

Exploratory Trials in Vulnerable Populations

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General Ethical Judgment:

- ▶ **Children and decisionally incapable adults should be enrolled in clinical trials only when the risks are low; OR**
 - ▶ **the research offers subjects a potential for direct benefit that is comparable to any alternative treatments available to them.**
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US Pediatric Research Regulations

- ▶ IRBs may approve pediatric studies presenting:
 - ▶ minimal risk (comparable to risks of ordinary life, routine medical care);
 - ▶ greater than minimal risk and prospect of direct benefit to subjects;
 - ▶ minor increase over minimal risk
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Otherwise Unapprovable Studies

- ▶ Approvable by DHHS Sec or FDA Comm'r and IRB after
 - ▶ Consultation with appropriate experts and opportunity for public comment finds that the study will:
 - ▶ provide knowledge on serious pediatric condition; and
 - ▶ be conducted “in accordance with sound ethical principles”
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Adults Lacking Decision-Making Capacity

- ▶ No regulations, but general ethical recommendations for similar protections
- ▶ E.g., National Bioethics Advisory Committee:
 - ▶ exclude incapable adults from studies presenting greater than minimal risk and no prospect of direct benefit (unless = prior competent consent)

Why Special Protections?

- ▶ “Children’s cognitive, psychological, and social immaturity limits their ability to understand what is involved in a research trial and to make sound decisions about participation.”
- ▶ de Melo–Martin et al., Novel Therapies, High–Risk Pediatric Research, and the Prospect of Direct Benefit: Learning from the Ethical Disagreements, *Molecular Biology* (2012)

Equitable Subject Selection

- ▶ **subjects who are capable of informed consent (i.e., competent adults) should be enrolled prior to subjects who cannot consent (children & impaired adults), assuming no strong scientific justification to enroll children or impaired adults**
 - ▶ **when such justification exists, should prefer older children and mildly impaired adults over those less able to participate in choice**
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Ethical Considerations

- ▶ **Choice to participate in higher-risk study purely to advance knowledge should be made by person bearing the risk**
 - ▶ **Direct benefit is individual health benefit produced by study intervention (not collateral benefits such as additional health assessments that can accompany trial)**
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Classifying FIH Studies

- ▶ Minimal risk? rare
 - ▶ Minor increase over minimal risk? rare
 - ▶ Most present more than minor increase over minimal risk → must be prospect of direct benefit to vulnerable subjects
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What Is Sufficient Evidence?

- ▶ “There is no consensus on the quality or quantity of nonclinical or adult evidence required to support direct benefit in pediatric FIH study.”
- ▶ Roth–Cline et al., Ethical Considerations in Conducting Pediatric Research, *Pediatric Clinical Pharmacology* (2011)

Final Considerations

- ▶ **Design of phase I trials – typically not designed to measure direct benefit**
 - ▶ **Expert opinion**
 - ▶ **Objective evidence supporting such opinion**
 - ▶ **Without such evidence, require independent expert evaluation of whether trial justified (as provided in pediatric regulations)**
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