Research Involving Children

(Focusing on FDA Regulations)

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Disclaimer

- The views expressed in this presentation do not necessarily represent the policies of the Food and Drug Administration or the Department of Health and Human Services.
- Robert Nelson has no financial conflicts of interest to disclose.

Topics Covered

1) Regulatory Bioethics and the Basic Ethical Principles of Pediatric Research (9 slides)
2) Extrapolation as an application of the Principle of Scientific Necessity (6 slides)
3) Prospect of Direct Benefit and Component Analysis
   - ✓ Case Study: Insertion of Indwelling Percutaneous Central Line for Placebo Administration (13 slides)
4) The “low risk” and “higher risk” pathways for pediatric product development (with examples) (17 slides)

Regulatory Bioethics?

- Takes place within an Agency which has regulatory oversight over a broad range of investigational and marketed products
- Must attend to the regulations governing that Agency, e.g., human subject protections (21 CFR parts 50 and 56), and other regulations found, for example, in 21 CFR part 312 (investigational new drugs)
  - Regulatory framework grounded in a set of ethical principles, as framed by The National Commission (late 1970s)
  - Difference between “should” (interpretation) and “must” (regulation)
- Regulatory bioethics should be conducted using an open and deliberative process, and use resources that have been produced by such processes (wherever possible)

FDA-Regulated Clinical Investigation

- Does use of an investigational product for one patient qualify as a "clinical investigation" if there is no intent to produce "generalizable knowledge"? *Yes.*
  - The administration of a "test article" to one "human subject" is a "clinical investigation" provided it is subject to prior submission under the IND regulations [21 CFR 50.3(c)]
  - A "test article" is any drug or biologic for human use that is subject to regulation under the Food, Drug and Cosmetic Act or the Public Health Service Act [21 CFR 50.3(j)]
  - A "human subject" is an individual who is a recipient of the test article [21 CFR 50.3(g)]
- FDA regulates research through regulating products.

Basic Ethical Framework in Pediatrics

1. Children should only be enrolled in research if the scientific and/or public health objective(s) cannot be met through enrolling subjects who can consent personally (i.e., adults).
2. Absent a prospect of direct therapeutic benefit, the research risks to which children are exposed must be "low."
3. 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.
4. Vulnerable populations unable to consent (including children) should have a suitable proxy to consent for them.

“Nested” Protections

1: Scientific Necessity

4: Parental Permission

4: Child Assent

2,3: Appropriate Balance of Risk and Benefit

Ethical Principle of Scientific Necessity

- Children should not be enrolled in a clinical trial unless necessary to answer an important scientific and/or public health question about the health and welfare of children
  - Practical application (using extrapolation): determine the type (and timing) of clinical studies required to establish "safe and effective" pediatric use of drugs or devices
- Derives from requirements for equitable selection†
  - Subjects capable of informed consent (i.e., adults) should generally be enrolled prior to children

† Minimize Risks and Equitable Selection [US 21 CFR 56.111(a)(1) and (b)]

General Justification of Research Risk (Both Adult and Pediatric)

- Criterion 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); 45 CFR 46.111(a)(2)
- This general criterion is modified by the additional protections for children enrolled in clinical investigations and/or research in that there is a limit to the risk that knowledge can justify.

Additional Safeguards for Children

21 CFR 50 Subpart D

(Appropriate Balance of Risk and Benefit)

- Research involving children either
  - must be restricted to “minimal” risk or a “minor increase over minimal” risk absent a potential for direct benefit to the enrolled child, or
    - 21 CFR 50.51/53;45 CFR 46.404/406
  - must present risks that are justified by anticipated direct benefits to the child; the balance of which is at least as favorable as any available alternatives.
    - 21 CFR 50.52;45 CFR 46.405

Additional Safeguards
21 CFR 50 / 45 CFR 46, Subpart D

- Not involving greater than minimal risk (§50.51; §46.404)
- Greater than minimal risk but presenting the prospect of direct benefit to individual subjects (§50.52; §46.405)
- Greater than minimal risk, no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about subjects' disorder or condition (§50.53; §46.406)
- Not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (§50.54; §46.407)[†]
- Requirements for permission by parents or guardians and for assent by children (§50.55; §46.408)

Two Key Concepts

- Prospect of Direct Benefit
  - The risks to which a child may be exposed depend on whether the intervention does or does not offer that child a prospect of direct benefit.
  - Thus, defining and assessing the possibility of direct (clinical or therapeutic) benefit is an essential aspect of the ethical acceptability of the (interventions included in a) research protocol.
- Component Analysis
  - A protocol may (and usually does) contain multiple interventions or procedures, some that offer a prospect of direct (clinical) benefit and others that do not.
  - These interventions and procedures must be analyzed and justified separately (i.e., as “components” of the protocol).
  - Thus, a protocol may include components that must be evaluated under 21 CFR 50.52 and others that must be evaluated under 21 CFR 50.53.

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Substantial Evidence of Effectiveness

- "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved" [1962]
  - Section 505(d), Food, Drug & Cosmetic Act
  - "Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness."
- "FDA has been flexible…, broadly interpreting the statutory requirements to the extent possible where the data on a particular drug were convincing."
  - In 1997, "Congress amended section 505(d)… to make it clear that [FDA] may consider 'data from one adequate and well-controlled clinical investigation and confirmatory evidence' to constitute substantial evidence if FDA determines that such data and evidence are sufficient to establish effectiveness."
  - In doing so, "Congress confirmed FDA's interpretation of the statutory requirements for approval."

FDA Guidance - May 1998 (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm078749.pdf)

Use of Extrapolation

- The use of extrapolation was first introduced in the 1994 Pediatric Labeling Rule, but did not have much of an impact until the pediatric incentives (BPCA “exclusivity” in 1997, and PREA “requirement” in 2003) were established.
- “A pediatric use statement may also be based on adequate and well-controlled studies in adults, provided that the agency concludes that the course of the disease and the drug's effects are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. Where needed, pharmacokinetic data to allow determination of an appropriate pediatric dosage, and additional pediatric safety information must also be submitted.”

59 Fed. Reg. 64241 1994

Extrapolation

- Generally understood, extrapolation is an inference from the known to the unknown.
  - to use known facts as the starting point from which to draw inferences or conclusions about something unknown
  - to predict by projecting past experience or known data
- Extrapolation of pediatric efficacy has specific legal definition.
  - "If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, [FDA] may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies." (21 CFR §355c)
- A powerful tool to be used carefully.

Summary of Approaches to Extrapolation

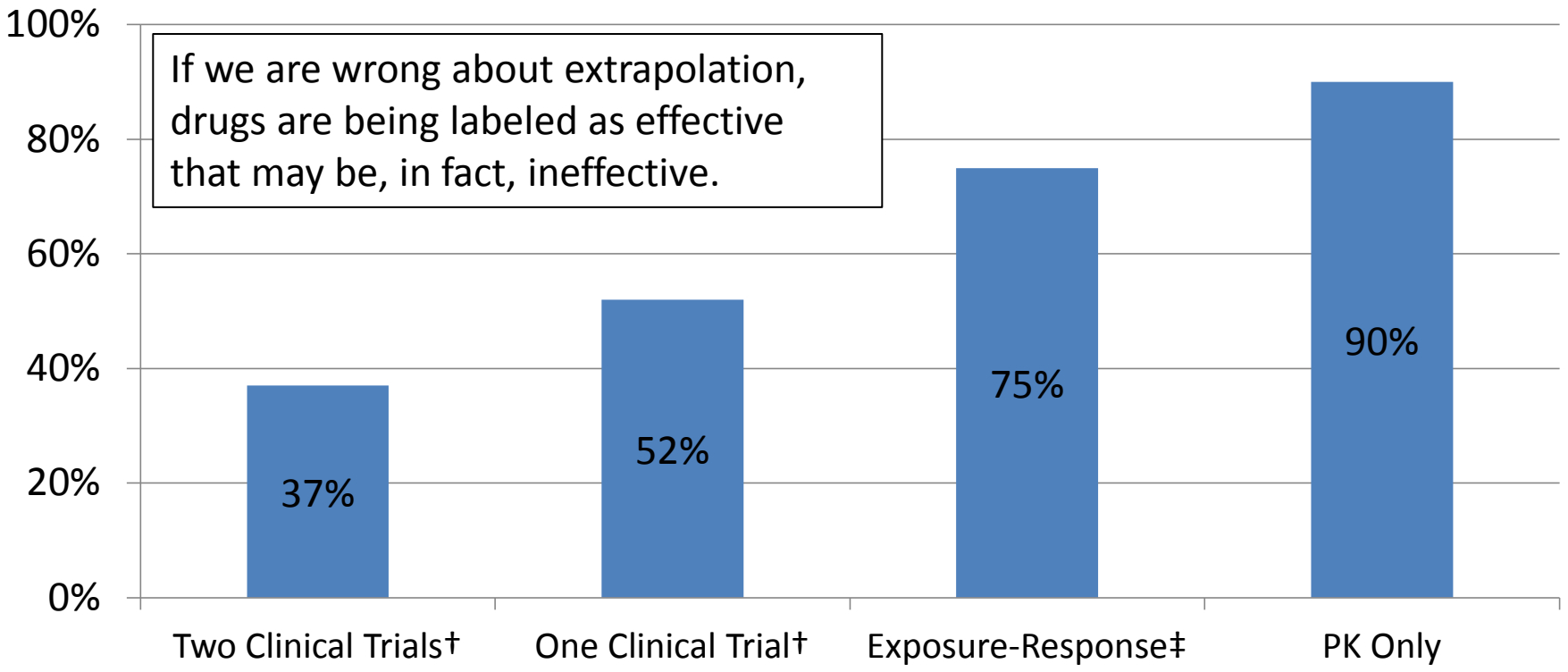
(Assessment of 166 products between 1998-2008)

Extrapolation	Supportive Evidence Requested From Pediatric Studies	Products n/N (%)	New or Expanded Indication
None 17%	Two adequate, well-controlled, efficacy and safety trials plus PK data.	19/166 (11)	7/19 (37)
	Oncology products only: sequential approach starting with phase 1/2. Do not proceed if no evidence of response.	10/166 (6)	3/10 (30)
Partial 68%	Single, adequate, well-controlled, efficacy and safety trial (powered for efficacy) plus PK data.	67/166 (40)	35/67 (52)
	Single, controlled or uncontrolled, efficacy and safety trial (qualitative data) plus PK data.	20/166 (12)	15/20 (75)
	Single exposure-response trial (not powered for efficacy) plus PK and safety data, PK/PD and uncontrolled efficacy plus safety data, or PK/PD plus safety data.	26/166 (16)	19/26 (73)
Complete 14%	PK and safety data.	10/166 (6)	9/10 (90)
	Safety data only.	14/166 (8)	6/14 (43)

Adapted from Table 1: Dunne J et al. Pediatrics 2011;128;e1242.

New or Expanded Indication

A powerful tool to be used carefully!

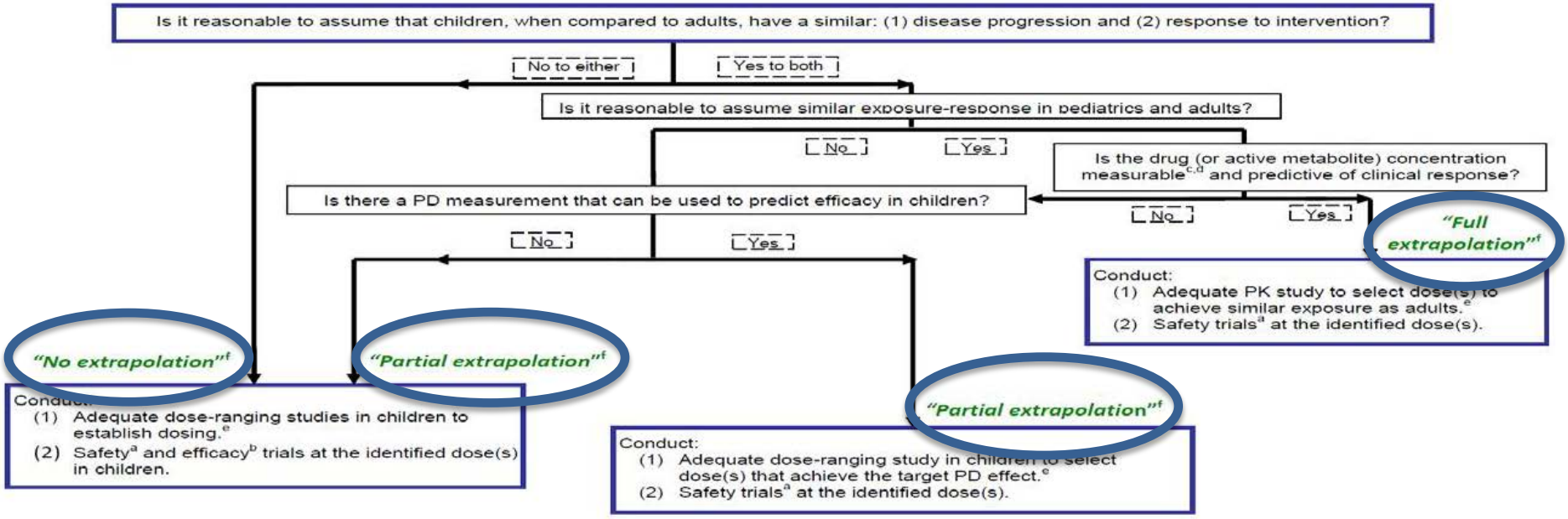


† Adequate, well-controlled, efficacy and safety trial(s) (powered for efficacy), plus PK data.

‡ Single, controlled or uncontrolled, efficacy and safety trial (qualitative data) plus PK data; or single exposure-response trial (not powered for efficacy) plus PK and safety data, PK/PD and uncontrolled efficacy plus safety data, or PK/PD plus safety data.

Adapted from Table 1: Dunne J et al. Pediatrics 2011;128;e1242

Pediatric Study Planning & Extrapolation Algorithm



Footnotes:

a. For locally active drugs, includes plasma PK at the identified dose(s) as part of safety assessment.
b. For partial extrapolation, one efficacy trial may be sufficient.
c. For drugs that are systemically active, the relevant measure is systemic concentration.
d. For drugs that are locally active (e.g., intra-luminal or mucosal site of action), the relevant measure is systemic concentration only if it can be reasonably assumed that systemic concentrations are a reflection of the concentrations at the relevant biospace (e.g., skin, intestinal mucosa, nasal passages, lung).
e. When appropriate, use of modeling and simulation for dose selection (supplemented by pediatric clinical data when necessary) and/or trial simulation is recommended.
f. For a discussion of no, partial and full extrapolation, see Dunne J, Rodriguez WJ, Murphy MD, et al. "Extrapolation of adult data and other data in pediatric drug-development programs." Pediatrics. 2011 Nov;128(5):e1242-9.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425885.pdf

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Prospect of Direct Benefit (PDB)

- A “direct benefit” of an experimental intervention or procedure should improve the health or well-being of the individual child.
- Whether intervention offers a “prospect of direct benefit” must be evidence-based (e.g., adult humans or animal disease models).
  - Do these data make us reasonably comfortable that children might benefit from this intervention/product? Is the dose and duration of treatment with the investigational drug sufficient to offer the intended benefit?
- Whether intervention offers PDB separate from whether PDB of sufficient probability, magnitude and type to justify the anticipated risks of the intervention, given the overall clinical context.
  - Risk/benefit evaluation is a complex judgment, similar to clinical practice.
  - Justification of appropriate balance of risk and potential benefit may include importance of “direct benefit” to child; possibility of avoiding greater harm from disease; degree of “tolerable” uncertainty; disease severity (e.g., degree of disability, life-threatening); and the availability of alternative treatments.

Component Analysis

- "To determine the overall acceptability of the research, the risk and anticipated benefit of activities described in a protocol must be evaluated individually as well as collectively."

  – The National Commission 1978

Simplification

- Procedures that present no more than minimal risk may or may not offer a prospect of direct benefit.
  - For example, a venipuncture for diagnostic blood work.
- Such procedures may be finessed when doing component analysis.
  - Caveat: numerous minimal risk procedures closely spaced together may exceed minimal risk (how many? how close?)

"Classic" component analysis

- A clinical investigation may include more than one intervention or procedure.
- Each intervention/procedure must be evaluated separately to determine whether it does/does not hold out the prospect of direct benefit to the enrolled child.
  - This "classic" approach is consistent with recommendations of the National Commission (1978) and the resulting regulations.
- Interventions or procedures that hold out the prospect of direct benefit should† be considered under 21 CFR 50.52.
- Interventions or procedures that do not hold out the prospect of direct benefit should† be considered under 21 CFR 50.51 or 50.53 (but not 50.52).

† Can be considered under 21 CFR 50.54 (thus "should" and not "must").

How is this "classic" component analysis different from what has been discussed in the literature?

- "Component Analysis$_w$" (with equipoise)
  - as proposed by Charles Weijer and Paul B. Miller (Nature Medicine, June 2004)
- "Net Risks" Test
  - as proposed by David Wendler and Frank G. Miller (Journal of Medical Ethics, August 2007)
  - refers to "component analysis$_w$" as "dual track"

"Component Analysis$_w$"

Adds "clinical equipoise" to evaluation of procedures that offer the prospect of direct benefit.

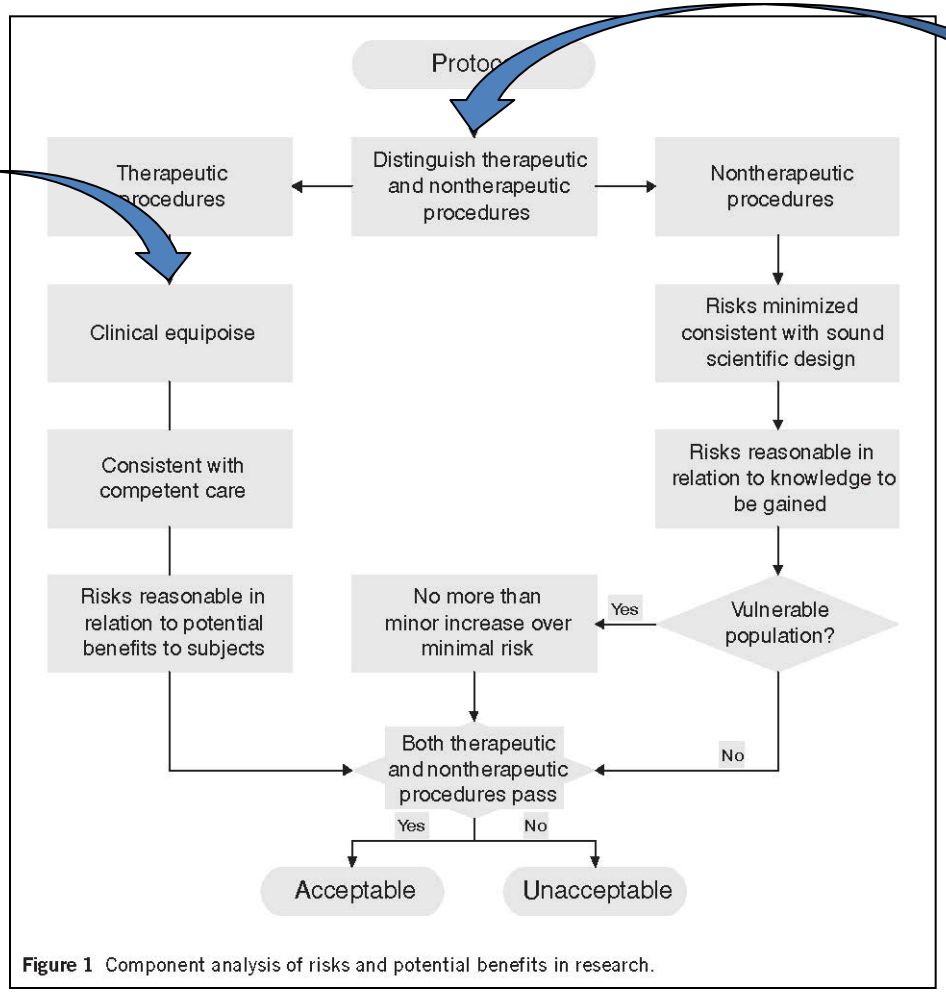


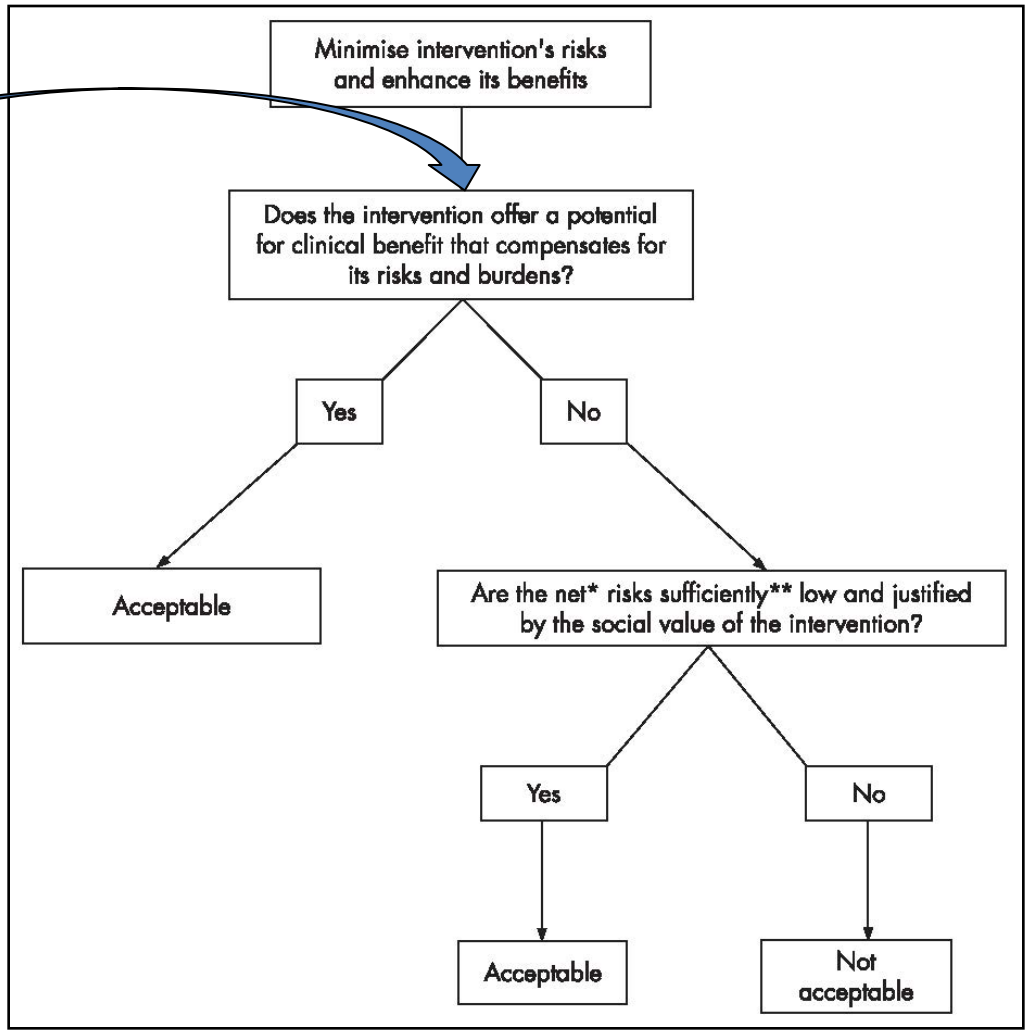
Figure 1 Component analysis of risks and potential benefits in research.

Distinguishes procedures by whether they do or do not offer the prospect of direct benefit.

Weijer, C. and P. B. Miller (2004). Nat Med 10(6): 570-573.

"Net Risks" Test

Distinguishes procedures by whether they do or do not offer the prospect of direct benefit.



Wendler, D. and F. G. Miller (2007). J Med Ethics 33(8): 481-486.

Clinical Equipoise

- Combines two separate concepts
  - Adequate "uncertainty" to justify the clinical trial.
  - Known effective treatment should be provided to subjects (based on a fiduciary "duty of care").
- Dispute about "component analysis$_w$" (i.e., "dual track") is primarily about whether a fiduciary "duty of care" should be the ethical basis for clinical research.
- Criteria in 21 CFR 50.52 bear resemblance to clinical equipoise, but do not entail that known effective treatment can never be withheld.

Assessment of the Debate

- Both the "dual track" (i.e., "component analysis$_w$") and "net risks" approach agree on the importance of assessing interventions/procedures individually as to whether they do or do not hold out a prospect of direct benefit.
- Neither approach offers advantages (and both have disadvantages) compared to a "classic" component analysis using categories in 21 CFR 50 subpart D.

Why is component analysis important?

- Failure to carefully distinguish the different components of a clinical investigation may result in the risks of an intervention or procedure that does not hold out the prospect of direct benefit exceeding the allowable ceiling of a minor increase over minimal risk (absent referral under 21 CFR 50.54).

Case Study: Background

- Multinational, placebo-controlled, study of an investigational product, in children ≥ 7 yrs. old.
- Product (or placebo) administered (double blind) by IV infusion over 4 hours each day for 14 days.
- FDA Pediatric Ethicist called by a concerned IRB Chair about proposal to use a peripherally inserted central catheter (PICC) to facilitate infusion.
- Upon review, the protocol and supporting documents provided by the sponsor to the FDA review division never mentioned PICC use.

FDA Assessment

- Insertion and use of a PICC for administration of the investigational product presented more than a minor increase over minimal risk.
- PICC use was justified in children receiving active product due to the prospect of direct benefit from the infusion.
- Children receiving placebo via PICC were offered no direct benefit from the infusion, but exposed to greater than a minor increase over minimal risk.
- Thus, PICC insertion and use in the placebo group was not in compliance with 21 CFR 50, subpart D (absent federal panel review under 21 CFR 50.54).

Use of Clinical Hold in Pediatrics

- Criterion for a clinical hold under 21 CFR 312.42: Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury.
- 21 CFR 50 subpart D sets the standards for "reasonable" risk exposure in pediatric clinical trials.
- If the risks of an intervention fall outside of these standards, the intervention exposes the enrolled child to an "unreasonable and significant risk of illness or injury."
- Thus, failure to be in compliance with 21 CFR 50 subpart D is sufficient grounds for imposing a clinical hold on a proposed or on-going pediatric clinical trial.

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Linking Science and Ethics

- To start a pediatric clinical trial, the ethical challenge is to establish sufficient evidence using either preclinical animal models or adult human clinical trials† to conclude:
  - "Low Risk" Pathway: Absent sufficient prospect of direct benefit, administration of investigational product to children presents an acceptably "low" risk (minimal, minor increase over minimal), or…
    - 21 CFR 50.51/50.53 (cf. ICH E-6 §4.8.14)
  - "Higher Risk" Pathway: Administration of investigational product to children presents a sufficient prospect of direct benefit to justify "higher" risks.
    - 21 CFR 50.52

† Data also may come from post-marketing pediatric (i.e., "off label") and/or adult data

"Low" Risk in FDA Regulations

- "Minimal risk" is defined as those risks "ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." [21 CFR 50.3(k)]
  - This definition should be indexed to the experience of "healthy children" (as originally proposed by The National Commission in 1978).
  - Generally, administration of an experimental drug/biological product is not considered "minimal" risk.
- Interventions/procedures that do not offer a prospect of direct benefit must be no more than a "minor increase over minimal risk;" and enrollment limited to children with a "disorder or condition" (absent a federal exception). [21 CFR 50.53]
  - There is no definition of a "minor increase over minimal risk." It is generally described as "slightly more" than minimal risk, and not presenting any "substantial risk."

Defining Acceptable Risks
(Note: Parent/Child Perspectives Important)

- The definition of risk as “the probability and magnitude of harm” gives the misimpression that risk assessment can be purely quantitative.
- The disvalue of a harm (or risk) cannot be quantified to where a uniform or comparative standard can be established.
- Defining “minimal risk” by using as a “reference” either “daily life” or “routine examinations” reduces a moral evaluation to a comparison of “factual” risks.
- The fact that a risk occurs outside of the research setting (whether in “daily life” or during “routine examinations”) does not make that same risk morally acceptable in the research context.

"Disorder or Condition"

- FDA regulations do not define 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†
- Key Concept: being "at risk" for disorder or disease.
- Using the word "healthy" can be misleading.
  - A child can be healthy and "at risk" (i.e., have a "condition"); a child with a condition may not have the condition related to the research (and thus be "healthy").

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

Key Points: "Low Risk" Pathway

- Need to be able to generate an accurate risk estimate for administration of the investigational product given adult testing experience AND this risk estimate needs to indicate that risks are sufficiently "low" to proceed under this pathway.
- If risks are not "low" OR insufficient information is available to generate an accurate risk assessment, product will be considered under the "higher risk" pathway.
- Some single-dose PK studies may be considered "low" risk.
- Longer-term dosing of investigational drugs or biological products generally not considered "low" risk.

OTC† Cough & Cold Products (1 of 2)

- Single-dose PK studies of OTC cough and cold products are necessary to establish the correct dose to be used in subsequent efficacy studies.
- Based on available data, a single dose of an OTC cough and cold product may not offer a prospect of direct benefit to the enrolled child, but can be considered a “minor increase over minimal” risk (but not “minimal” risk).
- Therefore, enrolled children must have a disorder or condition.

† OTC = "over the counter" (i.e., non-prescription)

OTC† Cough & Cold Products (2 of 2)

Who may be enrolled?

- Children who are symptomatic from a cold have a condition (disease).
- Asymptomatic children may be "at risk" for a cold based on empirical data that clearly defines an "at risk" population (using US data).
  - *Frequency Criterion*: >6 infections per year for children aged 2 to <6 yrs and >4 infections per year for children aged 6 to <12 yrs.; AND,
  - *Crowding Criterion*: ≥4 persons living in the home or ≥3 persons sleeping in one bedroom; AND,
  - *Exposure Criterion*: another ill family member in home or child in the family who is attending preschool or school with ≥6 children in group.

† OTC = "over the counter" (i.e., non-prescription)

“Higher Risk” Pathway

- Any clinical investigation… in which more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject… may involve children as subjects only if:
  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.

21 CFR 50.52 / 45 CFR 46.405

Justification of Risks

- Are data regarding the drug's potential (clinical) benefit to the patient (subject) sufficiently compelling to justify the potential (known, suspected, and unknown) risks?
- Is the balance of these risks and potential benefits at least as favorable as the (evidence-based) alternative treatments (if any)?
- This assessment is similar to the judgment a clinician might make regarding whether to use a therapy in clinical practice.

Timing of Pediatric Studies

- For “higher risk” interventions, administration of FDA-regulated products in a clinical investigation must present risks that are justified by anticipated direct benefits to the child; the balance of which is at least as favorable as any available alternatives.
  - Additional Safeguards for Children (21 CFR 50.52)
- Thus, we need “proof of concept” data from human adults and/or animal disease models establishing a sufficient prospect of direct benefit to justify exposing children to the known (and unknown) risks of the intervention.
- This requirement does not imply that adult studies must be completed before beginning pediatric studies. Rather, once sufficient adult and/or animal data exist to make this judgment, pediatric development should proceed without further delay.

"First-in-Children" under 21 CFR 50.52

- 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?
  - The data necessary to establish a sufficient prospect of direct benefit (PDB) to justify the risks of product administration varies with the severity of the disease and the adequacy of alternate treatments.
- Proposal: Sliding Threshold
  - 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 is frequently based on the "no observed adverse effect level" (NOAEL) in the tested animal species, with conversion of the NOAEL to a human equivalent dose with application of an additional 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 a sufficient Prospect of Direct Benefit to justify a "first-in-children" clinical trial, although the MRSD may present greater risks.

Placebo (Sham) Controls in Pediatrics

- Sham procedures (and placebos) do not offer any prospect of direct benefit to the enrolled child.
- Two types of risk
  - Risk of placebo itself may be “minimal” unless placebo is invasive (e.g. sham injections)
  - Risk of harm from not receiving “proven” or “effective” treatment.
- Both types of risk must be no greater than a “minor increase over minimal risk” (21 CFR 50.53)
  - This approach consistent with ICH E-10 and 2013 Declaration of Helsinki.

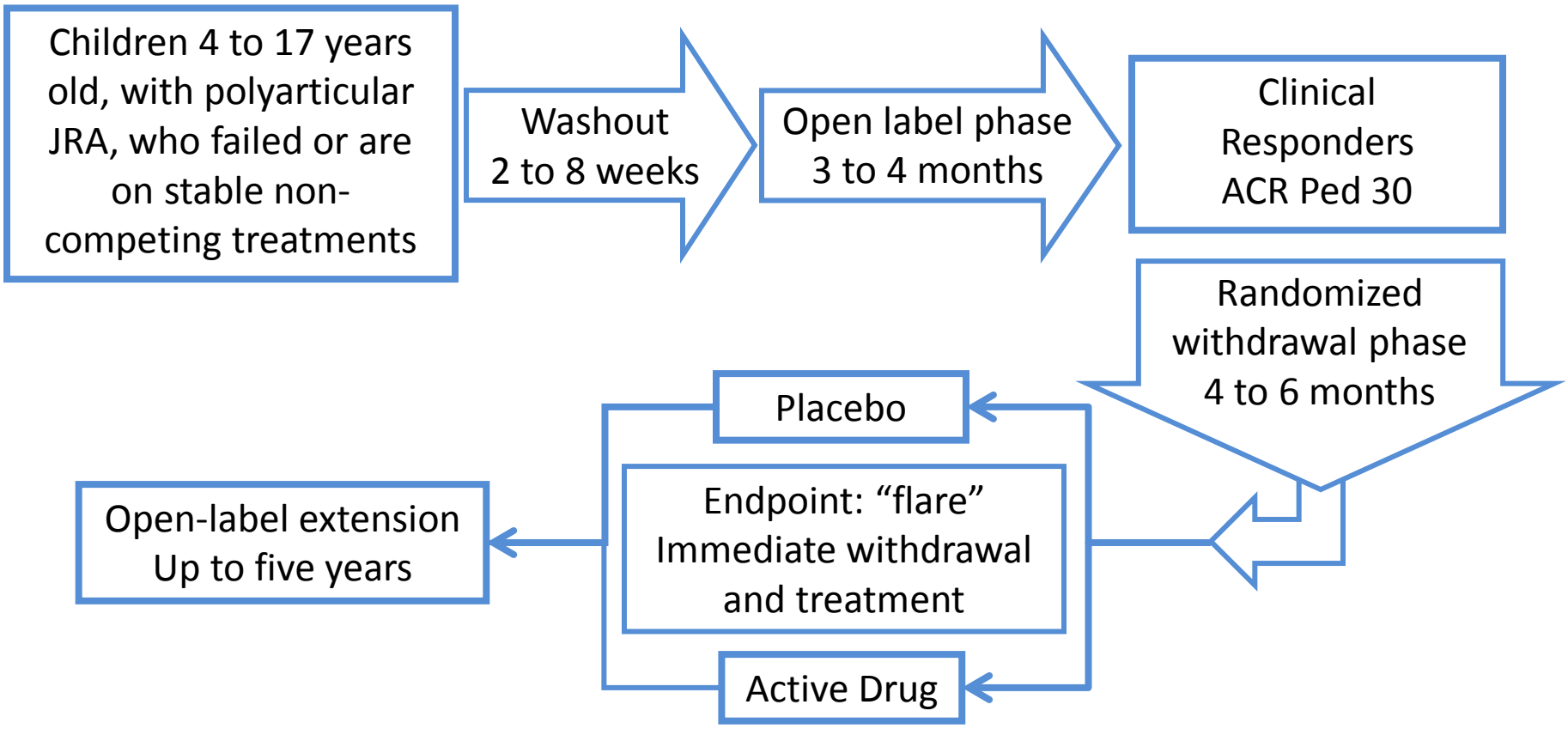
“Invasive” Placebos

- What is an acceptable placebo risk? One subcutaneous injection? An intramuscular injection? Peripheral Intravenous Catheters? For how long? Percutaneous inserted central catheters (PICC)? Sham surgery?
- How many “low” risk interventions (e.g. sham injections) are still “low” risk?
  - 1 year double-dummy study of oral versus weekly injectable drugs for multiple sclerosis?
  - 2 year placebo-controlled trial using daily injections of human growth hormone?

Example: RSV Treatment with Interferon-alpha 2a

- RCT of interferon for children with RSV
- 3 injections of either interferon or placebo
- (Assume interferon offers PDB)
- Placebo (sham) injections offer no medical benefit (even if other medical care is provided in the protocol) so the sham injections must be minimal risk or a minor increase over minimal risk

Enrichment Design with Randomized Withdrawal†



† Used for etanercept, adalimumab, abatacept and tocilizumab

Enrichment Design with Randomized Withdrawal

- Use of placebo injections
  - Limited in scope (i.e., only children with clinical response in open label phase) and duration (i.e., immediate withdrawal upon disease flare to open label treatment; re-induction of clinical response).
  - Thus "minor increase over minimal risk" (21 CFR 50.53)
- Valid test of the 'null hypothesis"
  - If "flare" rate of placebo > drug, then some (not all) treatment effect seen in open label study phase due to efficacy of the drug.
- Open label phase overestimates drug response rate as it includes placebo response (i.e., clinical response rate).
- No randomized placebo controlled safety data.

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