 CFR 50.52

Analysis of Prospect of Direct Benefit

- Prospect of direct benefit for an AWT should be based on data that support:
  1. Proof of concept (may include data from nonclinical studies, relevant clinical trials, and clinical experience)
  2. The device design and device performance characteristics are likely to have the intended treatment effect
  3. The duration of the use of the device is sufficient to have a measurable impact on a meaningful clinical outcome
- Data to support prospect of direct benefit should provide evidence that the use of the AWT is likely to increase survival or reduce critical morbidities for the enrolled neonatal subject

Analysis of Risks

- Assessment of risk is predicated on adequate safety data
  - Data should be adequate to determine the probability and magnitude of risks associated with an AWT device and the risks of other trial interventions and procedures
- The acceptability of the risks must be evaluated in the context of the anticipated benefits:
  - The risks of an AWT device must be justified by the anticipated benefit(s) to the individual neonatal subject, AND
  - The anticipated benefit/risk profile must be as favorable as routine clinical care for the neonatal subject of equivalent gestational age

    Survival and morbidity rates of the proposed study population should be considered
  - The potential risks of the procedures and interventions in the trial must be evaluated both individually and collectively

Parental Permission/Informed Consent

- Informed consent must be sought only under circumstances that
  - provide the parent(s) or guardian(s) sufficient opportunity to ask questions and consider whether to allow their child to participate in the trial
  - minimize the possibility of undue influence*
- Challenges in obtaining parental permission are anticipated
- These may include:
  - A parent may also be a potential research subject (i.e., the pregnant subject)
  - Therapeutic misconception
  - The parent(s) may perceive pressure to consent to experimental procedures
  - Emotional circumstances under which informed consent may be obtained

*21 CFR 50.20

Summary (1)

- FDA's human subject protection regulations governing enrollment of children in clinical investigations are intended to
  - Support evaluation of the safety and effectiveness of medical products to ensure the health and well-being of children AND
  - Ensure that the risks of research participation are reasonable and that higher risks are justified by the anticipated benefit to each individual pediatric subject
- Although an early feasibility study (EFS) of an AWT may be reasonable, an EFS that enrolls children must be compliant with the Additional Safeguards for Children in Clinical Investigations, 21 CFR 50, subpart D

Summary (2)

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

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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 Study Considerations for Artificial Womb Technology Devices
  Annabelle Crusan DVM, MS


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