Overview of FDA Perspective on the Ethics of Stem Cell Therapy

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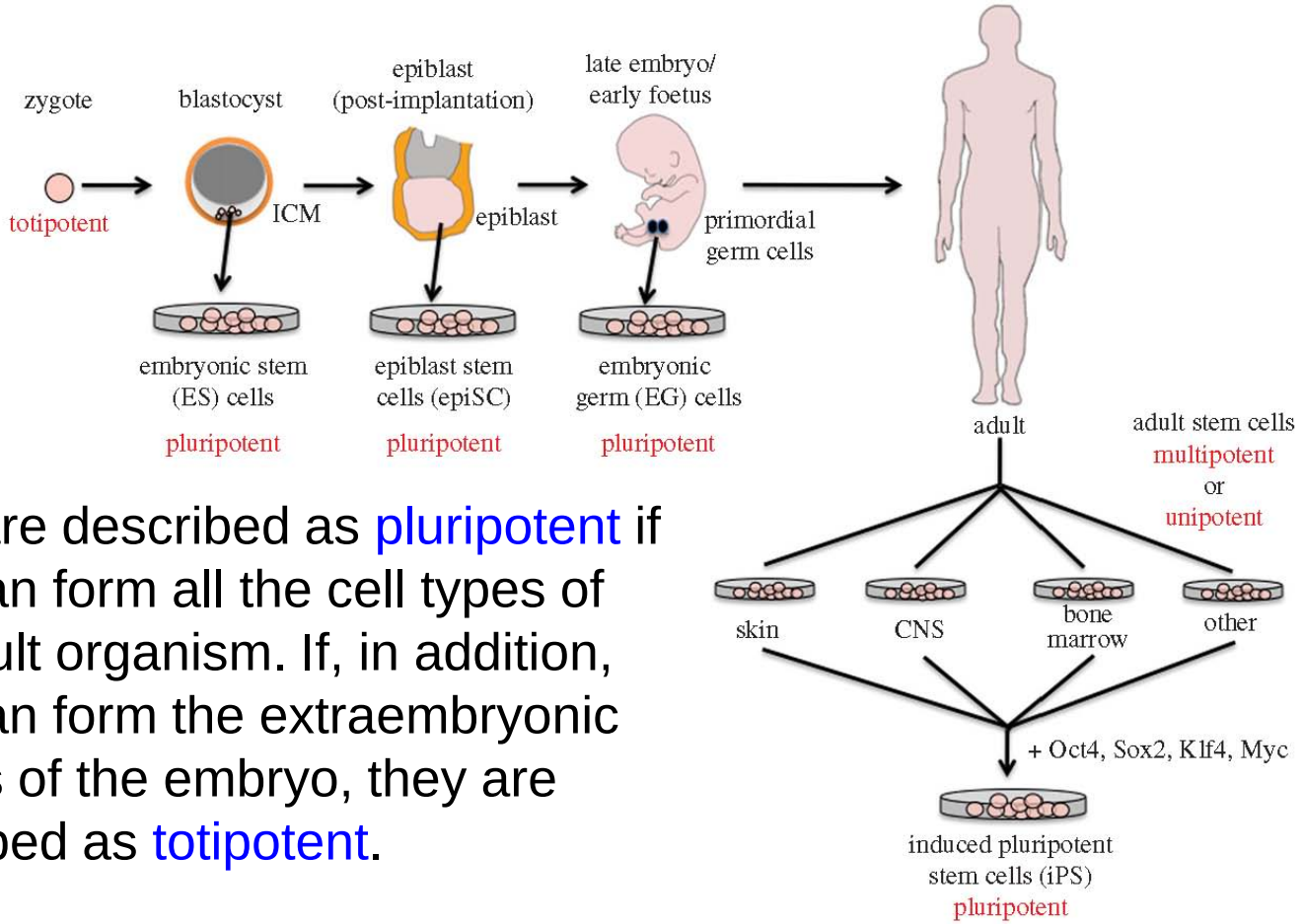
Disclosure

- The views expressed in this presentation are those of the speaker and do not necessarily represent the policy of either the Food and Drug Administration or the Department of Health and Human Services.
- The speaker has no financial interests to disclose with respect to the contents of this presentation.

Topics

- Origin and Clinical Uses of Stem Cells (SC)
- Ethical Issues in SC Research
  - NIH Criteria for hESC Registration
  - Evolving Debate over hESC/iPSC
- ISSCR Guidelines for SC Clinical Trials
- Ethics of FDA-Regulated Clinical Trials

Origin of Stem Cells



Cells are described as pluripotent if they can form all the cell types of the adult organism. If, in addition, they can form the extraembryonic tissues of the embryo, they are described as totipotent.

Watt and Driskell Philos Trans R Soc Lond B Biol Sci 2010;365:155-163.

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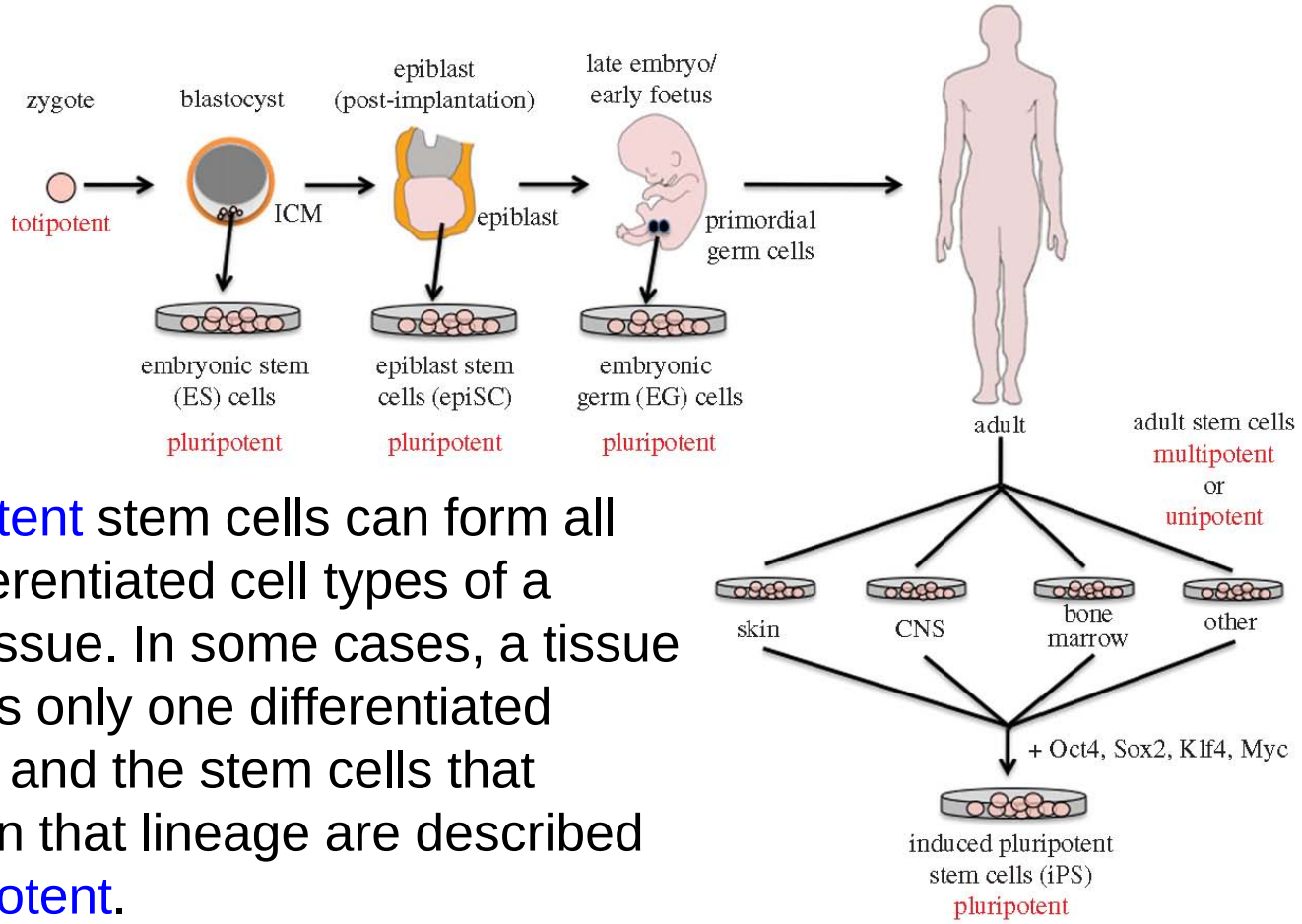

Multipotent stem cells can form all the differentiated cell types of a given tissue. In some cases, a tissue contains only one differentiated lineage and the stem cells that maintain that lineage are described as unipotent.

Watt and Driskell Philos Trans R Soc Lond B Biol Sci 2010;365:155-163.

Clinical Uses of Stem Cells

- Hematopoetic Stem Cell Transplantation
  - Bone marrow, peripheral or cord blood
- Ex vivo expansion of human epidermal and corneal stem cells
- Ex vivo manipulation (gene transfer) of autologous human stem cells
- Stem cell transplantation to foster tissue repair (CNS, spinal cord, cardiac, other)

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Focus of Human Stem Cell Debate

- Derivation of pluripotent human stem cell (hSC) lines from oocytes and embryos is fraught with disputes regarding the onset of human personhood and human reproduction.
- Several other methods of deriving stem cells raise fewer ethical concerns. The reprogramming of somatic cells to produce induced pluripotent stem cells (iPS cells) avoids the ethical problems specific to embryonic stem cells.
- With any hSC research, however, there are difficult dilemmas, including consent to donate materials for hSC research, early clinical trials of hSC therapies, and oversight of hSC research.

Lo and Parham Endocr Rev 2009;30(3):204-213.

Ethical Issues in SC Research

TABLE 1. Ethical issues at different phases of stem cell research

Phase of research	Ethical issues
Donation of biological materials	Informed and voluntary consent
Research with hESCs	Destruction of embryos Creation of embryos specifically for research purposes 1. Payment to oocyte donors 2. Medical risks of oocyte retrieval 3. Protecting reproductive interests of women in infertility treatment
Use of stem cell lines derived at another institution	Conflicting legal and ethical standards
Stem cell clinical trials	Risks and benefits of experimental intervention Informed consent

Lo and Parham Endocr Rev 2009;30(3):204-213.

NIH Definition of hESCs

- "human embryonic stem cells (hESCs)" are pluripotent cells that are derived from early stage human embryos, up to and including the blastocyst stage, are capable of dividing without differentiating for a prolonged period in culture, and are known to develop into cells and tissues of the three primary germ layers.

Federal Register 2010;75(35):8085-86.

NIH Criteria for hESC Registration

- Principle of “Separation” (cf. use of fetal tissue)
  - Created for reproductive (and not research) purposes
  - Reproductive decisions free from influence of research team
- Donors provided informed and voluntary written consent
  - Disclosure of Options; Voluntary Choice; Right of Withdrawal; Consent at Time of Donation; Specific Elements of Informed Consent.
- Review of Stem Cell Lines existing prior to July 7, 2009
  - Review by NIH Working Group
  - Limited to "spare IVF embryos"
  - Voluntary Written Consent

Federal Register 2009;74(128):32170-75.

NIH Criteria for hESC Registration

- Derivation and Use Restrictions
  - Stem cell lines derived from sources other than “spare IVF embryos” are ineligible for NIH funding, including:
    - Parthenogenesis (stimulation of unfertilized egg to produce a human embryo)
    - Somatic cell nuclear transfer into human oocytes (cloning)
    - Creation of human embryos specifically to derive hESC lines
    - Chimeras or hybrids (introduction of hSC into nonhuman primate blastocysts, and animal breeding where introduction of hESCs or human iPSCs might contribute to the germ line)
  - Permits NIH-funded research on SC lines derived from embryos discarded following preimplantation genetic diagnosis

Federal Register 2009;74(128):32170-75.

Regulation of iPSC Research

Table 1 | Emerging themes in regulation of iPSC research

	Canada	California (US)	UK	Japan	International (ISSCR)
Consent	Requires free and informed consent, provided voluntarily and with full disclosure of all information relevant to the consent	Requires specific and informed consent	Requires free and informed consent, although standard consent allows for unrestricted use in research. Not clear if informed consent requirement can be waived when donors are unable to give consent	Requires free and informed consent	Voluntary, contemporaneous and informed consent required (with a few exceptions for stored tissue samples)
Identity	Requires anonymity (for nonautologous lines)	Using identifiable cells requires notification to a designated SCRO	Unclear, although importance of phenotype/genotype relationships, and therefore traceability, is recognized	Use of identifiable cells possible, but requires IRB approval	Use of identifiable cells requires additional and comprehensive review
Use: derivation of human germ cells	Permitted, subject to regulation, but cannot create an embryo for research purposes; will trigger application of *AHRA*	Requires additional ethics review	No restrictions on derivation; can create (but not implant) an embryo, with a license; limit of 14 days *in vitro*	Permitted, subject to strict oversight; fertilization prohibited	Unclear or not addressed
Use: transplantation into humans	Requires SCOC approval	Requires additional ethics review	Subject to oversight, GTAC and MHRA approval	Requires additional ethics review; updated guidelines expected in 2010	Requires additional and comprehensive review
Use: grafting into nonhuman animals	Requires SCOC approval	Requires additional ethics review	Requires local ethics review and Home Office license	Requires approval and oversight	Subject to review, approval and ongoing monitoring
Clinical trials with humans	Requires overwhelming evidence from preclinical models for safety and efficacy[a]	Requires approval and oversight	Requires approval and oversight and overwhelming evidence from preclinical models for safety and efficacy[a]	Requires approval and oversight; regulation under development	Requires additional and comprehensive review

The wording for each jurisdiction is not standardized but is instead meant to paraphrase the relevant regulation or guideline, in order to capture subtle variations.

[a]Could make autologous clinical trials a challenge.

Caulfield et al. Nature Methods 2010;7(1):28-33.

Evolving Debate

- "While issues regarding the moral status of embryos remain relevant, the field is evolving and extending its consideration to current and emerging issues including patenting, policy approaches, procurement of embryos, stem cell tourism and new sources of stem cells, among others."

Zarzeczny and Caulfield Stem Cell Rev and Rep 2009;5:96-101.

FDA Perspective

- "Researchers who hope ultimately to develop products subject to FDA regulation may find it prudent to comply with NIH guidelines, since FDA requires assurance that cells were derived according to ethically accepted standards."
  - Meyer and Fossett KIEJ 2009;19(3):289-307.
- FDA may be "agnostic" about source of stem cells, apart from assurance of product characteristics. NIH funding limits do not apply to hESCs derived using private funding.
- "From a regulatory perspective, FDA considers stem cell-based products to be somatic cellular therapies that do not warrant a distinct regulatory approach."
  - Fink Science 2009;324:1662-63.

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ISSCR Guidelines for Responsible Translational HSC Research

Major Principles

- Independent Review and Oversight
- Voluntary Informed Consent
- Patient Monitoring/Adverse-Event Reporting
- Medical Innovation
- Social Justice and Other Aspirational Goals

Hyun et al. ISSCR Guidelines. Cell Stem Cell 2008;3:607-609.

Independent Review and Oversight

- "Individuals with stem-cell-specific expertise [must] be involved in the scientific and ethical review at each step along the translational research process."
- Such "individuals… are best able to assist investigators and human research review committees to assess the scientific underpinnings of the clinical trial protocol; the in vitro and in vivo preclinical studies that form the basis for proceeding to the clinical study; and the risks of abnormal product function, proliferation, and/or tumor development."
- "Rigorous preclinical testing in animal models - whenever possible for the clinical condition and the tissue physiology being studied - is especially important."

Hyun et al. ISSCR Guidelines. Cell Stem Cell 2008;3:607-609.

Voluntary Informed Consent

- "Special emphasis [should] be placed on the unique risks of stem-cell-based clinical research; …include sensitivities surrounding the source of cellular products, tumor formation, immunological reactions, unexpected behavior of the cells, and unknown long-term health effects."
- "Research volunteers must be educated about the realistic potential for therapeutic benefit as they may have recourse to…therapeutic alternatives and…[have] misconceptions about the potential for therapeutic efficacy."
- "Research subjects' comprehension of relevant information - especially of the risks and uncertainties – [should] be evaluated at the time of obtaining consent."

Hyun et al. ISSCR Guidelines. Cell Stem Cell 2008;3:607-609.

Medical Innovation

- "Exceptional circumstances [may] allow clinicians to attempt medically innovative care in a very small number of seriously ill patients, subject to stringent oversight."
  - independent peer review, institutional accountability, rigorous informed consent, close patient monitoring, transparency, timely adverse-event reporting, and a commitment to move to a formal clinical trial in a timely manner after, at most, a few patients.
- "Holding some current SC clinics to [ISSCR guidelines] would identify significant shortcomings and… question the legitimacy of… attempts at providing 'innovative care'."
- Opinion: The default position should be to conduct clinical trials of stem cell transplantation under an IND.

Hyun et al. ISSCR Guidelines. Cell Stem Cell 2008;3:607-609.

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Moving Forward to Clinical Trials

- "FDA considers stem cell- based products to be somatic cellular therapies that do not warrant a distinct regulatory approach."
  - Fink Science 2009;324:1662-63.

Clinical Hold (21 CFR 312.42(b))

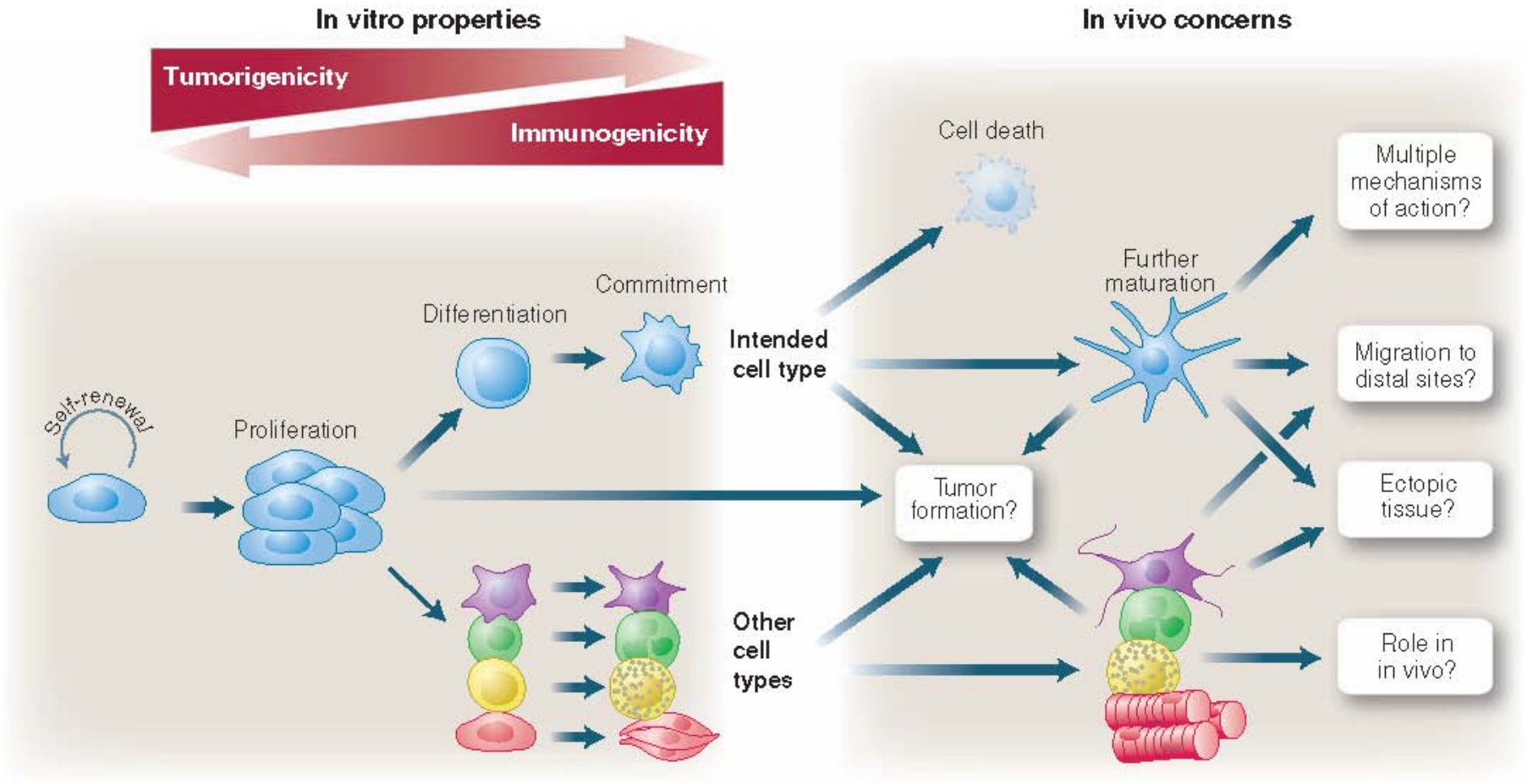
- "Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury."
- "The plan or protocol for the investigation is clearly deficient in design to meet its stated objectives."

Assessment of "Reasonable"

- "To determine whether it is reasonable to grant permission for a clinical trial to proceed, FDA evaluates potential risk based on results derived from analytical assessment of product characteristics as well as preclinical proof-of-concept and safety testing, which, collectively, are considered within the context of a proposed clinical study."

Fink. FDA Regulation of SC-Based Products. Science 2009;324:1662-63.

Risk assessment of stem cell-based products



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Preclinical Animal Testing

- Important design elements for preclinical animal studies
  - Selection of relevant disease/injury models
  - Testing of product intended for clinical administration
  - Using route and method of delivery comparable to clinical plan
  - Optimal timing of intervention relative to disease/injury onset, and
  - Duration necessary to assess AE and durable biological activity
  - Need for immunocompetence modification of animal model
- Robust proof-of-concept preclinical data are valuable and informative, particularly when targeted clinical indication requires administration of SC product into vulnerable anatomic sites such as CNS, joint capsule, or myocardium

Fink. FDA Regulation of SC-Based Products. Science 2009;324:1662-63.

General Justification of Research Risk
(Adult and Pediatric*)

- Criteria for IRB approval of research.
  - Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result.
    - 21 CFR 56.111(a)(2)
- Principles of ICH GCP
  - Foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
    - Section 2.2

*Necessary but not sufficient for protecting children

Sham controlled studies in adults

- May be used in limited circumstances
  - Scientific need: discriminate patient outcomes caused by the test treatment from outcomes caused by patient and observer expectations (subjective endpoints)
- Involve more risk than the placebo control arm in drug trials
- Withholding of treatment should not lead to serious harm, such as death or irreversible morbidity (cf. ICH E-10 Choice of Control Group)
- If a sham procedure/treatment is being considered in a clinical investigation involving children, the requirements of 21 CFR Part 50 Subpart D also apply

Additional Protections for Children

- Research involving children either
  - must be restricted to "minimal"/"low" risk absent potential for direct benefit to the child, or
    - 21 CFR 50.51/53; ICH E-6 §4.8.14; CIOMS Guideline 9 (2002)
  - must present risks justified by anticipated direct benefits to the child, and which are as favorable as any available alternatives.
    - 21 CFR 50.52; CIOMS Guideline 8 (2002).
- There is broad international consensus on this basic framework (albeit with some variation).

Principle of Scientific Necessity

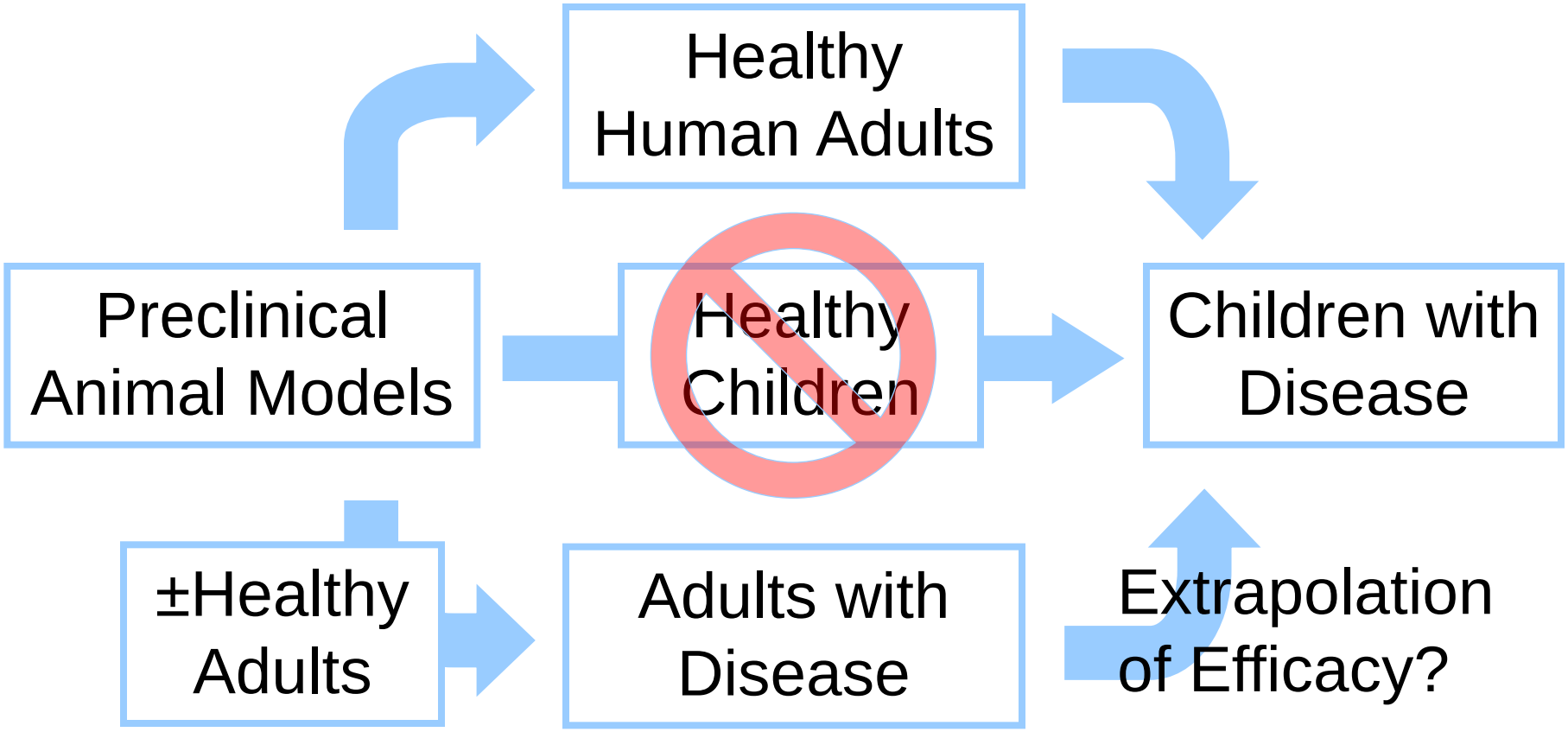
- Children should not be enrolled in a clinical investigation unless necessary to answer an important scientific question about the health and welfare of children.
  - Study design capable of answering question
    (e.g., sample size, control group, blinding, etc.)
  - Practical application: determine type and timing of clinical studies required for establishing “safe and effective” pediatric use (e.g., “extrapolation”)
  - Objective: "public health benefit" for children

21 CFR 56, Subpart C

- Equitable selection [21 CFR 56.111(b]
  - Subjects capable of informed consent (i.e., adults) should be enrolled prior to children
  - Do not enroll children unless essential (i.e., no other option, whether animal or adult human).
- Minimize Risks [21 CFR 56.111(a)(1)]
  - Eliminate any research procedures (as unnecessary) that do not contribute to scientific objective(s)

cf. 45 CFR 46, Subpart A

Pediatric Product Development



“Normal” or “routine” risks?

- National Commission defined “minimal risk” as those risks “normally encountered in the daily lives, or in the routine medical or psychological examination, of healthy children.”
- Although “healthy children” was deleted from the current definition, most ethicists and federal panels (e.g., SACHRP, IOM) agree with this limitation.
- The administration of an experimental product is neither routine nor minimal risk.
- Interventions and procedures that do not present a prospect of direct benefit must present a “low” (i.e., minor increase over minimal) risk.

National Commission - Introduction, Report on Research Involving Children (1978)

Minor Increase over Minimal Risk

- "Minor increase" refers to a risk which, while it goes beyond the narrow boundaries of minimal risk…, poses no significant threat to the child's health or well-being."
- "Given this conservative limit, the… promise of [substantial future benefits to children other than the subject] does justify research which goes beyond, but only slightly beyond, minimal risk."
- Interventions/procedures that do not present a prospect of direct benefit must present a "low" (e.g., minor increase over minimal) risk, and limited to children with a "disorder or condition" in 21 CFR 50.53 (absent a federal exception).

National Commission - Report on Research Involving Children, pages 139-40 (1977)

How is "disorder or condition" defined?

- The US federal research regulations offer no definition of either "disorder" or "condition."
- A Proposed Definition
  - "A specific (or set of specific)… characteristic(s) that an established body of scientific evidence or clinical knowledge has shown to negatively affect children's health and well-being or to increase their risk of developing a health problem in the future."

Institute of Medicine (US): Recommendation 4.3†

† IOM, Ethical Conduct of Clinical Research Involving Children (2004)

Use of Sham Controls in Pediatrics

- Sham procedures do not offer a prospect of direct benefit to the enrolled child.
- The risk to which a pediatric sham control group is exposed must be restricted to no more than a "minor increase over minimal risk" (21 CFR 50.53)
  - Example: single or perhaps multiple IM injections
- This approach is consistent with, but more restrictive than, the 2008 Declaration of Helsinki and ICH E-10 Choice of Control Group.

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Pediatric Drug Development

- If the experimental intervention is more than a minor increase over minimal risk, either
  - the intervention must offer a prospect of direct benefit (21 CFR 50.52) or
  - the IRB must refer the protocol for federal review under 21 CFR 50.54.
- Otherwise, the clinical investigation is not approvable under Subpart D.

"First-in-Children" under 21 CFR 50.52

- Any clinical investigation [presenting] more than minimal risk to children… by an intervention [with] the prospect of direct benefit… may involve children as subjects only if:
  - risk justified by anticipated benefit to subjects;
  - relation of anticipated benefit to risk as favorable to subjects as… available alternative approaches.
- Can one infer a sufficient prospect of direct benefit from animal studies alone to justify a "first-in-children" clinical trial under 21 CFR 50.52?

Prospect of Direct Benefit (PDB)

- A "benefit" is "direct" if it:
  - Accrues to individual subject enrolled in clinical trial;
  - Results from research intervention being studied (and not from other clinical interventions included in protocol)
  - Word "benefit" often modified by "clinical" to indicate that "direct benefit" relates to health of enrolled subject.
- PDB is based on the "structure" of an intervention (i.e., dose, duration, method of administration, etc.), and not the investigator's "intent" or the primary objective of the protocol.

Prospect of Direct Benefit (PDB)

- Evidence for PDB "weaker" than evidence for "efficacy"
- PDB may be based on surrogate endpoint (e.g., immune response) if sufficient evidence exists linking chosen surrogate to clinical efficacy.
- Need empirical evidence of sufficient "prospect of direct benefit" to justify exposure to the risks.
  - Complex quantitative and qualitative judgment
  - Risk/benefit evaluation similar to clinical practice
  - Contextual justification of risk by PDB can include:
    - Importance of "direct benefit" to subject
    - Possibility of avoiding greater harm from disease
    - Justification set in context of disease severity (e.g., degree of disability, life-threatening) and availability of alternative treatments.

Drugs Intended to Treat Life-threatening and Severely-debilitating Illnesses

- "FDA's application of the statutory standards for marketing approval shall recognize the need for a medical risk-benefit judgment in making the final decision on approvability. As part of this evaluation, …FDA will consider whether the benefits of the drug outweigh the known and potential risks of the drug and the need to answer remaining questions about risks and benefits of the drug, taking into consideration the severity of the disease and the absence of satisfactory alternative therapy."

21 CFR 312.84 (Revised April 1, 2009)

Proposal: Sliding Threshold

- Data (whether animal or human adult) necessary to establish sufficient prospect of direct benefit (PDB) to justify the risks varies with the severity of the disease and the adequacy of alternate treatments.
- Structure (generally insufficient for PDB)
- Function (based on mechanism of action)
  - Molecular target (receptor); Biomarker (RNA/protein); Physiologic pathway (metabolic product)
  - Transgenic Technology (human target + mouse)
- Clinical Disease Model
  - Surrogate endpoints
  - Clinical endpoint (e.g., survival) (FDA “Animal Rule”)

Maximum Recommended Starting Dose (MRSD) for "first-in-human" clinical trials

- MRSD frequently based on "no observed adverse effect levels" (NOAEL) in the tested animal species, and conversion of NOAELs to a human equivalent dose with the application of a safety factor.
- Risk/potential benefit for NOAEL "safe starting dose" may not be equivalent to MRSD dose associated with greatest efficacy in animal studies.
- A NOAEL dose may not offer sufficient PDB to justify "first-in-children" clinical trial, and the MRSD may present greater risks.

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