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 (14 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.

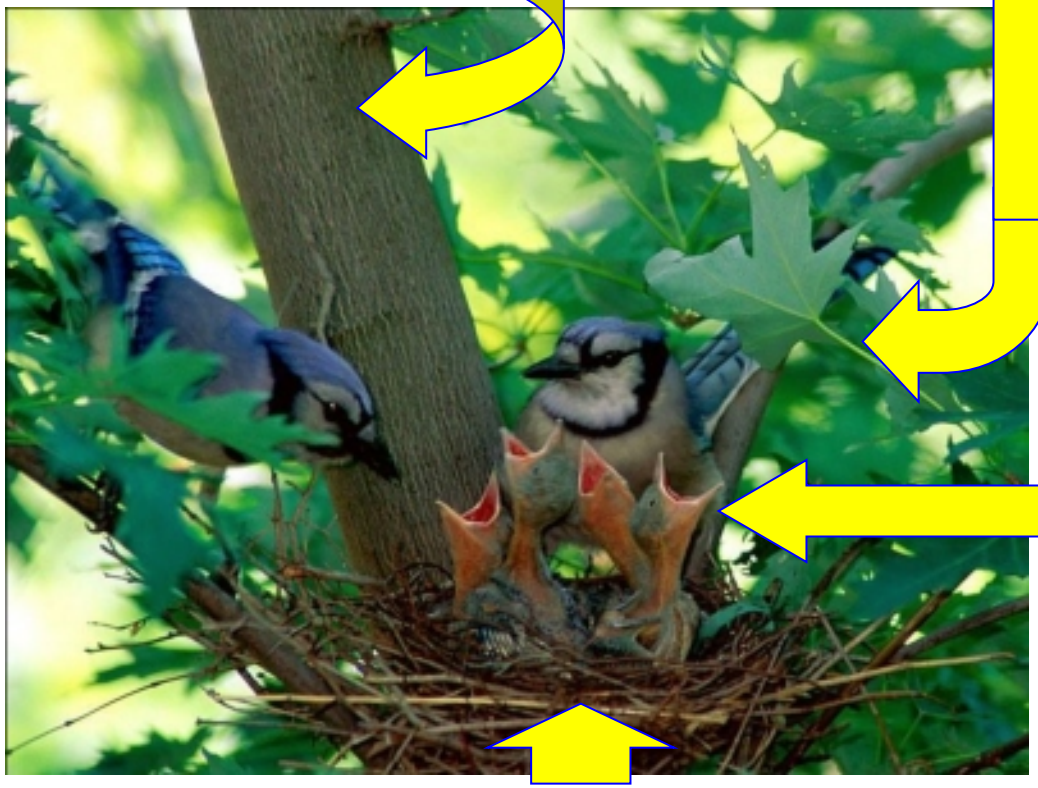
Basic Ethical Framework in Pediatrics

1. Children should only be enrolled if scientific and/or public health objective(s) cannot be met through enrolling subjects who can consent personally
2. Absent a prospect of direct therapeutic benefit, the 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
4. Vulnerable populations unable to consent (including children) should have a 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
(Practical Application: Extrapolation)

- 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 for establishing "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 (Adult/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 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
2,3: 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 benefit is an essential aspect of the ethical acceptability of the research protocol.
- Component Analysis
  - A protocol may (and usually does) contain interventions or procedures, some that offer a prospect of direct benefit and others that do not.
  - These interventions and procedures must be analyzed and justified separately (i.e., as "components" of the protocol).
- These concepts will be discussed in more detail in section 3.

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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."

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."

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.

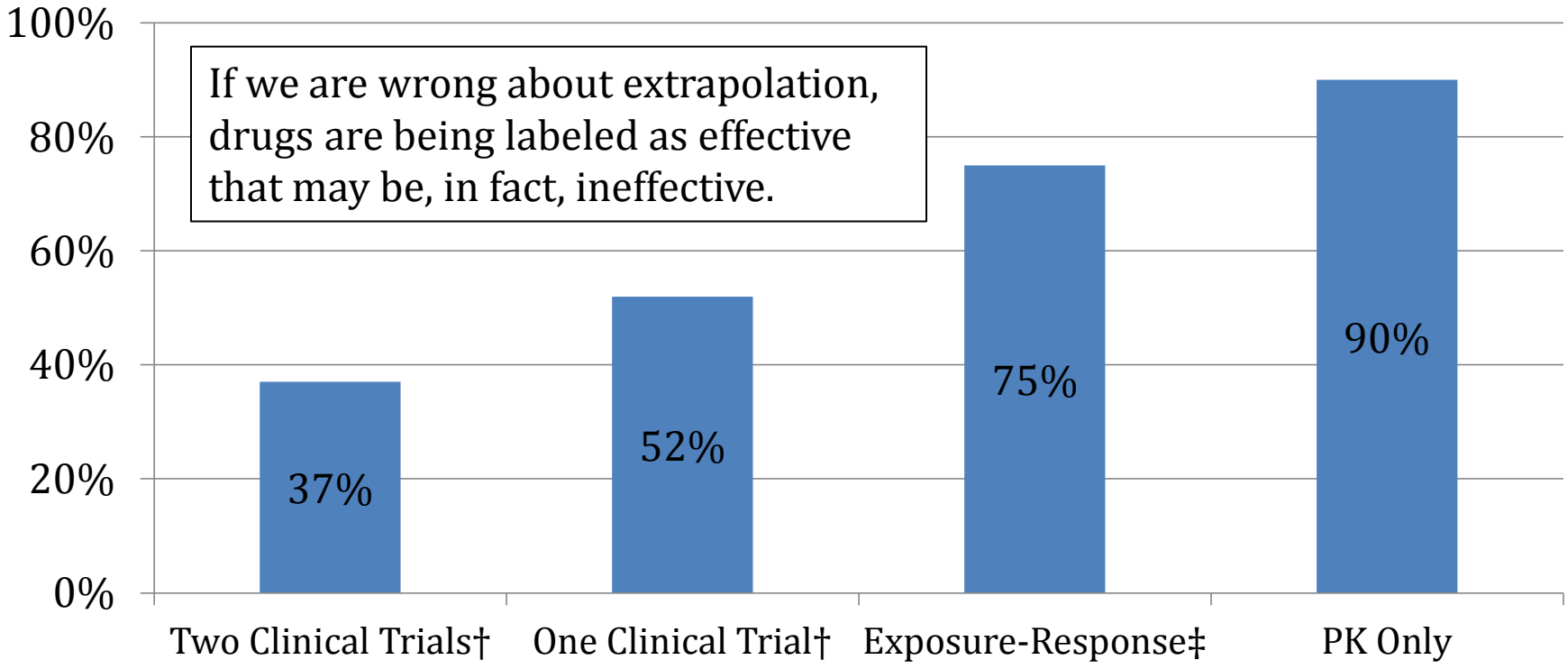
Summary of Approaches to Extrapolation
(Assessment of 166 products between 1998-2008)

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!

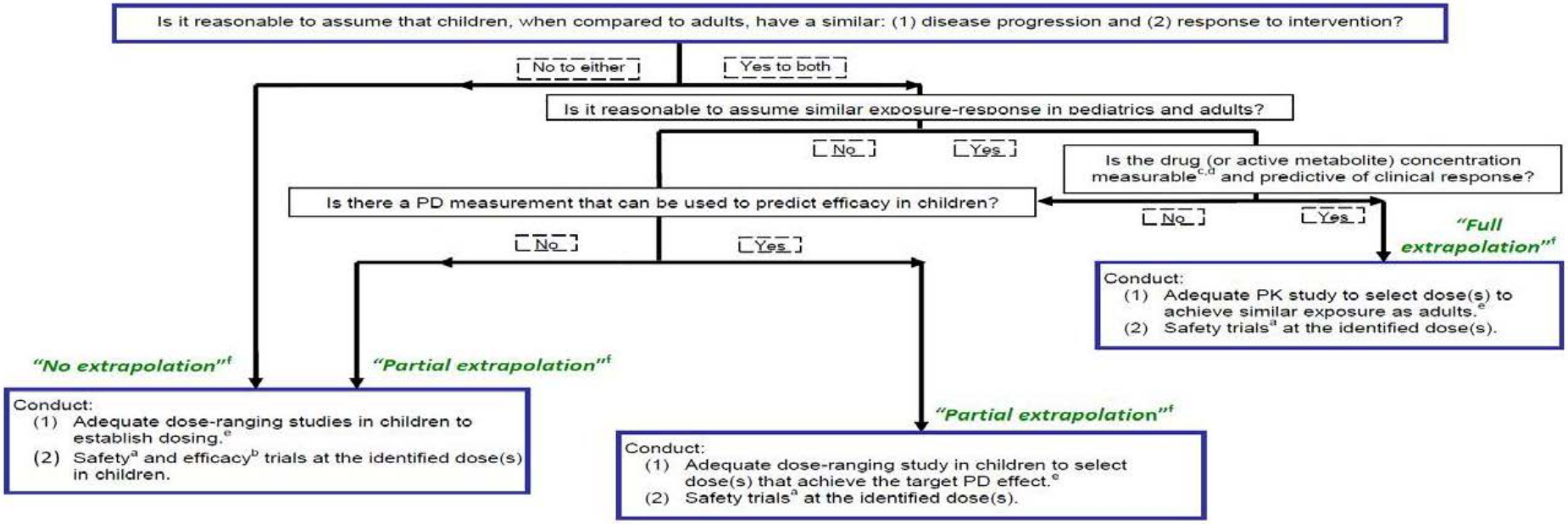


† Adequate, well-controlled, efficacy and safety trial(s) (powered for efficacy), plus PK data.

‡ 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.

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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.

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?)

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

"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.

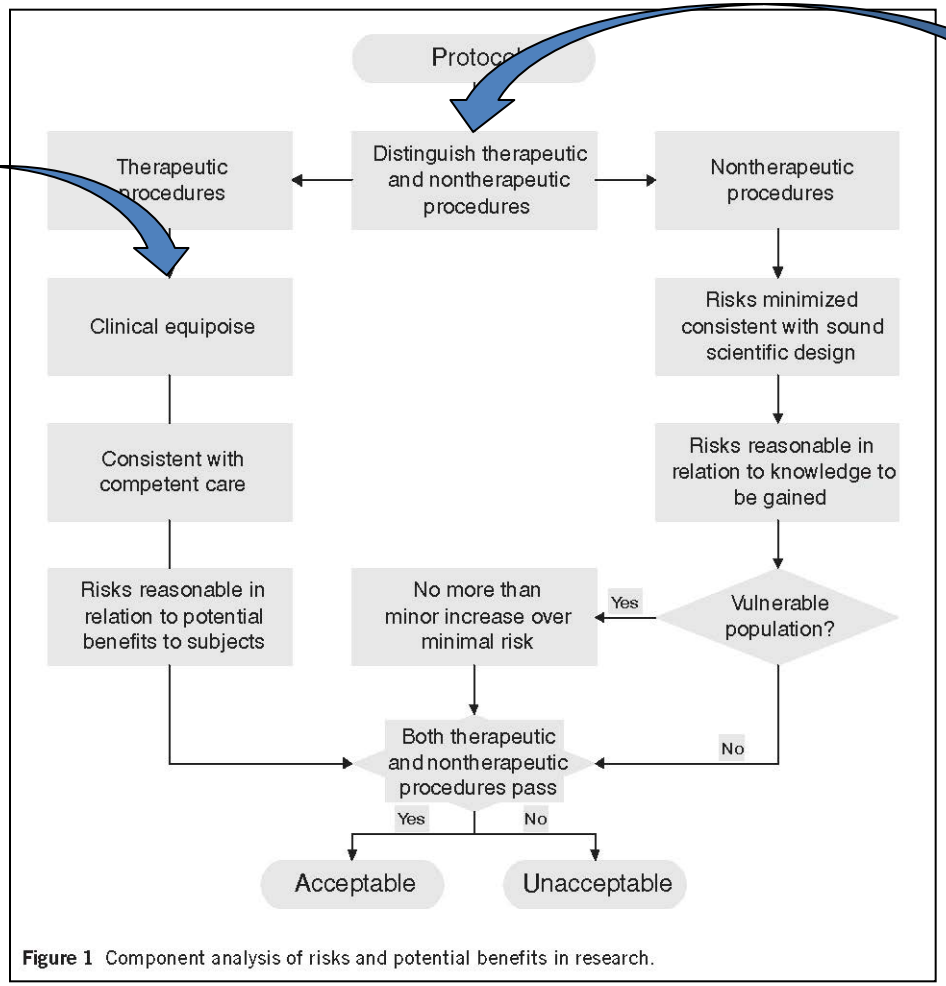


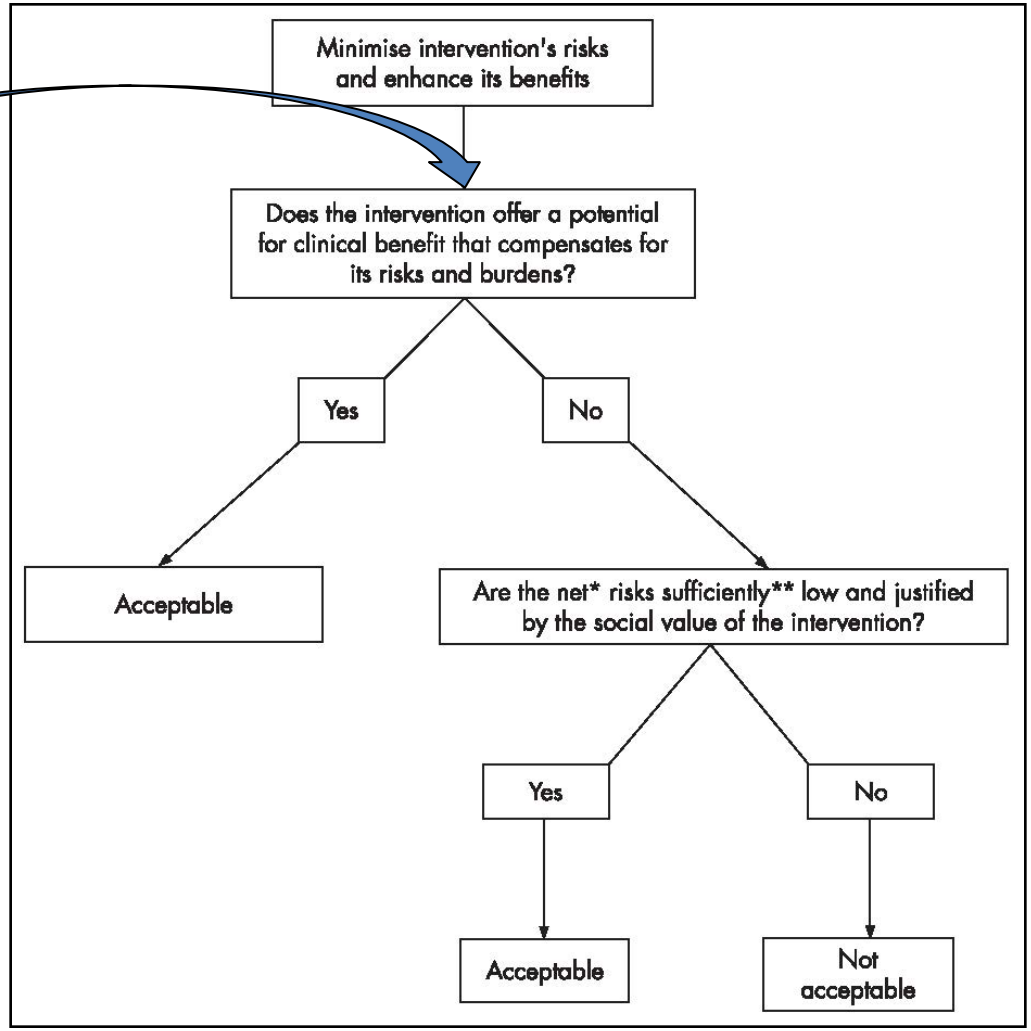
Figure 1 Component analysis of risks and potential benefits in research.

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.

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.

Corrective Actions

- Clinical trial had been suspended by the sponsor due to lack of product efficacy, so no future pediatric subjects were at imminent risk.
- FDA advised the sponsor that PICC utilization was not allowed for future pediatric subjects, and requested information from the participating IRBs.
- IRBs were asked whether PICCs had been used at each site, and if so, how PICC insertion was justified in the IRBs' assessment of the study.
  - The IRB responses and FDA analysis of those responses, along with FDA guidance on the topic, are provided in the supplemental slides for those who are interested.

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Linking Science and Ethics

- To conduct a pediatric clinical trial, the ethical challenge is to establish sufficient evidence (e.g., from 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)]
  - The recommendation is that this definition be indexed to the experience of "healthy children."
  - Generally, administration of an experimental drug/biological product is not considered "minimal" risk.
- Thus, interventions and/or procedures that do not present a prospect of direct benefit must present no more than a "minor increase over minimal risk," and thus must be 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

- The definition of risk as a product of "probability" times "magnitude" gives the misimpression that risk assessment can be purely quantitative.
- 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 lower risk
- Longer-term dosing of investigational drugs or biological products generally not considered low risk

Example:
OTC Cough & Cold Products

- 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.

Example:
OTC Cough & Cold Products
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.

"Higher Risk" Pathway

- Any clinical investigation… in which more than minimal risk to children is presented by an intervention or procedure that holds to 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 Risk and Alternatives

- Are the data regarding the potential benefit of the drug sufficiently compelling to justify the potential (known, suspected, and unknown) risks?
- Is the balance of these risks and benefits at least as favorable as (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.

Role of Adult Human or Animal Data

- To enroll children in "higher risk" trials, we need sufficient "proof of concept" for prospect of direct benefit to justify exposing children to known (and unknown) risks of intervention (§50.52).
- Adults and/or animal disease models should be studied before adolescents/children to obtain data supporting this judgment.
- However, this requirement does not imply that adult studies must be completed before beginning pediatric studies.
- Rather, once *sufficient adult or animal data* exist to make this judgment, pediatric development should proceed without further delay.

First-in-Children Studies under 21 CFR 50.52

- The non-clinical animal model data necessary to establish a sufficient prospect of direct benefit (PDB) to justify the risks varies with the severity of the disease and the adequacy of alternate treatments.
- Changes in Structure (generally insufficient for PDB)
- Changes in Biomarkers (based on mechanism of action)
  - Molecular target (receptor); Biomarker (RNA/protein); Physiologic pathway (metabolic product)
  - Transgenic Technology (human target + mouse)
- Clinical Disease Model (functions and/or survives)
  - Surrogate and functional endpoints (e.g., water maze)
  - 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.
- NOAEL dose may not offer sufficient PDB to justify "first-in-children" clinical trial, and the MRSD may present greater risks (i.e., balancing risk and potential benefit).

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 IM injections, intrathecal administration)
  - 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 Choice of Control Group and 2013 Declaration of Helsinki.

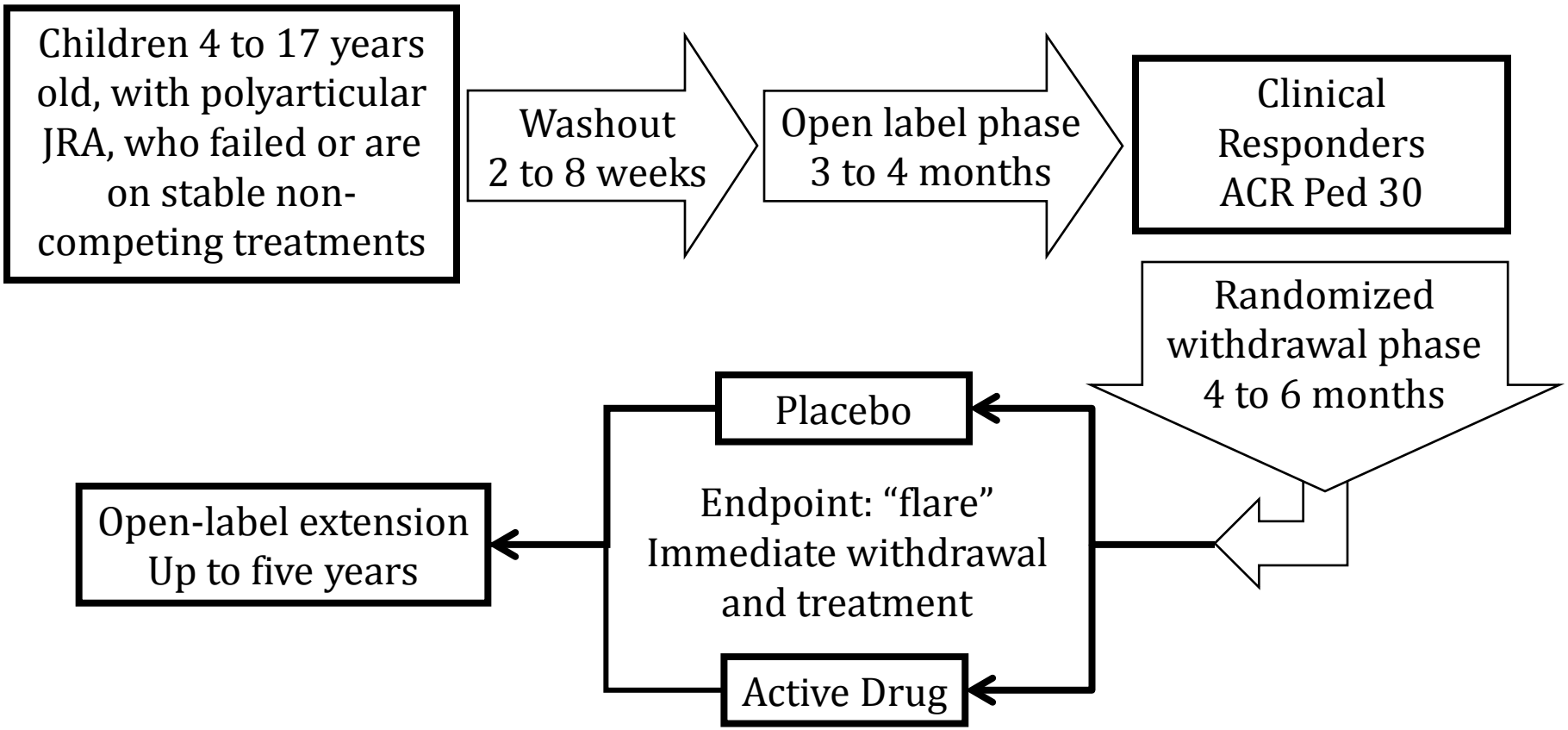
"Invasive" Placebos

- 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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Thank you.

Supplemental Slides: Component Analysis Case Study

Questions for IRBs

- How were the risks of PICC insertion and use, and the need for procedural sedation in some subjects, justified in the IRB's assessment of the approvability of the study under 21 CFR 50, Subpart D?
- Was the justification for PICC insertion and use different among subjects randomized to the placebo arm than for subjects randomized to the active treatment?
- What information about the risks of PICC use, including insertion and procedural sedation, was included in the parental permission and child assent forms?

IRB Responses

- PICCs used at 19 (of over 100) sites, approved by 12 IRBs.
- 10 of 12 IRBs answered FDA's questions.
- 9 of 12 reported a risk determination for the study
  - 7 of 9 IRBs approved both arms under § 50.52
  - 1 of 9 approved both arms as "more than minimal risk" (no category specified)
  - 1 of 9 approved the active arm under § 50.52 and the placebo arm under § 50.53
  - 2 of 9 used component analysis.

IRBs and Component Analysis

- Of the two (2/12) IRBs that used component analysis to assess the protocol, one applied the principle correctly but came to a different conclusion about the appropriateness of PICC use under 21 CFR 50.53, and the other applied component analysis incorrectly.
- We do not have information about IRBs (>80 sites) that did not approve PICC use, and thus do not know if they considered and rejected PICC use.

FDA's Response

- FDA provided a written analysis of the information and comments obtained from the IRBs, explaining the application of component analysis and the risks that are allowable under 21 CFR 50.53.
- The letter (signed by the responsible division director) was sent to the sponsor, with instructions to disseminate it to all IRBs that participated in studies of the investigational product.

IRB Responses: Justification for PICC Use

1) Parents and children were given a choice about whether to use PICC catheters or peripheral IVs.
2) All subjects have the possibility of directly benefiting if randomized to active treatment.
3) PICCs offer less discomfort and are easier to insert than multiple venipunctures.
4) PICCs are standard-of-care for children with difficult venous access.

FDA Analysis: 1) Parental Choice?

- The implication that PICC insertion may be appropriate if parents and children choose to use it undermines the intended protective function of 21 CFR 50 subpart D and abdicates the responsibility of IRBs.
- 21 CFR 50 subpart D caps the risk that parents may allow their children to assume for non-beneficial procedures at a “minor increase over minimal risk.” It is the IRBs’ role to ensure that these safeguards are followed at each site.

FDA Analysis:
2) All subjects may benefit?

- If the prospect of direct benefit is attributed to all subjects prior to randomization, it becomes impossible to do an individual assessment of the risks and benefits of each intervention or procedure as required by 21 CFR 50 subpart D.
- As a result, children could be exposed to excessive risk from non-beneficial research procedures simply by adding other beneficial procedures (such as warranted health care) to the protocol

FDA Analysis: 3) Ease of Use?

- Discomfort does not alter the potentially serious risks of PICC use, and the procedural sedation that may be necessary for insertion.
- To use this discomfort as a justification inappropriately ignores these risks.
- If establishing venous access is difficult in conventional pharmacokinetic studies, children are routinely withdrawn from the research given that the intervention does not offer a prospect of direct benefit.

FDA Analysis:
4) PICCs as Standard-of-Care?

- PICC use is "standard of care" only when use of these catheters offers the child a prospect of direct benefit (children would not receive a PICC in clinical practice absent a potential benefit of the infusion).
- In the current study, 50% of the enrolled children would be infused with placebo. The infusion of placebo does not offer a child a prospect of direct benefit from the infusion, because (by definition) the placebo is physiologically inactive.

IRBs and Component Analysis

- Of the two IRBs that used component analysis to assess the protocol,
  - one IRB applied the component analysis correctly but came to a different conclusion about the appropriateness of PIC catheters under subpart D, and
  - the other IRB applied component analysis incorrectly.

One IRB's Analysis

- "For subjects receiving placebo, the study met the requirements of 45 CFR 46.406 and 21 CFR 50.53…The placebo arm was approvable based on the finding that the study procedures represented only a minor increase over minimal risk."
- Children on active treatment were approved under 45 CFR 46.405 and 21 CFR 50.52 as having a prospect of direct benefit.

Another IRB's Analysis

"The placebo arm of the randomized clinical trial was not treated as a separate non-therapeutic intervention (a la Miller and Brody)…[the placebo arm] was treated as a "substitute" for an active treatment intervention and both placebo and active treatment were evaluated against the standard of best available alternative treatments… If it is not known at the outset of the trial whether the risk-benefit ratio of the placebo arm will be more or less favorable for subjects than the active treatment arm, then the requirements of 21 CFR 50.52 are satisfied."

FDA Response

- To treat the placebo arm as a "substitute" for an active treatment intervention appears to be equivalent to a pre-randomization analysis discussed earlier.
- The fact that one is uncertain at the start of a trial whether the intervention arm will be better than placebo does not mean that the placebo can be viewed as offering a prospect of direct benefit.

Information in Most ICFs

- The disclosed risks of PICC insertion included "catheter occlusion (blood clot in the tube), phlebitis (inflammation of the vein), hemorrhage (excessive bleeding), thrombosis (blood clot in your vein) and infection."
- The disclosed risks of procedural sedation included: "low oxygen and low blood pressure, allergic reaction, aspiration (taking food or fluid into the lungs), or in very unusual circumstances, death."

Limitations of Disclosed Information

- The difference in magnitude of risks for a PICC compared to a peripheral IV catheter were not discussed, or the risks of PICC insertion were inappropriately minimized as being "similar to an IV".
- Procedural sedation was sometimes considered "minimal risk", despite disclosures noting that procedural sedation carries a small risk of death.

Supplemental Slides: FDA Guidance on Component Analysis

Current FDA Guidance (ABOM)

"There are concerns that institutional review boards (IRBs) or investigators may consider a placebo-controlled trial in ABOM to be unethical. The general issue of the ethics of placebo-controlled trials is addressed in ICH E10. For such a trial to be approvable by a local IRB under 21 CFR part 50, subpart D, the risk to children randomized to a comparator group that involves the withholding of antibacterial treatment (whether placebo or delayed therapy) must be no more than a minor increase over minimal risk (21 CFR 50.53). In addition, clinical trials must be designed so that risks to patients are minimized (21 CFR 56.111)." (Final Guidance – Sept 2012)

ABOM = Acute Bacterial Otitis Media

Current FDA Guidance (ABOM)

"Given the… rare infectious complications that may be associated with nontreatment of ABOM (e.g., mastoiditis or meningitis), the design for a placebo-controlled trial should include an early clinical assessment for clinical failure at approximately 48 hours after enrollment. A review of all previous placebo-controlled trials of ABOM have not shown a substantial risk to placebo-treated recipients that make future placebo-controlled trials unethical; overall risk from placebo treatment may be similar to that associated with antibacterial therapy because low-frequency severe events (e.g., pseudo-membranous colitis or serious allergic reactions) have been observed with almost all antibacterial drugs. If necessary, effective antimicrobial rescue treatment can be initiated at the time of a clinical failure, thus limiting the risk exposure of the children randomized to the placebo-controlled arm of the trial."

Current FDA Guidance (ABOM)

"If tympanocentesis is included in the trial design, it should be performed only by individuals with expertise in this procedure to ensure that the procedure poses no more than a minor increase over minimal risk to patients (21 CFR 50.53). Making unblinded culture results available so that effective antimicrobial treatment can be initiated in response to a treatment failure may provide prospect of direct benefit to the enrolled children, and thus be acceptable under 21 CFR 50.52. In addition, targeted therapy based on culture results from repeat tympanocentesis performed to assess clinical failures may offer prospect of direct benefit."

Current FDA Guidance (ABOM)

"Finally, for an isolated single-dose PK trial in children, sufficient evidence of drug safety in adults would be needed so that the risk exposure for children is limited to no more than a minor increase over minimal risk (21 CFR 50.53). If the PK data are used to adjust the dose of the investigational drug for individual patients, an IRB may consider this aspect of the trial as offering the prospect of direct benefit (21 CFR 50.52). If additional PK data are collected in an efficacy trial, the PK component of the efficacy trial may be acceptable as a minor increase over minimal risk, based on a component analysis of risk (21 CFR 50.53)."

Preamble to 2001 Interim Final Rule
21 CFR 50 subpart D

"The agency also recognizes that the requirement for the prospect of direct benefit to individual subjects may create ambiguity about whether placebo-controlled clinical investigations may be conducted in children. FDA believes that clinical investigations involving placebos in children may be conducted in accord with § 50.52. There is evidence of direct benefit to subjects from participating in placebo-controlled trials, including increased monitoring and care of subjects, even though a subject may not actually receive the test product."

Preamble to 2001 Interim Final Rule
21 CFR 50 subpart D

"In our discussion of § 50.52 in the preamble to the interim rule (66 FR 20589 at 20593), we …noted that there is evidence of direct benefit to children from participating in placebo-controlled trials, including increased monitoring and care of subjects, even though a child may not actually receive the test product. *This statement has been misinterpreted, and we provide clarification in the paragraphs that follow.*" (emphasis added)

Preamble to Final Rule
21 CFR 50 subpart D

"The general consensus of the [FDA Pediatric Ethics Subcommittee of the Pediatric Advisory Committee, meeting in June 2008] was that the placebo arm of a trial cannot be considered to confer the prospect of direct benefit under §50.52… In general, the PES advised that the so-called "inclusion" benefit is not a "direct" benefit, and that children enrolled in the placebo arm of a trial should be exposed to no more than minimal risk or a minor increase over minimal risk."

Preamble to Final Rule
21 CFR 50 subpart D

"FDA agrees with [the Pediatric Ethics Subcommittee's] position. Because we do not consider the administration of a placebo to offer a prospect of direct benefit, part 50, subpart D, therefore requires that the placebo arm must present no more than minimal risk (§ 50.51) or a minor increase over minimal risk (§ 50.53), unless the clinical investigation is referred for review under 21 CFR 50.54."

Preamble to Final Rule
21 CFR 50 subpart D

"A placebo-controlled study… may involve the withholding of known effective treatment (section 2.1.3, ICH E 10). In such situations, however, the risks of such withholding of known effective treatment in the placebo control group should present no more than minimal risk or a minor increase over minimal risk, i.e., the placebo control arm of such a clinical trial must be approvable under either § 50.51 or § 50.53. The arm that receives the investigational product often would be approvable under § 50.52."

Supplemental Slides: Ethical and Regulatory Considerations in Adolescent HIV Treatment and Prevention Research

Concurrent Licensure

- The goal of product development for the treatment and/or prevention of HIV in adolescents† ought to be concurrent licensure at the time these products are approved and marketed for adults.
- Our ability to meet this goal requires thoughtful consideration of the relevant scientific and ethical issues so that adolescent product development can be incorporated into or proceed alongside of adult phase 3 development.

† For the purposes of this presentation, adolescents are considered to be between 12 and 18 years of age.

When Should Adolescent Trials Begin?

- We need "proof of concept" for a sufficient prospect of direct benefit (PDB) to justify exposing adolescents to the known (and unknown) risks of the intervention (21 CFR 50.52).
- Adults should be enrolled prior to adolescents to obtain the necessary data in support of this judgment.
- The adult data necessary to support a sufficient PDB may be less than the level of evidence required to establish efficacy.
- Once *sufficient adult data* exist to make this judgment, pediatric development should proceed without further delay.
- Whether we need an "adequate and well-controlled" study in pediatrics depends on our ability to "extrapolate" efficacy.

Scientific Issues - Dosing

- We anticipate no differences between adolescents and young adults with respect to the pharmacokinetics (i.e., absorption, distribution, metabolism and excretion) of anti-retroviral drugs. Thus, the same adult formulation and dosing regimen can be evaluated in adolescents.
- Observed differences between adolescent and adult pharmacokinetics are usually explained by differences in adherence.
- Thus, one does not need to obtain intensive PK data from adolescents, but blood levels can be used as a measure of adherence (i.e., population PK samples, at most).

Scientific Issues – Efficacy/Safety

Treatment:

- Evidence of efficacy in HIV-infected adults may be extrapolated to adolescents, given the similarity of the disease and response to treatment.
- Dosing and "proof of concept" with respect to potential clinical benefit are established in early phase adult trials.
- A cohort of HIV-infected adolescents (> 12 years of age) can be included in (or run parallel with) an adult phase 3 trial in order to obtain sufficient safety data (e.g., impact on growth given potential for bone toxicity) and demonstrate a similar pharmacodynamic response (i.e., plasma HIV-1 RNA)

Scientific Issues – Efficacy/Safety

Prevention:

- Pre-exposure prophylaxis (PrEP) with oral (men and women) or vaginal† (women) products can be effective, provided they are used consistently
- Although PrEP efficacy can be extrapolated from adults to adolescents, adolescent adherence of greater concern
- If lack of adherence undermines adolescent efficacy, safety concerns (e.g., bone and/or renal toxicity) in an uninfected population may alter the balance of risk/potential benefit
- To date, there are no data in support of (and some against) the hypothesis of "risk compensation" or "disinhibition"

† Note: Vaginal microbicides are not usually referred to as PrEP.

Enrollment of Adolescents in HIV Vaccine Trial?

Selected Recommendations (consultation - August 14, 2007)

- Not enroll adolescents until after interim efficacy and cell-mediated immunity (CMI) analysis of adult data
  - Require trend in favor of experimental HIV vaccine
- If extrapolation appropriate, base adolescent sample size on descriptive CMI data from interim analysis
  - Descriptive comparison between adult and adolescent immune response data could serve as bridge for extrapolation of efficacy
  - Reasonable to increase adolescent sample to improve power to detect a significant safety signal at an incidence of <1-3%
- Extrapolation of efficacy would permit concurrent labeling based on supporting dosing and safety data.

Scientific Observations

- From a scientific perspective, adolescents may be enrolled into adult phase 3 trials or in concurrent adolescent trials provided there are data establishing a sufficient "prospect of direct benefit" to justify the risks.
- Risk/potential benefit may differ across the adolescent age range for treatment vs. prevention (e.g., ≥12 years of age for HIV treatment; ≥15 years of age for PrEP) given differences in age-related risk factors for sexually acquired diseases.
- A proper evaluation of adolescent safety requires a longer duration of observation (at least 6 months) given the potential impact, for example, on bone formation and growth.
- Adherence (i.e., assuring, measuring) of central concern.

Ethical Considerations

Then why can it be so difficult to enroll adolescents in (adult) HIV treatment and prevention trials?

- Logistically, adolescents who are HIV-infected or at risk for acquiring HIV generally are cared for in pediatric clinics (thus requiring a sponsor to set up a clinical trial enrolling both adolescents and adults in two different networks).
- Ethically, two issues are worth highlighting
  - Measures to assure adherence with the treatment or prevention regimen (such as financial compensation)
  - The ability of an adolescent to provide informed consent without parental permission and/or knowledge

Influencing Adherence

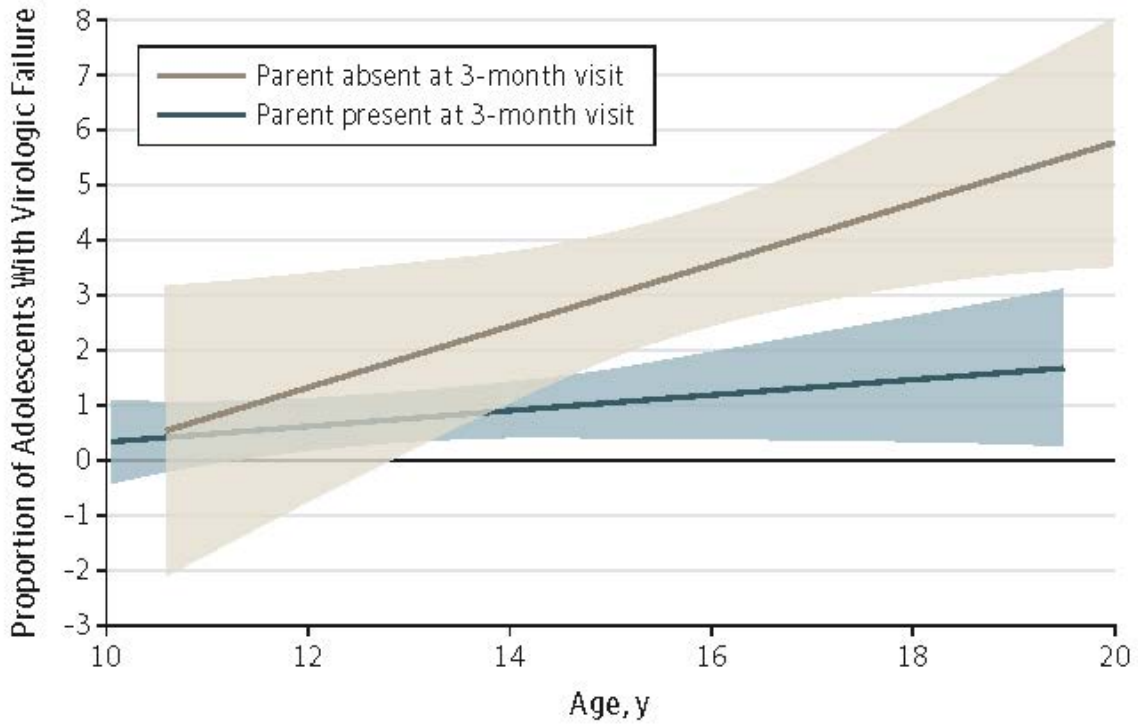
- Financial compensation is often limited to a "minimum wage" model (based on time) out of a misplaced concern that higher levels of compensation may undermine voluntary choice.
- Although financial compensation influences decision-making, the view that it "unduly" influences adolescent choice to enroll in an IRB-approved protocol rests on a faulty analysis of the concept of "voluntary choice."
- However, there may be legitimate concerns about excessive levels of financial compensation (e.g., placing participants "at risk" of harm from others).
- In addition, compensation alone (in the absence of other positive behavioral interventions) may be ineffective in assuring adherence to the study regimen.

Influencing Adherence

- Rather than relying on usual tools for assuring adherence in a clinical trial, HIV treatment and prevention trials may need to incorporate interventions to improve "retention in care"
  - For example, attention to psychosocial development needs, inadequate educational attainment, limited health literacy, coping ability, structural environment and individual case management.
- Disclosure (versus confidentiality)? (some observations)
  - Disclosure of gel use to sexual partners in CAPRISA 004 was associated with a modest 4.2 % increased adherence (71.0 vs. 66.8 %, p = 0.03).
  - When adolescents viewed parents as supportive, they disclosed more and kept fewer secrets. Monitored adolescents did not provide information to parents, even when they accepted parental authority.
  - However, "outness" predicted physical health benefits for higher SES men but health problems for lower SES men.

Importance of Parental Support?

Figure. Proportion of Patients With Virologic Failure by Age Stratified by Parental Absence



The shaded areas indicate 95% CI bands.

Lowenthal, E. D., et al. (2015). JAMA Pediatr. 169(5): 498-500.

Adolescent Consent

- When FDA adopted the "Additional Safeguards for Children in Clinical Investigations (21 CFR 50 subpart D) as an "interim final rule" in 2001, it did not adopt the waiver of parental permission found in 45 CFR 46.408(c).
- This decision generated some controversy, as the waiver had been (and is being) used to permit adolescent "consent" for HIV (and other) research absent parental knowledge and/or permission.
- In the Preamble to the Final Rule on 21 CFR 50 Subpart D, published in the Federal Register on February 26, 2013, FDA clarified the decision not to adopt the waiver of parental permission.

Comment Opposing FDA's Decision

- "The comment cited the example of research studies using new therapeutic modalities for the human immunodeficiency virus (HIV) and the acquired immunodeficiency virus (AIDS) in the HIV epidemic in the late 1980s and early 1990s and stated that many adolescents who sought treatment for HIV requested that their diagnosis be kept confidential from their parents.
- The comment stated that such confidential treatment was provided to these adolescents based on State laws allowing physicians to treat adolescents for sexually transmitted diseases without parental involvement."

Federal Register. 78(38);Feb 26, 2013:12945.

FDA's 2013 Response

"We recognize that mature adolescents may contract diseases such as HIV–AIDS and other sexually transmissible diseases, and that there are important issues relating to the confidentiality of treatment sought. We note that in some situations a State may grant certain classes of mature adolescents of a specific age the right to consent to treatments or procedures involved in a clinical investigation. **These mature minors would not meet the definition of children under § 50.3(o) and thus would not be subject to the requirements of this subpart.** Similarly, minors deemed "emancipated" by state law also would not meet the definition of children under § 50.3(o) and would not be subject to the requirements of this subpart. **Mature or emancipated minors would be allowed to consent to participation in FDA-regulated research without the need for parental or guardian permission.** Thus, we consider reliance on established state and/or local laws that establish an adolescent as mature and/or emancipated to be appropriate in this context."

Federal Register. 78(38);Feb 26, 2013:12946 (emphasis added).

Definition of Child

- "Children means persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted."

  21 CFR 50.3(o)

- The National Commission (1978), in framing this definition, intended State-based treatment laws to apply to research.
- The waiver of parental permission was included for when a parent/guardian should be disqualified as an appropriate decision-maker, not for when an adolescent was thought to be developmentally capable of providing informed consent or desired confidentiality (absent enabling State law).

Analysis of State Law

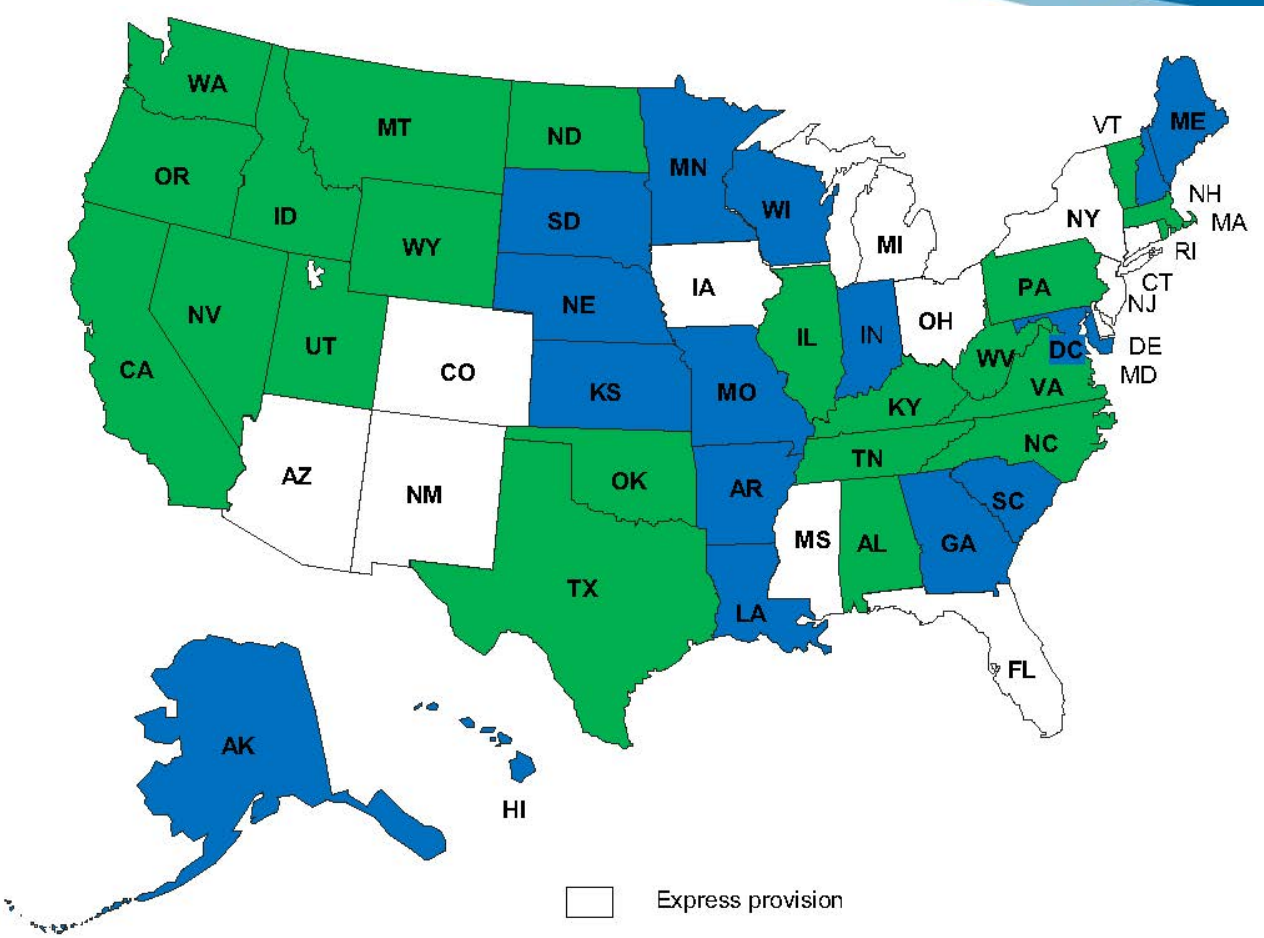


Figure 3. Minor's capacity to consent to HIV services, by type of service
STI, sexually transmitted infection

Culp, L. and L. Caucci (2013). Am J Prev Med. 44(1 Suppl 2): S119-124.

Concluding Remarks

- From a scientific perspective, adolescents ought to be included in HIV treatment and prevention studies during the adult phase 3 trials so that the product may be licensed concurrently in both populations.
- Consistent with the National Commission's analysis, FDA is permissive in allowing local jurisdictions to apply State HIV/STI minor treatment laws to enroll HIV and "at risk" adolescents in these trials, absent parental permission.
- In addition to disputes about the applicability of State law, local decisions may be influenced by attitudes towards, for example, parental supervision vis-à-vis adolescent confidentiality, and the morality of adolescent behavior.

Suggestion

- The success of various HIV intervention strategies, especially treatment, appears related to the degree to which an adolescent is surrounded by a supportive environment.
- Similar "retention in care" interventions that may impact on risk behavior, and build a supportive environment, could be included in adolescent HIV prevention trials.
- The ethical and legal tension between an adolescent's right to confidential care, and a parent's responsibility for adolescent welfare (which requires knowledge of adolescent behavior), could be reframed within a broader strategy of building a supportive environment, rather than one of conflict . This approach may be more acceptable to local IRBs/communities.

Thank you.