Prospect of Direct Benefit in Pediatric Clinical Trials
Welcome & Introductions

Gregory Daniel, Duke-Margolis Center for Health Policy
Opening Remarks from FDA
Disclaimer

• The views presented here are personal and do not necessarily reflect the views of the Agency

• All specific drug development questions should be discussed with the relevant review division
Development of Regulations for the Protection of Human Subjects

The New York Times

Syphilis Victims in U.S. Study Went Untreated for 40 Years

By JEAN HELLER
The Associated Press

WASHINGTON, July 25—For 40 years the United States Public Health Service has conducted a study in which human beings with syphilis, who were induced to serve as guinea pigs, have gone without medical treatment for the disease and a few have died of its late effects, even though an effective therapy was eventually discovered.

The study was conducted to determine from autopsies what the disease does to the human body.

Officials of the health service who initiated the experiment have long since retired. Current officials, who say they have serious doubts about the morality of the study, also say that it is too late to treat the syphilis in any surviving participants.

Doctors in the service say they are now rendering whatever other medical services they can give to the survivors while the study of the disease's effects continues.

Dr. Merlín K. DuVal, Assistant Secretary of Health, Education and Welfare for Health and Scientific Affairs, expressed shock on learning of the study. He said that he was making an immediate investigation.

The experiment, called the Tuskegee Study, began in 1932 with about 600 black men,
SPECIAL ARTICLE

ETHICS AND CLINICAL RESEARCH*

Henry K. Beecher, M.D.†

BOSTON
Ethical Issues in Neonatal and Pediatric Clinical Trials

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The Potential Benefits of Research May Justify Certain Research Risks
David Wendler, Robert M. Nelson and John D. Lantos
Pediatrics 2019;143;
DOI: 10.1542/peds.2018-1703 originally published online February 20, 2019;
Development of Regulations for the Protection of Human Subjects


Department of Health and Human Services (HHS) 45 CFR 46 1981

Food and Drug Administration (FDA) 21 CFR 50 1981

Additional Safeguards for Children in Clinical Investigations 21 CFR 50 Subpart D 2013

Institutional Review Boards (IRBs) 45 CFR 46; 21 CFR 56

45 CFR 46 Subpart D 1983

Informed Consent

www.fda.gov
Additional Safeguards for Children in Clinical Investigations
21 CFR 50 Subpart D

21 CFR 50.51 Minimal Risk

21 CFR 50.52 More than a Minor Increase Over Minimal Risk
Prospect of Direct Benefit

21 CFR 50.54 Federal Panel

21 CFR 50.55 Permission & Assent

21 CFR 50.53 Minor Increase Over Minimal Risk
Drug Development Paradigm

Right Drug

Right Population

Right Dose

Right Trial Design

Right Endpoints
Considerations in Designing a Development Program

• What is the quality and robustness of the evidence of an effect (including the totality of the evidence)?
• Given that it exists, how meaningful will this effect be in the overall context of the disease? How much will it matter to patients?
• If it matters, what would be the impact of failing to provide this benefit, if real?
• This reasoning has to be weighed against the potential harms of the intervention
Innovative Trials in Rare Diseases

• Carglumic acid for N-acetylglutamate synthase (NAGS) deficiency
  • Rare urea cycle disorder (~ 10 patients in U.S.)
  • Retrospective review of a 23 patient case series in Europe
  • Short-term (ammonia) and long-term (neurocognitive) outcomes
  • Compared to historical control (not formally conducted)

• Deferiprone for transfusional iron overload in patients with thalassemia syndromes not responding to other therapies
  • Planned pooled analysis of patients from several studies (n=236)
  • Endpoint was change in serum ferritin, not a clinical outcome

• Cysteamine bitartrate for nephropathic cystinosis
  • 2 open-label studies (n=94) children treated with product or innovator cysteamine HCl
  • Largely a pharmacodynamic comparison based on WBC cystine levels vs. historical control pharmacokinetic/pharmacodynamic levels

www.fda.gov
What Did These Have in Common?

- Highly plausible mechanistic hypothesis
- Natural history data on untreated patients
- Highly plausible biomarkers; most could be measured in a standard manner
- Serious unmet medical need
- Relatively large treatment effect
Classic Design for Pediatric Trials

- Adult trials done to establish dose, efficacy, and adverse events
- Pediatric trials done in a step-wise fashion starting in adolescents and moving sequentially into younger children
- Infants and neonates as the last group to be studied
- Pediatric trials done to demonstrate both efficacy and safety
New Innovative Designs for Pediatric Trials

- Diseases may be pediatric only so the first in human trials need to be done in pediatric patients
  - How do we establish dose and what are the logistics of PK trials that then provide the prospect of direct benefit
  - What non-clinical data are sufficient to start clinical trials
- Disease may be sufficiently similar in adults and children that it is possible to extrapolate efficacy
  - How do we establish dose and what are the logistics of PK trials that then provide the prospect of direct benefit
- Disease may be similar in adults and children but no data yet available
  - Can pediatric patients be enrolled at the same time as adults
    - Balance of potential benefit of therapy and potential adverse events
  - Can biomarkers be used as surrogate endpoints and are they relevant in the pediatric population
Why Does Prospect of Direct Benefit Matter in Pediatric Clinical Trials?

**Moderator:** Gregory Daniel, Duke-Margolis Center for Health Policy
Prospect of Direct Benefit and The Additional Safeguards for Children in Clinical Investigations 21 CFR 50, Subpart D

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Office of Pediatric Therapeutics
Office of the Commissioner

Duke-Margolis Center for Health Policy
Prospect of Direct Benefit in Pediatric Clinical Trials Workshop
March 29, 2019
Disclosure

• 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.

• The speaker has no relevant personal, professional or financial relationship(s) with respect to this presentation.
The Challenge
Balance ethical considerations with scientific requirements

Children are vulnerable and require additional safeguards

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

- Food Drug and Cosmetic Act amended in 1962 after the thalidomide disaster
  - Drugs must be safe and effective (Kefauver-Harris Drug Amendments)
  - Overprotection resulted discouraging pediatric use of drug products and lack of testing in children (children as therapeutic orphans)
- Exploitation of both adults and children (Tuskegee, Willowbrook School) led to concerns regarding the protection of adults and children in research
- The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research issued the Belmont Report and the Report and Recommendations on Research Involving Children in 1978
- The ethical framework to support studies in children proposed by the National Commission was adopted by the Department of Health and Human Services in 1983 (45 CFR 46, Subpart D) and by FDA in 2013 (21 CFR 50, Subpart D)
Historical Context

• The American Academy of Pediatrics published guidelines for the ethical conduct of pediatric research in 1977 and again in 1994
  • Catalyzed thinking for development of legislation to encourage pediatric drug development*

• Legislation enacted to encourage pediatric labeling and drug development
  • Pediatric Labeling Rule, allowing pediatric extrapolation 1994
  • Best Pharmaceutics for Children Act (BPCA) 2002
  • Pediatric Research Equity Act (PREA) 2003
  • Pediatric Rare Disease Voucher 2012

• Significant knowledge has been gained that can inform the design of contemporary pediatric therapeutic development programs

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 clinical 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 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
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.

- Derives from requirements for equitable selection and minimizing risk:
  - Subjects capable of informed consent (adults) should generally be enrolled prior to children [21 CFR 56.111(b)].
  - Eliminate any research procedures (as unnecessary) that do not contribute to scientific objective [21 CFR 56.111(a)(1)].

- Grounded in the ethical principle of Social Justice (Belmont Report):
  - …”Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children)”…
General Justification of Research Risk
(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))

- This criterion is modified by the additional protections for children enrolled in FDA-regulated clinical investigations in that there is a limit to the risk that knowledge can justify
Additional Safeguards for Children
21 CFR 50 Subpart D

- 21 CFR 50.51: Minimal Risk
- 21 CFR 50.52: More than a Minor Increase Over Minimal Risk
  - Prospect of Direct Benefit
- 21 CFR 50.53: Minor Increase Over Minimal Risk
- 21 CFR 50.54: Federal Panel
- 21 CFR 50.55: Permission & Assent
• 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 (21 CFR 50.51/53) or
  – 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)

• Permission by parents or guardians and assent by children must be solicited (21 CFR 50.55)
Additional Safeguards for Children
21 CFR 50 Subpart D

• Not involving greater than minimal risk (21 CFR 50.51)
• Greater than minimal risk but presenting the prospect of direct benefit to individual subjects (21 CFR 50.52)
• Greater than minimal risk, no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about subjects’ disorder or condition (21 CFR 50.53)
• Not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (21 CFR 50.54)*
• Requirements for permission by parents or guardians and for assent by children (21 CFR 50.55)

*Requires review by a federal panel
Additional Safeguards for Children
21 CFR 50 Subpart D
Additional Safeguards for Children
21 CFR 50 Subpart D

- **21 CFR 50.51**: Minimal Risk
- **21 CFR 50.52**: More than a Minor Increase Over Minimal Risk
  - Prospect of Direct Benefit
- **21 CFR 50.53**: Minor Increase Over Minimal Risk
- **21 CFR 50.54**: Federal Panel
- **21 CFR 50.55**: Permission & Assent
“Low” Risk

- **“Minimal risk”** is defined as those risks “normally encountered in the daily lives, or in the routine medical or psychological examination, of healthy children”

- **“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,” are limited to children with a “disorder or condition,” and must contribute to generalizable knowledge about the child’s disorder or condition

- Studies that meet criteria as a “**minor increase over minimal risk**” must be performed in subjects with (or at risk for) a disorder or condition

Additional Safeguards for Children
21 CFR 50 Subpart D

21 CFR 50.51
Minimal Risk

21 CFR 50.52
More than a Minor Increase Over Minimal Risk
Prospect of Direct Benefit

21 CFR 50.54
Federal Panel

21 CFR 50.53
Minor Increase Over Minimal Risk

21 CFR 50.55
Permission & Assent
Additional Safeguards for Children
21 CFR 50.52

• “Any clinical investigation within the scope described in 50.1 and 56.101 of this chapter [21 CFR] 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, or by a monitoring procedure that is likely to contribute to the subject's well-being, may involve children as subjects only if the IRB finds that:

  (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; and
  (c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in 50.55”
Prospect of Direct Benefit (PDB)

• A “benefit” is “direct” if it:
  – Accrues to individual subject enrolled in the 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 “structure” of an intervention (i.e., dose, duration, method of administration, etc.)
  – Dose and duration of treatment must be adequate to provide a prospect of direct benefit

Prospect of Direct Benefit (PDB)

• Adult data to support the proof of concept may not be needed to initiate studies in pediatric patients
  – Nonclinical data may be sufficient, especially for diseases that are primarily pediatric
• A minimally effective dose must be tested to provide a PDB
  – Although a lower dose may be “safer,” if there is no benefit then testing in pediatric patients is not justified
• The clinical investigation must be of a sufficient duration to provide a PDB
  – Judgment is similar to what might be made in clinical practice
  – An accepted surrogate marker might be considered to confer a benefit
Component Analysis

• A clinical investigation may include more than one intervention or procedure
• Evaluate each intervention or procedure separately to determine whether it holds out the prospect of direct benefit to the enrolled child
  – “...the risk and anticipated benefit of activities described in a protocol must be evaluated individually as well as collectively”*
• 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)

Component Analysis

- Examples of components to consider include: “research only” procedures such as biopsies, diagnostic imaging studies, non-therapeutic procedural sedation*
- Placebo as a component
  - Risk of placebo itself may be “minimal” unless placebo is invasive (for example, sham injections)
  - Risk of harm from not receiving “proven” or “effective” treatment
  - Duration of placebo/sham injections may impact the risk determination
  - All aspects must be no greater than a minor increase over minimal risk

*http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM510177.pdf
Pediatric Pharmacokinetic (PK) Studies*

- The administration of a single dose of an investigational product to collect PK data generally does not offer a PDB to the individual child enrolled in the study.

- Administration of a single dose of an investigational product presents more than minimal risk, but the risks of a single dose of some products (with existing safety data) may be no more than a minor increase over minimal risk. Children enrolled in such a PK study must have a condition (21 CFR 50.53).

- Alternatively, a PK study of a drug that presents greater than a minor increase over minimal risk could be performed as part of a clinical trial that offers a PDB (21 CFR 50.52).

*General Clinical Pharmacology Considerations for Pediatric Studies [https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm425885.pdf]
Pediatric Extrapolation

• The use of extrapolation was first introduced in the 1994 Pediatric Labeling Rule

• “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...”

• Pediatric extrapolation allows efficacy to be extrapolated from adults to children or from one pediatric subpopulation to another

• Use of pediatric extrapolation, when acceptable, may streamline the pediatric drug development program
Alternative Pediatric Study Designs

• Certain study designs may reduce or eliminate the need for a dedicated pediatric study
  • Use of modeling and simulation may eliminate the need for a dedicated PK study in pediatric patients
  • Use of pediatric extrapolation may limit studies to those needed to establish dosing and safety depending on the certainty about extrapolation
• Adaptive study designs*, (e.g. prospectively planned dose ranging or dose titration) with continued dosing once a dose is established, should be considered to offer PDB and reduce the need to conduct multiple studies in children

*Adaptive Designs for Clinical Trials of Drugs and Biologics
Parental Permission

• Agreement... to participation of child... in clinical investigation. Permission must be obtained in compliance with 21 CFR 50 Subpart B, 21 CFR 50.3(r) and 21 CFR 50.55

• The parental permission form must contain adequate information to allow the parent or guardian to make an informed decision

• Informed consent is a “process,” including the opportunity to ask questions and consider participation, and continuing to provide information as the study progresses and situation requires

• “The description of potential benefits should be clear, balanced, and based on reliable information to the extent such information is available”*

Child Assent

• The child must provide **affirmative agreement** to participate in research
  – Failure to object may not be considered as **assent***

• Adequate provisions for soliciting a child’s **assent**
  – when a child is capable of providing **assent** (age 7 or older***)
  – age, maturity, and psychological state

• **Assent** may be waived if...
  – capability so limited that cannot be consulted, or
  – prospect of direct benefit important to child’s health or well-being available only in research, or
  – minimal risk research that otherwise is not feasible

*21 CFR 50.3(n); 50.55
Why Does PDB Matter?

• The National Commission recognized the vulnerability of children and determined that except for certain types of research interventions or procedures that are considered “low” risk, children must be offered a PDB to participate in research.

• Pediatric drug development programs are complex.
  – Support for PDB varies and depends on a number of factors such as the rarity of the disease, alternative treatments and the availability of adults with the condition under study.

• Strategies such as adaptive study designs, extrapolation and modeling and simulation may streamline pediatric product development and should be considered to maximize the benefit that children receive from participation in research.

• We have an obligation to have ongoing discussions with parents and children about the perceived benefits of participation in research.
Thank you!
Why Does Prospect of Direct Benefit Matter in Pediatric Clinical Trials?

Moderator: Gregory Daniel, Duke-Margolis Center for Health Policy
Understanding Direct Benefit and Challenges
Incorporating the Concept into Clinical Trials

Steven Joffe, MD, MPH
Founders Professor
Department of Medical Ethics & Health Policy

Establishing Prospect of Direct Benefit in Pediatric Clinical Trials
Margolis Center for Health Policy/FDA
Washington, DC
March 29, 2019
Safeguarding Children — Pediatric Research on Medical Countermeasures

Amy Gutmann, Ph.D.

In 2011, a bioterrorism-preparedness exercise conducted by the U.S. government examined the likely result of a large-scale release of weaponized anthrax spores in a city such as San Francisco.
Anthrax vaccine & children

- Anthrax vaccine is approved for pre-exposure prophylaxis in adults
  - Not approved for use in kids; no safety or efficacy data

- In major anthrax event, FDA can authorize use in adults under emergency designation
  - However, because of lack of safety data, cannot authorize use in kids outside of experimental protocol
Anthrax vaccine & children

• Absent an exposure event, children are not at risk of anthrax
  – Therefore do not have a “prospect of benefit” from inclusion in a vaccine trial
  – Yet risks of anthrax vaccine are considered greater than minimal
  – Therefore difficult to approve the trial, without federal committee review, under current regs
Paul Ramsey:  
*Children should never be used as subjects in nonbeneficial research*  

Ramsey P. Consent as a canon of loyalty with special reference to children in medical investigation.  
“The principle of an informed consent is a statement of the fidelity between the man [sic] who performs medical procedures and the man on whom they are performed.”
“From consent as a canon of loyalty in medical practice it follows that children, who cannot give a mature and informed consent...should not be made the subjects of medical experimentation unless, other remedies having failed to relieve their grave illness, it is reasonable to believe that the administration of a drug as yet untested or insufficiently tested on human beings, or the performance of an untried operation, may further the patient’s own recovery.”
Ramsey 3

“The limits this rule imposes on practice are essentially clear: where there is no possible relation to the child’s recovery, a child is not to be made a mere object in medical experimentation for the sake of good to come. The likelihood of benefits that could flow from the experiment for many other children is an equally insufficient warrant for child experimentation”
“...we owe the individual child the highest fiduciary loyalty we know how to perform. Basically contradictory to this it would be to consent to submit a child to procedures believed not to be in the child’s behalf. Parenthood was not made for this.”
But there’s a problem: without research, children become “therapeutic orphans”

“By an odd and unfortunate twist of fate, infants and children are becoming ‘therapeutic or pharmaceutical orphans.’ … drugs introduced since 1962 must be safe and efficacious, but only a small number of these have been studied in the pediatric age group....”

Current compromise

• Allow research if there’s a prospect of direct benefit (+ conditions)
• Allow research without prospect of direct benefit if low-risk
• Allow (burdensome) pathway for rare exceptions
Defining “direct benefit”

• **Benefit**: live longer, feel or function better
  – Everything else is a surrogate
  – But: study can offer the possibility of living longer or feeling or functioning better even if its endpoint is a surrogate

• **Direct**: results from/intrinsic to the research intervention
Defining “prospect”

“The second kind of research that presents relatively few ethical problems is that in which the risk is related to an intervention that holds out a reasonable promise of benefit for individual subjects... if the anticipated benefit to the children...is greater than the attendant risk, the intervention is justified.”

National Commission, Research Involving Children, 1977, p. 125
If only it were so simple!
Defining “prospect”: some possible rules of thumb

• Would you be surprised if the child experienced direct benefit?

• Would you consider it a miracle if the child experienced direct benefit?

• Would you endorse the statement, “There is no prospect of direct benefit from participating?”
  – If not → there is a prospect
Some final thoughts

• “Prospect of direct benefit” may not be the critical question
  — So long as there is at least a minimal possibility, focus on the relative-benefit question:
    • How does benefit-risk balance of participating compare with that of best alternative(s)?
  — Ask, Could a reasonable parent agree to allow the child to participate in the trial in hopes of benefit?
    • If yes, IRB should not stand in the way
Thank you!

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Session 1—Characterizing Prospect of Direct Benefit

**Moderator:** Gregory Daniel, Duke-Margolis Center for Health Policy
Subpart D Made Me Do It!

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Implications of Direct Benefit Skepticism in Pediatric Research

• Points to consider:
  • Benefit creep
  • Therapeutic misconception
  • Surrogate endpoints
  • Definitional challenges
  • Informed decisionmaking

• Not much different from research in adults
  • Except for the difference between grasping at straws for oneself and for one’s child
“Most Drugs Fail”

• RCTs rarely if ever pose a direct benefit problem
  • by virtue of equipoise
• Any remaining pediatric issues seem adequately addressed by component analysis
  • (which I usually understand fully only while Skip Nelson is explaining it)
• Early-phase research can be problematic
  • phase designations are fluid
  • novel biologics affect study design and prioritization of patient-subject group selection
  • but prospect of direct benefit remains elusive
Benefit Creep Increases Risk of Therapeutic Misconception

• Prospect of direct benefit is needed for pediatric research in which the experimental intervention presents more than a minor increase over minimal risk
• Prospect of direct benefit will be asserted by PIs and sponsors, found by IRBs, and believed by parents
• All are eager to help sick children; “doing something” is better than “doing nothing”
Defining Terms & Using Clear Language

• Prospect of direct benefit:
  • “a certain probability of success, and not the mere possibility of benefit” – Lainie Ross
  • “fairly immediate” and well-founded scientifically – National Commission
  • reasonable people under the circumstances would consider it sufficient to choose to participate in anticipation of the benefit – my definition (which does not mean all would/should choose participation)
Amassing Evidence

• Surrogate endpoints
  • Validated?
  • Reasonable connection with symptom relief or life prolongation?

• Comparison with available alternatives
  • “no treatment alternatives” may be very different from comparing investigational intervention with palliation
  • “nothing else has worked” doesn’t mean this will
  • severity of illness doesn’t increase likelihood of benefit
  • “nothing to lose” is never true

• Is risk minimization most important?
Informed Decisionmaking

- How much detail is enough?
- Nature:
  - Prolonging the status quo? Improvement in symptoms or function? Cure? “It depends”? Or just SE?
- Magnitude (size, duration)
  - Ditto
- Likelihood
  - How to be more specific than “may or may not”?
- Uncertainty!!
  - How to talk about it
  - Why is it so hard to talk about it?
Is There a Path Forward?

• Robust guidance needed about what evidence is needed for prospect of direct benefit, and how much is enough
• Standing 54/407 panel needed?
• Why not give IRBs better information & see what they do with it?
  • more realistic assessment of prospect of direct benefit & uncertainty
• AND give parents better information & help them understand it
  • supports frank assessment of prospect of direct benefit & uncertainty
• Seek amendments of 52/405 and/or 53/406?
• Add Lainie Ross’s “secondary direct benefit”?
• Goal: promote thorough discussion, realistic comparison with palliative/supportive care & assessment of commensurability with child’s experience, even in light of “do everything” desire
Session 1–Characterizing Prospect of Direct Benefit

Moderator: Gregory Daniel, Duke-Margolis Center for Health Policy
Is Therapeutic Benefit in Early Phase Pediatric Trials: Oxymoron?
1: children: sentinels
why are children special?
Biologics Control Act, 1902
Food, Drug, and Cosmetic Act, 1938
Kefauver Harris 1962
2: intervention ensembles
drug +
co-interventions
dose
schedule
diagnosis
monitoring
side effect mgmt

therapy
3: systematic review
Risk and surrogate benefit for pediatric Phase I trials in oncology: A systematic review with meta-analysis

Marcin Waligora¹, Małgorzata M. Bala²*, Magdalena Koperny¹,³, Mateusz T. Wasylewski¹, Karolina Strzebonska¹, Rafał R. Jaeschke⁴, Agnieszka Wozniak⁵, Jan Piasecki¹, Agnieszka Śliwka¹,⁶, Jerzy W. Mitus⁷,⁸, Maciej Polak¹,⁹, Dominika Nowis¹⁰,¹¹,¹², Dean Fergusson¹³, Jonathan Kimmelman¹⁴*
| Type of participants | Number of studies | Total number of patients | SOLID TUMORS | | HEMATOLOGICAL MALIGNANCIES | | BOTH TYPES OF MALIGNANCY |
|---|---|---|---|---|---|---|
| | | | Response rate | Drug-related death rate | Response rate | Drug-related death rate | Response rate | Drug-related death rate |
| Horstmann 2005 | adults | 460 | 11,935 | - | - | - | - | 10.6% | 0.49% |
| Italiano 2005 | adults | 10 | 190 | 7.2% | 0.5% | - | - | - |
| Kim 2008 | adults | 16 | 262 | 4.0% | 0.4% | - | - | - |
| Roberts 2004 | adults | 213 | 6,474 | 3.8% | 0.54% | - | - | - |
| Wong 2016 | adults | 49 | 1,353 | - | - | - | - | 2.95% | - |
| Lee 2005 | pediatric | 69 | 1,973 | - | - | - | 9.6% | 0.5% |
| CURRENT REVIEW | pediatric | 170 | 4604* | 3.17% | 1.85% | 27.90% | 10.29% | 4.04% | 2.09% |

* Rates calculated only for a fraction of studies reporting objective response rates and AE. Please be aware of the differences in methodologies of compared studies.
4: policy implications
RIGHT TO TRY ACT
Stop FDA restrictions that kill.
5: preclinical evidence
FDA Guidance on INDs for Phase 1

To the extent that such studies may be important to address safety issues, or to assist in evaluation of toxicology data, they may be necessary; however, lack of this potential effectiveness information should not generally be a reason for a Phase 1 IND to be placed on clinical hold.
"[t]here is just not much emphasis on the sponsor’s basis or rationale for hoping the drug will be effective. That determination is largely left to the sponsor. I can’t think of any cases where [FDA has] said you can’t do this [phase 1] study because we’re just too skeptical."

Robert Temple, FDA, 2016
“these data raise questions about… the lack of FDA requirements for in vivo testing of intended cell lines.”
6. way forward
10% → 80%
Correction of ADA-SCID by Stem Cell Gene Therapy Combined with Nonmyeloablative Conditioning

Alessandro Aiuti,¹ Shimon Slavin,² Memet Aker,² Francesca Ficara,¹ Sara Deola,¹ Alessandra Mortellaro,¹ Shoshana Morecki,² Grazia Andolfi,¹ Antonella Tabucchi,³ Filippo Carlucci,³ Enrico Marinello,³ Federica Cattaneo,¹ Sergio Vai,¹ Paolo Servida,⁴ Roberto Miniero,⁵ Maria Grazia Roncarolo,¹,⁶ * Claudio Bordignon¹,⁶ #†
a) less 50.52*; more 50.54*

* i.e. less 405; more 407
b) narrow conditions for 50.52
1) confirmatory preclinical evidence
1) confirmatory preclinical evidence

2) mechanism understood
1) confirmatory preclinical evidence
2) mechanism understood
3) narrow range of conditions
1) confirmatory preclinical evidence
2) mechanism understood
3) narrow range of conditions
4) performance metrics
Session 1 Discussion Questions

1. Does the level of evidence needed to support a prospect of direct benefit differ based on disease severity and available alternative therapies?
2. Has our understanding of prospect of direct benefit changed since the National Commission issued their recommendations on research involving children in 1978?
3. When is the likelihood that a child will experience benefit so doubtful that we should not be willing to say a prospect of direct benefit exists?
4. How does prospect of direct benefit differ from demonstrating direct benefit?
5. How does direct benefit differ from collateral benefit?
6. How do we avoid promoting a “therapeutic misconception” in pediatric clinical trials?
Break

The meeting will continue after a 15 minute break.

**WiFi**: Hyatt Meeting

**Password**: Duke2019
Session 2—Prospect of Direct Benefit and Pediatric Extrapolation

Moderator: Gregory Daniel, Duke-Margolis Center for Health Policy
Prospect of Direct Benefit and Pediatric Extrapolation

March 29, 2019

Robert “Skip” Nelson, MD PhD FAAP
Senior Director, Pediatric Drug Development
Pediatric Development Team (PDT) Leader, Immunology

At the heart of it all
Disclosure

• This presentation is intended for educational purposes only. Statements of fact and opinions expressed are those of the participant individually and, unless expressly stated to the contrary, are not the opinion or position of any company, institution or third party entity.

• Robert Nelson is a full-time employee of Johnson & Johnson.
Topics

• Surveying the Moral Terrain
• Extrapolation of Causal Inferences
  – Efficacy
  – Prospect of Direct Benefit
• Scientific Necessity
• Quantifying Uncertainty
• Closing Reflections
Surveying the Moral Terrain

- **Pediatric Development Team Vision**: A world in which children have access to safe and effective medicines for immune mediated diseases at the same time as their parents.
  - Achieving this vision requires the innovative use of partial or full extrapolation to reduce the need for generating pediatric evidence.

- **Window of Opportunity**: A pediatric development program should start as soon as there are data supporting a sufficient prospect of direct benefit to justify the risks so that the pediatric clinical trial(s) can be finished before off-label use makes these clinical trials difficult if not impossible to complete (estimate: about 2 to 3 years after adult approval).
Topics

• Surveying the Moral Terrain
• Extrapolation of Causal Inferences
  – Efficacy
  – Prospect of Direct Benefit
• Scientific Necessity
• Quantifying Uncertainty
• Closing Reflections
Extrapolation†

• Extrapolation is an inductive inference that extends known experience and/or data (“source”) into an area not known or previously experienced (“target”) to arrive at a (credible, but inherently uncertain or probabilistic) knowledge of the unknown area.

†In mathematics, extrapolation is the process of estimating, beyond the original observation range, the value of a variable on the basis of its relationship with another variable. It is similar to interpolation, which produces estimates between known observations. The use of modeling in population pharmacokinetics is an example of this type of mathematical extrapolation.
(Pediatric) Extrapolation of Efficacy

• Efficacy is a causal inference that is extrapolated from the “source” population to the “target” population based on a descriptive inference (i.e., sufficiently similar).

• The (reasonable) clinical assumption that the course of the disease and the response to treatment are the two key “descriptive” attributes on which extrapolate efficacy was proposed a priori by FDA in 1992.

• As the science of extrapolation evolves, these attributes may change (e.g., tissue agnostic targeted therapies).

†“Specific Requirements on Content and Format of Labeling for Human Prescription Drugs: Proposed Revision of “Pediatric Use” Subsection in the Labeling” Federal Register/Vol. 57, No 201, dated October 16, 1992
“Sufficiently Similar” Populations

DIFFERENT  DISSIMILAR  SIMILAR  SAME

INSUFFICIENT  ?  SUFFICIENT

SOURCE POPULATION

TARGET
“Sufficiently Similar”: Source/Target

• Age (e.g., pediatric/adult) is an arbitrary distinction from a disease perspective, and is based on ethical, social and operational (care location) considerations.

• Disease examples:
  – Asthma (clinical studies in ages > 12 years and older)
  – Depression (generally clinical studies divided by age, i.e., adolescent/adult, but would 12-24 years of age be a more rational grouping?)
Extrapolation and Prior Pediatric Trial Results

• A successful pediatric clinical trial establishes that efficacy can be extrapolated.
  – Our confidence in this conclusion may depend on the extent to which the pediatric result used prior adult data (i.e., amount of borrowing).

• Does a failed pediatric clinical trial mean that efficacy cannot (or no longer) be extrapolated?
  – No. Clinical trials may fail for many reasons, only one of which may be an inability to extrapolate efficacy.
## Treatment of Asthma ≥ 12 years of age
(inhaled corticosteroid and long acting beta agonist)

<table>
<thead>
<tr>
<th>Product; current asthma indication by age</th>
<th>Approval (≥ 12 yrs. old)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVAIR DISKUS (fluticasone/salmeterol); patients ≥ 4 yrs. old</td>
<td>August 24, 2000</td>
</tr>
<tr>
<td>ADVAIR HFA (fluticasone/salmeterol); patients ≥ 12 yrs. old</td>
<td>June 6, 2006</td>
</tr>
<tr>
<td>SYMBICORT (budesonide/formoterol); patients ≥ 6 yrs. old</td>
<td>July 21, 2006</td>
</tr>
<tr>
<td>DULERA (mometasone/formoterol); patients ≥ 12 yrs old</td>
<td>June 22, 2010</td>
</tr>
<tr>
<td>BREO ELLIPTA (fluticasone/vilanterol); patients ≥ 18 yrs. old (NOTE: The adolescent sample size was relatively small.)</td>
<td>Not approved for 12-18 years of age; April 30, 2015.</td>
</tr>
<tr>
<td>AIRDUO RESPICLICK (fluticasone/salmeterol); patients ≥ 12 yrs. old</td>
<td>January 27, 2017</td>
</tr>
</tbody>
</table>
Topics

• Surveying the Moral Terrain
• Extrapolation of Causal Inferences
  – Efficacy
  – Prospect of Direct Benefit
• Scientific Necessity
• Quantifying Uncertainty
• Closing Reflections
Causal Inferences

• Whether administering a drug is efficacious and/or offers a prospect of direct benefit are both causal inferences (that is, if [drug intervention], then [clinical benefit]).

• From a policy perspective, the two judgments differ in the degree of tolerable uncertainty.
  – Efficacy (from a regulatory perspective) requires either two clinical trials (p<0.05), one clinical trial (p<0.025), or one clinical trial (p<0.05) with additional supporting evidence.
  – PDB does not (and should not) require this same level of certainty.
Clinical Judgment
Prospect of Direct Benefit (21 CFR 50.52)

• “The IRB should evaluate research protocols of this sort in the same way that comparable decisions are made in clinical practice. It should compare the risk and anticipated benefit of the intervention under investigation (including the monitoring procedures necessary for care of the child) with those of available alternative methods for achieving the same goal, and should also consider the risk and possible benefit of attempting no intervention whatsoever.”

Prospect of Direct Benefit (PDB)

• Whether intervention offers “prospect of direct benefit” must be evidence-based.
  – This judgment involves extrapolation from a “source” population (e.g., adult human or non-human animal model) to the “target” pediatric population.
  – Do the data make us reasonably comfortable that children may benefit from intervention? Is dose/duration of treatment with investigational drug sufficient to offer intended benefit?

• Whether intervention offers PDB is separate from whether that PDB of sufficient probability, magnitude and type to justify risks of intervention, given clinical context.
  – Risk/benefit is a complex scientific, clinical and moral judgment, similar to clinical practice.
  – The justification of an appropriate balance of risk and potential benefit may include the importance of “direct benefit” to the individual child; the possibility of avoiding greater harm from the disease; the degree of “tolerable” uncertainty; the disease severity (e.g., degree of disability, life-threatening); and the availability of alternative treatments.
Tolerable Uncertainty
What is the Acceptable Risk of Being Wrong?

• The tolerable uncertainty concerning the decision to approve a new drug (i.e., efficacy) is framed by the risk of being wrong across an entire population.

• The tolerable uncertainty concerning the decision to expose a child to the risks of a new drug in a research protocol (i.e., prospect of direct benefit) is framed by the risks and potential benefits to that individual child.

• Arguably, the lack of safe and effective treatment options for a smaller pediatric population with severe life-threatening disease argues for a level of tolerable uncertainty closer to that of individual clinical decisions.
There are at least three dimensions of uncertainty when extrapolating the prospect of direct benefit:

- Are the source and target populations sufficiently similar (in the relevant descriptive characteristics) to support this extrapolation?
- Are we using a surrogate endpoint that may be associated with a relevant clinical endpoint, but not acceptable as an efficacy endpoint?
- What should be the tolerable level of uncertainty (i.e., control of type 1 error) associated with the assessment that the intervention offers a sufficient prospect of direct benefit to justify the risks?
Topics

• Surveying the Moral Terrain
• Extrapolation of Causal Inferences
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• Closing Reflections
Children should only be enrolled in a clinical trial if the scientific and/or public health objective(s) about the health and welfare of children cannot be met through enrolling subjects who can consent personally.

- Derives from justice of equitable selection and minimizing risks [21 CFR 56.111(a)(1) and (b); 45 CFR 46.111(a)(1) and (b)]
- Practical application (using **extrapolation**): determine type (and timing) of clinical studies required to establish "safe and effective" pediatric use.
- Claim: effective and efficient use of extrapolation is a **moral obligation**.

"A more targeted generation of evidence should help to ensure that **children only participate in clinical trials with specific objectives that further the scientific understanding of a medicinal product for use in children** and, address the requirements for regulatory decision-making.” (emphasis added)

- EMA Reflection Paper on Use of Extrapolation (7 October 2018)
Scientific Necessity and Extrapolation

• Balancing two ethical principles
  – Avoid unnecessary exposure to risks (i.e., not too early or too much)
  – Assure timely access to safe and effective medicines (i.e., not too late)

• Pediatric studies should start as soon as data exist supporting a sufficient prospect of direct benefit to justify the risks
  – This moment will be before adult efficacy data are available
  – What (concurrent) pediatric studies should be performed?
  – The answer may depend on whether pediatric development would continue if the adult program fails to demonstrate efficacy
    • If yes, a full pediatric development program (e.g., efficacy) may be justified
Dosing and Safety Only
What is the impact on pediatric sample size?

• Usually pediatric exposure-response (E-R) data are needed, rather than PK (exposure) matching alone.
• For an E-R design, robust adult E-R data likely are needed to predict (at least two) pediatric doses to which children will be randomized.
• Differences in response between two doses are evidence of efficacy; however, extrapolation of adult efficacy still may be necessary.
  – Descriptive comparison of pediatric to adult E-R curves requires extrapolation of adult efficacy.
  – Comparison of responses at two doses may not require extrapolation, if adequately powered.
  – Sufficient numbers of children would need to be randomized to the higher dose to assess safety.
• Extrapolation of adult efficacy may avoid pediatric exposure to a placebo control, the use of which may be ethically unacceptable.
Topics

• Surveying the Moral Terrain
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• Scientific Necessity
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• Closing Reflections
Extrapolation

EMA Reflection Paper (7 October 2018)

• Extrapolation - inference from known (source) to unknown (target).
  – uses quantitative methods to assess the relevance of known information and conclusions in the source population(s) to the target population(s) with respect to the disease, drug pharmacology and clinical treatment response.
  – reduces amount of, or need for, additional evidence (e.g., types of studies, design modifications, number of patients required) to reach conclusions.

• Requirements for evidence generation to support licensing in target population will be a continuum, ranging from identification of an appropriate posology to a full clinical development in the event that no extrapolation is possible.
Choice of Level of Weighting Prior Data
Impact on Simulated Type 1 Error and Power
Choice of Level of Weighting Prior Data

Impact on Simulated Type 1 Error and Power

Clinical and moral judgment about extrapolation and tolerable uncertainty (NOT statistical decision)
Topics

• Surveying the Moral Terrain
• Extrapolation of Causal Inferences
  — Efficacy
  — Prospect of Direct Benefit
• Scientific Necessity
• Quantifying Uncertainty
• Closing Reflections
Closing Reflections (1 of 2)

- Extrapolation is not a yes or no question.
  - How do we know we can’t extrapolate? What are the nature of those differences? For example, a different inflammatory burden (in an immune-mediated disease) between children/adolescents and adults may translate to a difference in efficacy at the population level (that might be overcome by targeting a different exposure), but we could still extrapolate from an adult subpopulation selected, for example, based on propensity score matching.

- Strictly speaking, if you can’t extrapolate based on the pediatric and adult disease not being sufficiently similar (as opposed to the disease being sufficiently similar, but the response different), any data about prospect of direct benefit in adults also could not be extrapolated to children.
Formulating an extrapolation concept does not require any positive adult efficacy studies (e.g., establish disease similarity using shared pathophysiology, natural history; similar response using real-world evidence).

- Characterize the degree of uncertainty that should be mitigated by the extrapolation plan.
- Extrapolation of efficacy can be appropriate for a new mechanism of action, provided that pediatric and adult efficacy has been previously established for other drug targets. If adult efficacy is demonstrated with the new MOA, why would we assume that the new target mysteriously disappears when we move from adults to children/adolescents?

The extrapolation plan (i.e., pediatric clinical studies) can run concurrently with adult program once prospect of direct benefit has been established.

- Percent borrowing of adult data directly proportional to the certainty about extrapolation.
Thank you
Session 2—Prospect of Direct Benefit and Pediatric Extrapolation

Moderator: Gregory Daniel, Duke-Margolis Center for Health Policy
Prospect of Direct Benefit in Pediatric Clinical Trials

Duke-Margolis Center for Health Policy and FDA
March 29, 2019

Anne Zajicek, MD, PharmD
Deputy Director, Office of Clinical Research
Office of the Director, NIH
Key Points

• The Best Pharmaceuticals for Children Act (BPCA) trials have used full extrapolation of efficacy from adults to children, leaving PK/dosing and safety studies to be performed.

• For PK studies, opportunistic study design, sparse sampling techniques, use of scavenged samples (extra blood/plasma remaining from other lab tests), and development/validation of dried blood spot assay methods has reduced the need for additional blood draws.

• Background medication use and safety data from large databases reduces the need for unnecessary clinical trials, and prevents unfeasible trials from being developed.

• Data sharing is required: FDA Docket, NICHD Data and Specimen Hub (DASH)

• Incorporation of Good Clinical Practice (GCP) training is being incorporated into pediatric clinical trials.
Meropenem Label for Neonates

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dose (mg/kg)</th>
<th>Dose Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants less than 32 weeks GA and PNA less than 2 weeks</td>
<td>20</td>
<td>Every 12 hours</td>
</tr>
<tr>
<td>Infants less than 32 weeks GA and PNA 2 weeks and older</td>
<td>20</td>
<td>Every 8 hours</td>
</tr>
<tr>
<td>Infants 32 weeks and older GA and PNA less than 2 weeks</td>
<td>20</td>
<td>Every 8 hours</td>
</tr>
<tr>
<td>Infants 32 weeks and older GA and PNA 2 weeks and older</td>
<td>30</td>
<td>Every 8 hours</td>
</tr>
</tbody>
</table>

- Intravenous infusion is to be given over 30 minutes.
- There is no experience in pediatric patients with renal impairment.

GA: gestational age and PNA: postnatal age

DOSAGE FORMS AND STRENGTHS

500 mg meropenem for Injection Vial (3)
1 gram meropenem for Injection Vial (3)

https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/050706s037lbl.pdf
Population Pharmacokinetics of Intravenous Acyclovir in Preterm and Term Infants.

Characterization of the Population Pharmacokinetics of Ampicillin in Neonates using an Opportunistic Study Design.

Pediatric Studies of Ampicillin Conducted in Accordance With the Public Health Service Act

A Notice by the Food and Drug Administration on 04/25/2017

Welcome to the Data and Specimen Hub

DASH is a centralized resource for researchers to store de-identified data and to access data and associated biospecimens from NICHD supported studies for use in secondary research.

Search for studies...

Recently Submitted Studies

Pharmacokinetics of Antistaphylococcal Antibiotics in Infants - Rifampin (BPCA STA01-Rifampin)
Submission Date: MARCH 21, 2019

Study Description: NICHD-2012-STA01 was a multiple center, open label, multiple-dose pharmacokinetic study. The primary objective of this study was to determine the pharmacokinetics (PK) of rifampin, tetracycline-clindamycin, and clindamycin in infants to address gap in pediatric labeling of these drugs. Only the data for rifampin is reported here. Twenty seven participants were enrolled. Overall, a total of 66 plasma concentrations from 22 participants were used to construct the population PK model. Rifampin PK was well characterized by a 1 compartment PK model, only postnatal age (PNA) was retained as significant for clearance. No adverse events were related to rifampin and there were no serious adverse events reported. Rifampin was well tolerated in the study population. In addition, body weight and PNA were significant covariates for clearance, indicating that rifampin in infants should be dosed using weight and PNA.

A Randomized Trial of Colpocexy and Urinary Reduction Efforts (CARE Trial)
Submission Date: MARCH 19, 2019

Study Description: This study will determine which, if any, clinical tests are useful for predicting post-operative urinary incontinence. The study will also determine if a Burch urethropexy should be performed routinely or selectively at the time of sacrococpopexy in continent women.

https://dash.nichd.nih.gov/
Session 2—Prospect of Direct Benefit and Pediatric Extrapolation

Moderator: Gregory Daniel, Duke-Margolis Center for Health Policy
Comments re: Prospect of Direct Benefit and Extrapolation

Lainie Friedman Ross, MD, PhD
Carolyn & Matthew Bucksbaum Professor of Clinical Medical Ethics
University of Chicago
Research on Children: Access versus Protection

- Pre-1960: “cheaper than calves”

- National Commission for the Protection of Human Subjects in Biomedical and Biobehavioral Research: children are a vulnerable population
- Federal Regulations, Subpart D
- Shirkey H. “Therapeutic Orphans” (1999 Pediatrics)
- 1990-today: Pediatric Rule, Pediatric Research Equity Act, FDAMA and BPCA: carrot and stick to encourage research involving children.
Prospect of Direct Benefit

- Prospect of direct benefit (PDB) requires less certainty than efficacy
- As Nelson noted, for ethical participation of children in research, 2 separate questions
  - Does the intervention offer PDB?
    - Different amount of risks permitted in Fed Regulations depending on whether PDB
  - Is the PDB of sufficient probability, magnitude and type to justify risks of intervention, given clinical context, alternatives, and the risks of non-intervention?
    - Risk-benefit analysis
- When, if ever, can other benefits of research be considered? (King’s distinction between)
  - Direct Benefit
  - Collateral Benefit
  - Aspirational Benefit
- Can we/should we use other benefits in determining PDB for Fed Reg Classification?
  - No
- Can we/should we consider other benefits in risk-benefit analysis?
Extrapolation

“Primary rationale for using extrapolation approaches is to avoid unnecessary studies in the paediatric population for ethical reasons, for efficiency, and to allocate resources to areas where studies are the most needed” at p. 660.

The use of pediatric extrapolation is now not only a strategy to increase the efficiency of paediatric medicines development but also an ethical imperative and part of a new paradigm in global paediatric drug development” at p. 659

When is extrapolation permissible?

- **US**: Extrapolation is permissible if sufficient similarity:
  - Disease progression
  - Response to intervention between source and target population

- **EMA**: “expanded and refined algorithm” for extrapolation based on:
  - Pharmacology (drug disposition and effect)
  - Disease manifestation and progression
  - Clinical response to treatment (efficacy and safety)

- Perspectives are quite similar although EMA may place greater emphasis on quantitative extrapolation (modelling and simulation)
Challenges to extrapolation

• Extrapolation may be more useful for PDB and efficacy than for safety
  – Need to identify gaps in knowledge and uncertainties and develop plans to address them
  – Need to evaluate long-term risks related to growth and maturation

• Extrapolation may be less useful
  – Youngest populations (e.g. premature and full-term infants)
  – Orphan diseases

• Utility of registries
  – (Not all registries are created equal)
Uncertainty

• Nelson described that there are at least three dimensions of uncertainty when extrapolating the prospect of direct benefit.
  – Are the source and target populations sufficiently similar
  – Are we using a surrogate endpoint that may be associated with a relevant clinical endpoint, but not acceptable as an efficacy endpoint?
  – What should be the tolerable level of uncertainty (i.e., control of type 1 error)

• Mitigation of uncertainty
  – Long-term follow-up (esp. for chronic conditions)
  – Post-authorization safety and efficacy surveillance
  – (The utility of well-designed and well-funded registries)
  – Use of data generated in routine clinical practice
Research on Children: Access versus Protection

- Focus on prospect of direct benefit
  - (Other benefits are good and important but cannot define the type of study being proposed)
- Extrapolation
  - To reduce the number of children exposed to risk
  - To reduce the time from safety and approval in adults to studies in children
- Need for long-term follow-up to ensure both safety and efficacy
  - Robust registries
- Proceed with caution
Session 2 Discussion Questions

1. How are the concepts of scientific necessity and prospect of direct benefit interrelated? From an ethical perspective, if pediatric extrapolation is appropriate, should pediatric studies be limited to data needed to support safety and dosing? What if efficacy studies in pediatrics could be completed sooner without data from adults and are the pediatric studies ethical if more burdensome to children?

2. Is it possible to make a determination that pediatric extrapolation is acceptable prior to completing adult studies? Can pediatric studies be designed to run concurrently with adult studies and still have sufficient prospect of direct benefit?

3. If we have doubts about our ability to extrapolate, and we anticipate differences in efficacy between pediatric patients and adults, do we need some adult human efficacy data to support prospect of direct benefit or can pediatric studies be initiated based on nonclinical proof-of-concept once we have adequate human data to support safety and dosing?
Lunch

We will resume at 1:00 pm.

WiFi: Hyatt Meeting
Password: Duke2019
Case Study 1—Use of Nonclinical Models as Proof-of-Concept to Support Pediatric Clinical Trials

Moderator: Mark McClellan, Duke-Margolis Center for Health Policy
Case Study 1: Can Nonclinical Studies Establish PoC for Pediatric Indications?

Wendy Halpern, DVM, PhD, DACVP
Genentech, Inc
Efficacy Models for Pediatrics Must Consider Development

Mechanistic Hypothesis + Drug Candidate

Nonclinical Data: Mfr (Potency, Purity), Safety, DMPK and Evidence of Efficacy

Clinical Study Design

& compressed development timelines for nonclinical models can impair interpretation

- Dose:exposure relationship may change during development
- *Time can overlap with development
- *Efficacy may change across development
Maybe? Sometimes? It depends…

All models are wrong, but some are useful.


…and for some pediatric diseases they are the best we have
Value Depends on Relevance

• How well do we understand the **disease**?
  – Complex vs simple pathogenesis
  – Severity and progression

• How good is the **model** is for the disease?
  – Cellular/Molecular Pathogenesis
  – Onset/Presentation
  – Progression
  – Outcome

• How relevant is the **pharmacology**?
  – For humans and for animals
  – Comparable?
  – How well do we understand ADME and Safety?

• How do all of these relate to **development** (and vice versa)?
Broad Spectrum of Nonclinical Models Supporting Pediatrics

Genetic Models of Genetic Diseases
- Inborn errors of metabolism
- Cystic Fibrosis
- Neurodegenerative diseases of childhood
- Primary immunodeficiencies

Models of Infectious Disease
- Shared across species
- Specific relevance to pediatrics
- Endpoints
  - Mortality?
  - Biomarkers
  - Pathology

Cell Line Models of Pediatric Cancers
- In vitro proliferation
- SC Xenografts
- Orthotopic xenografts
- Cell lines vs PDX

Companion Animal Models of Pediatric Cancers
- Naturally occurring cancers in pets
  - Gliomas
  - Lymphomas
  - Sarcomas

- Lack of pediatric-specific models for CIT
Recent Models Developed for SMA and CF

• Inactivation of human SMN1 & low SMN2 leads to severe disease
• Pigs only have SMN1 gene
• AAV-delivered intrathecal antisense (shRNA) knockdown results in phenotypically compelling disease

• Challenges include timing, progression and mode of therapy


• CF disease models include mouse, rat, pig, ferret and organoids
• In vivo models tend to have more GI disease and less lung disease than human CF patients

• How much relevance, in vitro or in vivo, is enough to be useful?


Cell line to *in vivo* data bridging the gap from adult to pediatric tumors

- **Pathway Biology Most Relevant for Pediatric Brain Tumors**
  - Adult POC established for extracranial solid tumors
  - CNS exposure of concern
    - Higher exposure in juvenile rodents than adult rodents
  - Orthotopic rodent model using pediatric patient-derived xenograft, BUT:
    - Mice are adult
    - Mice can tolerate higher doses of drug than rats or humans (adult patients)
    - Tumors are physically small—relevant?
    - Process of engraftment disrupts BBB

**Key Questions:**

*How much does model success increase confidence in efficacy?*

*How much does model failure decrease confidence in efficacy?*


Challenges and Opportunities with Naturally Occurring Cancers in Companion Animals: Oncology drugs with potential benefit in OSA

- Difficult to study in children due to rapid progression in relapsed setting

- Potential utility of canine study in dogs with OSA
  - Disease biology and presentation fairly comparable to humans
  - Presurgical intervention possible, access to primary tumor tissue
  - Typically progresses rapidly due to early metastases
    - Can identify effects of intervention over relatively short period

- But first:
  - Need to establish **canine relevance**
    - Target and efficacy profile
  - Need to address potential **immunogenicity** in dogs
  - Need to manage **safety** profile

  ...and the best pediatric opportunity may be in **combination** with other therapies
  - Requires partnership
  - Relevance in dogs adequate to enable study

https://www.csuanimalcancercenter.org
FAQs of the GNE comparative oncology team

• What is the underlying molecular biology in canine cancer?

• How do you account for breed differences in dosing and pharmacokinetics?

• What happens if there is a safety finding in a comparative oncology study?

• Does the drug engage the canine target ~ human target?

• Do you have comparable tools to interrogate pathway modulation and immune system response?

• Does this require our internal resources?

• What is the intellectual property agreement?

• What is the enrollment rate / time to data?

• Dogs get cancer?
Increased industry collaborations and data sharing demonstrate the inability to go it alone

• Open Science & Robust informatics solutions → meaningful data at scale
• Shared sense of urgency → impact
• Cross-functional → leverage expertise
• Creative fiscal solutions → overcome limited budgets
• Strategic alignment → advance the field together
• Passionate
• Practical

Can Nonclinical Models Establish Pediatric PoC?

- Many models have been used
- No model is perfect—know limitations
- Pathway relevance vs therapeutic efficacy

- **Goal:** Enable an expeditious path to address high unmet need in rare patient populations
Case Study 1—
Use of Nonclinical Models as Proof-of-Concept to Support Pediatric Clinical Trials

Moderator: Mark McClellan, Duke-Margolis Center for Health Policy
Nonclinical Models and Proof-of-Concept for Pediatric Trials

Kathleen M. Donohue, MD

Division of Gastroenterology and Inborn Errors Products (DGIEP)
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Center for Drug Evaluation and Research

Prospect of Direct Benefit in Pediatric Clinical Trials
Duke-Margolis Center for Health Policy
March 29, 2019
Disclosure Statement

• No conflicts of interest
• Nothing to disclose
• This talk reflects the views of the author and should not be construed to represent FDA’s views or policies
• In this talk “drug” refers to both drugs and biologics
Infantile Pompe Disease

acid α-glucosidase (GAA)

Van der Ploeg et al. Lancet 2008
Pompe Disease

Prospect of Direct Benefit?

- Deficiency acid α-glucosidase (GAA)
- Gaa exon –/–
- Glycogen accumulation
- Motor function – wire hang test, weak waddling gait, muscle wasting

- Dose-dependent reduction of glycogen accumulation and increased GAA activity in mice
- Proof of concept with similar biologic in pediatric patients

Myozyme reviews Drugs@FDA
Infantile Pompe Trial

- n=18 ≤ 7 months
- n=61 dx by 6 months

Survival:
- 2% survival
- 89% survival

Dosages:
- 20 mg/kg
- 40 mg/kg

Avalglucosidase alfa for ~ 18 months (2003-2005)

Historical controls (1982-2002)
Late-infantile neuronal ceroid lipofuscinosis type 2 (CLN2)

Lysosome

- Nerves
- Muscles
- Eyes

Ezaki et al. J Biochem 2000
Late-infantile neuronal ceroid lipofuscinosis type 2 (CLN2)

Symptoms
- Progressive psychomotor regression
- Myoclonus
- Seizures
- Blindness
- Early mortality

Fietz et al. Mol Genet Metab 2016
CLN2 Disease

Prospect of Direct Benefit?

- Reduction of lysosomal storage material accumulation in CNS of canine model
- Improvement of cognitive and motor function
- Delay in or prevention of neurodegenerative clinical signs
- Extension of lifespan

- Spontaneous canine null mutation in TPP1
- Autoflourescent LSM accumulation in neurons
- ↓ TPP1 in retina, brain, CSF on ELISA
- Menace response, tremors, ataxia, circling behavior, early mortality
- T-maze test, ophtho exams
Late-infantile CLN2 Trial

- n=24 TPP1 deficiency
- n=42 TPP1 deficiency
- 21 months cerliponase alfa
- (2000s to 2010s)
- 300 mg QOW intraventricular
- slower loss of ambulation

faster loss of ambulation

historical controls (1980s to 2000s)
Questions

1. If the disease only exists in pediatric patients, how should nonclinical models be used to support proof-of-concept and prospect of direct benefit in the pediatric population? In what situations might human data from healthy volunteers be informative?

2. How, if at all, does the utility of nonclinical models that demonstrate improvement in a biomarker differ from the utility of nonclinical models that demonstrate improvement in a clinical manifestation of the disease?

3. In what situations may an *in vitro* model be used to support proof-of-concept?

4. Assuming a serious disease with limited therapeutic options, are data to support proof-of-concept for a product in a nonclinical model of the disease sufficient to support the prospect of direct benefit and allow enrollment of pediatric patients, if an adult population with the disease exists?
Acknowledgements

• Jackye Peretz
• Dina Zand
• Dragos Roman
Case Study 1—
Use of Nonclinical Models as Proof-of-Concept to Support Pediatric Clinical Trials

Moderator: Mark McClellan, Duke-Margolis Center for Health Policy
Prospect of Direct Benefit: Model Systems

Forbes “Denny” Porter
Prospect of Direct Benefit: Model Systems

- What models are available?
  - *In vitro*
    - Cell type
  - *In vivo*
    - Species

- What aspect of the human disease is modeled?

- How well is the human pathology modeled?

- What is the “therapeutic” response and how does that relate to a potential clinical benefit?
Prospect of Direct Benefit: Model Systems

NPC1⁻/⁻ i³neurons

Prabu et al. (unpublished)

Prospect of Direct Benefit: Model Systems

Davidson et al. (2009) PlosOne 4: e6951
Liu et al. (2009) PNAS 106: 2377
Case Study 1—Use of Nonclinical Models as Proof-of-Concept to Support Pediatric Clinical Trials

Moderator: Mark McClellan, Duke-Margolis Center for Health Policy
Babies in Bio-bags

John D. Lantos MD
Children’s Mercy Bioethics Center
Kansas City, MO
Schematic of the artificial womb, which supported the premature lambs for four weeks. Credit: The Children’s Hospital of Philadelphia
"We've been extremely successful in replacing the conditions in the womb in our lamb model."
Life after EXTEND

Roger
107d GA – 1.1 kg
29 days on Extend
12 hours to extubation
Made rapid progress in ambulation, feeding
Died at 12 days post delivery of Pyelonephritis

Greta
113d GA – 1.46 kg
20 days on Extend
12 hours to extubation
Normal growth and development
Some great headlines
Brave New Wool? Artificial Womb Sustains Premature Lambs for Weeks

The technology may someday help babies born in their second trimester survive

By Ike Swetlitz, STAT on April 25, 2017
Researchers perfect an artificial womb that works as well as ewe do

Rania Spooner
Ewe, get a womb! Docs grow baby lambs in shrink-wrap plastic bags
Moving from sheep to humans
This Artificial Womb Could Be The Future Of Pregnancy

by Kate Prince – on Mar 30, 2018 in Incredible
The Future of Neonatology
What would first-in-human studies look like?

• Which babies?
• Informed consent?
• Endpoints? (survival? NDI? Cost?)
• Interim monitoring
Using non-clinical data

• Impossible to get relevant clinical data

• Alternatives
  • Use animal data
  • Never do human studies
Case Study 1 Discussion Questions

1. If the disease only exists in pediatric patients, how should nonclinical models be used to support proof-of-concept and prospect of direct benefit in the pediatric population? In what situations might human data from healthy volunteers be informative?

2. How, if at all, does the utility of nonclinical models that demonstrate improvement in a biomarker differ from the utility of nonclinical models that demonstrate improvement in a clinical manifestation of the disease?

3. In what situations may an in vitro model be used to support proof-of-concept?

4. Assuming a serious disease with limited therapeutic options, are data to support proof-of-concept for a product in a nonclinical model of the disease sufficient to support the prospect of direct benefit and allow enrollment of pediatric patients, if an adult population with the disease exists?
Case Study 2—Challenges in Designing Pediatric Pharmacokinetic Studies to Offer a Prospect of Direct Benefit

Moderator: Mark McClellan, Duke-Margolis Center for Health Policy
CASE STUDY 2:

CHALLENGES IN DESIGNING PEDIATRIC PHARMACOKINETIC STUDIES TO OFFER A PROSPECT OF DIRECT BENEFIT

John N. van den Anker, MD, PhD
Children’s National Health System, Washington, DC & University of Basel Children’s Hospital, Basel, Switzerland
**Pharmacokinetics (PK):** A mathematical approach used to quantitatively describe the absorption, distribution, metabolism and excretion of drugs in biological systems by enabling the calculation of necessary PK parameters.

**Population Based PK:** A mathematical approach used to estimate necessary PK parameters for drugs using minimal or sparse sampling. When sparse sampling from data-rich parts of the plasma concentration vs. time curve are used, POP-PK can reliably estimate PK parameters for a given patient.
“The mg/kg scaling.....has unfortunately led to the widespread misunderstanding that children have higher drug CLs than adults do. This myth is still being propagated.....the higher mg/kg (dose requirement) is simply an artifact of widely used but biologically inappropriate scaling.”

Holford N. Clin Pharmacol Ther 2010;87:367-370
Figure 2  Relationship between age and weight in 1,529 infants, children, and young adults (derived mainly from data in ref. 8 along with other unpublished data from studies in infants).
“When young infants – especially neonates – are being considered, although size is still an important factor, the maturation processes and status are even more important. Age (PMA) then becomes essential for defining PK in infants compared with children – in this respect, infants can be viewed as young children”.

Holford N. Clin Pharmacol Ther 2010;87:367-370
So, children can be considered as small adults, but neonates are not small children!!
THE MOLECULE: BASIC FACTS

• High lipid solubility
• Plasma protein binding of 80-90% (albumin)
• Approximately 50% excreted into bile
• Approximately 50% excreted into urine as desacetylated metabolites
• Can induce its own metabolism
• Is a substrate for SLC01B1
• Apparent average plasma elimination half life in children appx. 2.8 hours
## Individual Empirical Bayesian Post hoc Parameter Estimates
### Stratified by Age

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PNA &lt; 14 days (n=15)</th>
<th>PNA &gt; 15 days (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (L/hr)</td>
<td>0.11 (0.061-0.549)</td>
<td>0.31 (0.12-0.77)</td>
</tr>
<tr>
<td>CL (L/hr/kg)</td>
<td>0.098 (0.055-0.223)</td>
<td>0.244 (0.129-0.328)</td>
</tr>
<tr>
<td>VD (L/kg)</td>
<td>1.1 (0.84-1.9)</td>
<td>1.1 (0.67-1.4)</td>
</tr>
<tr>
<td>Elimination half life (hr)</td>
<td>7.1 (3-23.9)</td>
<td>3.5 (1.9-6.5)</td>
</tr>
</tbody>
</table>
What is Contributing to the Variability??

- Ontogeny of:
  - Renal function
  - DME
  - Transporters
  - Plasma protein binding
- Potential induction of DME
- Residual variability in the model
Variability: control what you can and account appropriately for the rest…

- *Inherent variability in the model*
  - Less is better
  - Fewer observations make more

- *Intrinsic variability*
  - Development
  - Pharmacogenomic
  - Disease

- *Extrinsic variability*
  - Concomitant treatments
  - Food/environment interactions
Drug X clearance in children increased with increasing age, reaching adult values in adolescents.
Once normalized by body weight, pediatric clearances were consistent across age groups.
Anti-Xa activity (AXA)-guided dosing in neonates

1. A subject will receive the **1st dose** (equivalent to 10 mg in adults) based on the PK simulation using a population PK model of Drug X in pediatrics using the totality of PK data in all pediatric studies.

2. Anti-Xa activity (which is a PK surrogate for Drug X, as is for LMWH) will be measured at 8-10 hours after the 1st dose (trough).

3. This subject’s oral clearance will be estimated using the trough AXA value and the population PK model (above) and daily AUC with BID dosing at steady-state will be predicted with the 1st dose.
   - If daily AUC > 9836 ng*hr/mL, that next dose will be reduced to make a daily AUC ≤ 9836 ng*hr/mL.
   - If daily AUC < 2271 ng*hr/mL, that next dose will be increased to make a daily AUC ≥ 2271 ng*hr/mL.

4. If adjusted, another AXA will be measured at 8-12 hours (trough) after the new dose.

*Date and time of each Drug X dose and anti-Xa activity measurement need be collected accurately.*
Example of a subject

**0.7 mg at 07:00**

Blood draw for AXA at 15:00

AXA read-out at 16:00

CL and AUC estimation at 16:30

**AUC target range**

1. Decrease dose to \( \text{AUC} \leq 9836 \)
   - If \( \text{AUC} \) is 25000, the next dose is 0.2 mg.
   - If \( \text{AUC} \) is 12000, the next dose is 0.5 mg.

2. Keep 0.7 mg

3. Increase dose to \( \text{AUC} \geq 2271 \)
   - If \( \text{AUC} \) is 1000, the next dose is 1.6 mg.
   - If \( \text{AUC} \) is 1500, the next dose is 1.1 mg.

*Date and time of each Drug X dose and anti-Xa activity measurement need be collected accurately.*
<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provide investigators with a sense of assurance since anti-Xa monitoring is real time. This may improve enrollment</td>
<td>Develop a “new” algorithm to adjust doses based on anti-Xa activity (PK surrogate of Drug X) as there is no defined therapeutic range of Drug X and monitoring was never done for Drug X.</td>
</tr>
<tr>
<td>Generate clinical data in a timely manner for the use of Drug X in neonates</td>
<td>First dose will be based on limited PK data in neonates (currently the youngest subject with PK is 33 day old)</td>
</tr>
<tr>
<td>Potential to improve safety of Drug X in neonates considering that 1) the ad board feedback that cardiac neonates are extremely frail and vulnerable and 2) Potential larger variability in Drug X PK in neonates</td>
<td></td>
</tr>
</tbody>
</table>
First-in-patient trial: 48 DMD 4-7 years GC naïve
Phase 2a design = Open label dose escalation
24-fold dose range (1/3 GC to 10x GC)

Pharmacodynamic biomarkers: Context of use
• Secondary outcomes – bridged to safety concerns (bone turnover, insulin resistance, adrenal suppression)
• Exploratory outcomes – objective read-out in open label trial of anti-inflammatory efficacy (Dr. Conklin)
Redefining the Problem: It’s All About “Exposure”

What is the therapeutic goal of drug administration?

What exposure is required to achieve the desired response?

What dose must be administered to achieve that exposure?

Dose → Exposure → Response

Response → Exposure → Dose
Case Study 2—Challenges in Designing Pediatric Pharmacokinetic Studies to Offer a Prospect of Direct Benefit

Moderator: Mark McClellan, Duke-Margolis Center for Health Policy
Case Study 2: Challenges in Designing Pediatric Pharmacokinetic Studies to Offer a Prospect of Direct Benefit

Melanie E. Bhatnagar, MD
Office of Pediatric Therapeutics
Office of the Commissioner

Duke-Margolis Center for Health Policy
Prospect of Direct Benefit in Pediatric Clinical Trials Workshop
March 29, 2019
Sponsor Proposal 1

Conduct a single ascending dose (SAD) study to assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamic (PD) response for a new drug product in adults and pediatric patients as young as 1 month of age with a chronic, slowly progressive disease (the disease is primarily pediatric, but some adults with the disease do exist).

FDA Response

Risks associated with the proposed SAD study exceed a minor increase over minimal risk (21 CFR 50.53).

Lowest proposed starting dosages are unlikely to have a treatment effect and a single dose is insufficient to provide a prospect of direct benefit (PDB) for pediatric patients with this chronic condition (21 CFR 50.52).
Sponsor Proposal 2

Establish a minimally effective dosage (MED) in adults with the disease

Using at least a MED, continue with the single-dose PK study in pediatric patients because the long drug half-life (1 month) ensures the PDB, and confirmation of the PK/PD in pediatric patients is needed

FDA Response

Even 1 month of drug activity is unlikely to provide sufficient benefit to pediatric patients, so add an extension study for continued dosing and PD evaluation

Dosing from the single-dose PK study to the extension study needs to be seamless and the dosing must be adjusted in the extension study as more information becomes available
Case Study 2

Sponsor Proposal 3
Seamless transition to extension study is not feasible for logistical reasons
Sufficient PK/PD information is now available from adults, so the pediatric dosage will be predicted solely based on modeling and simulation and pediatric patients will enroll directly into the phase 2/3 program

FDA Response
Based on the limited available data, your model may be inadequate for predicting the optimal pediatric dosage
Concern for exposing a large number of pediatric patients to a potentially ineffective dosage in the phase 2/3 program
Case Study 2

Adaptive dose-ranging phase 2 study design that allows for a prospectively planned interim analysis of accumulating exposure-response study data to identify the optimal dose for evaluation in the second phase of the study.
Questions

• What are strategies for designing dose-ranging PK studies in pediatric patients that offer a prospect of direct benefit?

• Do considerations for prospect of direct benefit differ if extrapolation of efficacy from the adult population is acceptable (i.e., when the objective of the PK study is to identify the pediatric dose with an exposure similar to that in adults)? Might a single dose offer a prospect of direct benefit?

• What are the considerations for ensuring prospect of direct benefit when the objective of the PK study is focused on safety and tolerability?

• To what extent can we rely on modeling and simulation to identify an optimal pediatric dosage?

• Discuss the need for adding an extension study to a single-dose PK study to ensure the prospect of direct benefit. Is a seamless transition to the extension with minimal break in dosing necessary to ensure prospect of direct benefit?
Case Study 2—
Challenges in Designing Pediatric Pharmacokinetic Studies to Offer a Prospect of Direct Benefit

Moderator: Mark McClellan, Duke-Margolis Center for Health Policy
A. J. Allen, MD, PhD
Senior Medical Fellow, Pediatric Capabilities
Lilly Research Labs
Comments on Case #2: Challenges in Designing Pediatric Pharmacokinetic Studies to Offer a Prospect of Direct Benefit (PDB)

- This is reality for industry teams
  - “First in pediatrics” studies especially an issue when single dose PK
  - Modeling & simulation *sometimes* helps
  - Challenges:
    - Lack of access to pediatric experience/expertise
    - Delays in discussing/planning/preparing for pediatric development

- Lack of awareness/understanding of subpart D in industry
  - Conservative interpretation of “prospect of direct benefit” as requiring positive phase 2 or phase 3 data in adults
Comments on Case #2: Challenges in Designing Pediatric Pharmacokinetic Studies to Offer a Prospect of Direct Benefit (PDB, slide 2)

• Lack of global scientific consensus regarding how to investigate PK and determine dose in pediatrics
  – How much to trust modeling & simulation?
  – Variations across:
    • Companies
    • FDA review divisions
    • Regulatory agencies (FDA, EMA, PMDA, etc.)
    • IRBs/IECs
Comments on Case #2: Challenges in Designing Pediatric Pharmacokinetic Studies to Offer a Prospect of Direct Benefit (PDB, slide 3)

• More attention needs to be paid to the ethical AND scientific justification for long-term open-label extensions (when used), and related ethical issues
  – Ethical justification:
    • Helps address PDB with single dose PK study, but
    • Still a clinical trial, so needs scientific justification
  – Scientific justification:
    • Preliminary data on safety (more than just acute), effectiveness (direct benefit) and acceptability of formulation/dosing
    • Preliminary data provides support for later trials in the program
  – Other ethical issues: How long? When to stop? What “benefit” criteria to continue/stop? What happens if drug fails in subsequent development? All sorts of continued access questions…
Case Study 2 Discussion Questions

1. What are strategies for designing dose-ranging PK studies in pediatric patients that offer a prospect of direct benefit?

2. Do considerations for prospect of direct benefit differ if extrapolation of efficacy from the adult population is acceptable (i.e., when the objective of the PK study is to identify the pediatric dose with an exposure similar to that in adults)? Might a single dose offer a prospect of direct benefit?

3. What are the considerations for ensuring prospect of direct benefit where the objective of the PK study is focused on safety and tolerability?

4. To what extent can we rely on modeling and simulation to identify an optimal pediatric dosage?

5. Discuss the need for adding an extension study to a single dose PK study to ensure the prospect of direct benefit. Is a seamless transition to the extension with minimal break in dosing necessary to ensure prospect of direct benefit?
Break

The meeting will continue after a 15 minute break.

WiFi: Hyatt Meeting
Password: Duke2019
Case Study 3—Endpoints and Duration of Pediatric Clinical Trials and Prospect of Direct Benefit

Moderator: Mark McClellan, Duke-Margolis Center for Health Policy
When do Pediatric Trials Offer a Prospect of Direct Benefit?

The views expressed in this talk are my own.
They do not represent the position or policy of the NIH.

David Wendler
Department of Bioethics
NIH Clinical Center
Disclaimer

The views and opinions expressed in this talk are my own. They do not represent the position or policy of the NIH, Public Health Service, or Department of Health and Human Services.
Review in 405/50.52

HHS will conduct or fund research in which the IRB finds that 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, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that:
Approval in 405/50.52

A. The risk is justified by the anticipated benefit to the subjects; and

B. The relation of the anticipated benefit to the risk is at least as favorable as available alternatives
BIOETHICS AT THE NIH

3 Questions

Determining when pediatric trials offer a prospect of direct benefit requires answering 3 questions.

• What is a ‘benefit’?

• What is a ‘direct’ benefit?

• What is a ‘prospect’ of direct benefit?
What is a Benefit?

- Anything that makes an individual better off. If X makes Mariam better off, X is a benefit for Mariam.

- Less pain; More movement; Improved vision

- Smaller tumor?
Philosophical Guidance

• Benefits are things that an individual has reason to want for him or herself, leaving aside concern for others. (Scanlon)

• Benefits are things we want for our children for their own sake. (Darwall)
What is a ‘Direct’ Benefit?
Direct Benefits as Research Specific

• “IRBs should consider only benefits that might result strictly from study participation.” (NBAC)

• Direct benefits are those from the scientifically necessary procedures. (Friedman et al)

• Direct benefits are “benefits arising from receiving the intervention being studied.” (King)
Direct Benefits of Participation

• Some commentators regard non-health related benefits of contributing to research as direct.

• Bob Levine discusses economic, psychosocial and kinship benefits that subjects realize as a result of contributing to the research as direct.
Direct Benefits as Likely Benefits

• Others define direct benefits based on the likelihood of benefit.

• The National Commission defined direct benefits as “fairly immediate” benefits (as opposed to speculative, uncertain ones).
Direct Benefits as Important Benefits

• A direct benefit is a significant positive outcome for the subject. (IOM)

• A direct benefit is a significant improvement in the condition of the subject. (Keyserlingk et al)
Protection without Direct Benefits

• Many guidelines and regulations that do not mention direct benefits offer appropriate protection for subjects who cannot consent.

• For example, the Declaration of Helsinki does not mention direct benefits.
What is Going On?

• 405/50.52 involves studies that expose subjects who cannot consent to greater risks based on the potential for them to benefit personally.

• Commentators define ‘direct’ benefits in order to address what they see as the most likely reason enrollment in a riskier study might not be appropriate.
A Comprehensive Approach

• When research poses significant risk “review committees should be extraordinarily insistent on the justification of the risk.” (Belmont Report).

• Regard the requirement for ‘direct’ benefits as the National Commission's admonition to require extra diligence when evaluating whether greater risks are justified by potential benefits to subjects.
What is a ‘Prospect’ of Direct Benefit?

• A prospect of direct benefit is a possibility or chance of realizing a direct benefit.

• The chance of benefit should be assessed for each arm of the trial.

• Because participants in the placebo arm do not receive the tested intervention, the potential benefits of the tested intervention cannot justify the risks they face.
Common Mistakes

Some IRBs assume a 'prospect' of direct benefit requires more than just a chance of benefit:

• The study must be designed to benefit subjects
• Clinical benefit must be a primary outcome
• The investigators must intend to benefit subjects
• There must be a good chance of benefit
• Treatment being tested must be FDA approved
• The trial must not be phase 1
Diagnosis?

These views are mistaken.

• **Possible diagnosis:** IRBs may be assuming that a finding of *prospect* of direct benefit requires that the potential benefits justify the risks.

• But: a prospect of direct benefit determines only that a study can be *reviewed* in 405/50.52.
Question #1

• What design issues should be considered to ensure the prospect of direct benefit for products that are intended for chronic use?

• Answer: The trial must be designed (e.g. dose, duration) to provide sufficient potential benefit to justify the risks.
Question #2

• Does a change in an exploratory biomarker constitute benefit?

• Answer: No. The fact that a change in a biomarker may be valuable for scientific or regulatory purposes does not mean it is beneficial for subjects.
Question #2

• Or should the trial include a change in a clinically meaningful outcome?

• **Answer:** Yes, assuming the trial is being reviewed as prospect of direct benefit.
Question #3

• If the biomarker is “reasonably likely” to predict a clinically meaningful outcome, does a change in the biomarker constitute benefit?

• **Answer:** No. It constitutes a potential benefit.

Whether that potential is sufficient to justify the risks depends on the chances it predicts a clinically meaningful outcome and the value of that outcome for the subjects.
Question #4

• Is an extension study necessary to allow continued treatment until a validated surrogate or clinically meaningful outcome has been observed?

• **Answer:** Yes. If the study without an extension does not provide sufficient treatment to offer a chance of benefit that justifies the risks.
Summary

When do Pediatric Trials offer a Prospect of Direct Benefit?

• What is a *Benefit* is pretty clear.
• What is a *Direct* benefit is less clear, but is an admonition to exercise diligence.
• What is a *Prospect* of direct benefit is pretty clear.
The Real Challenges

1. Do the potential direct benefits justify the risks?

2. R/B profile at least as favorable as the available alternatives?

• Informed Clinician: Would an informed and expert clinician (parent) support enrollment?

• If the answer is unclear: default to the option that is more likely to help those who cannot consent.
Case Study 3—Endpoints and Duration of Pediatric Clinical Trials and Prospect of Direct Benefit

Moderator: Mark McClellan, Duke-Margolis Center for Health Policy
Case Study 3: Endpoints and Duration of Pediatric Clinical Trials and Prospect of Direct Benefit

Melanie E. Bhatnagar, MD

Office of Pediatric Therapeutics
Office of the Commissioner

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Case Study 3: The Disease

• “Merrill’s Disease” is a chronic, systemic illness caused by prolonged exposure to abnormally elevated levels of “sigma (Σ) protein”

• Renal injury resulting from high levels of circulating Σ protein is the most prominent clinical manifestation of the disease, progressing to end-stage renal disease (ESRD) within 10 years of diagnosis in 50% of patients

• No approved therapies; several products are used off-label and are associated with substantial toxicities
Case Study 3: The Drug

- Sponsor has developed a new product ("Curezal") as a potential treatment for the kidney damage associated with Merrill’s Disease
- **Curezal** directly inhibits Σ protein production
Case Study 3: The Outcome Measures

Clinically meaningful outcome for Merrill’s Disease would be reduced progression to ESRD.

A validated surrogate endpoint does not exist.

Reduction in sigma (Σ) protein is being assessed as an exploratory biomarker.

Reduction in proteinuria is “reasonably likely” to predict clinical benefit, but has not been validated.
Case Study 3: The Sponsor’s Proposal

Reduction in Σ protein and proteinuria has been observed in:

- 3 distinct murine models of the disease
- 12-week, open-label exploratory pharmacokinetic (PK) and pharmacodynamic (PD) study in adults with the disease

Sponsor proposes to conduct a phase 2 study in adults and pediatric patients, noting the Merrill’s Disease is more prevalent in children and earlier treatment may have the greatest impact.

The sponsor anticipates Curezal will be used chronically as a once daily oral (PO) treatment for the disease.
Case Study 3: Proposed Trial Design

- Randomized, double-blind, placebo-controlled phase 2 study to assess the safety, tolerability, and efficacy of Curezal in 30 adults and pediatric patients 6 years of age and older with Merrill’s Disease

- Participants will be randomized (1:1) to receive Curezal or placebo PO daily for 12 weeks

- Curezal will be given to participants using the optimal dose identified in the PK/PD study in adults
Case Study 3: Proposed Endpoints

• Primary endpoint: change in urine protein to creatinine ratio from baseline to Week 12

• Secondary endpoints: change in the following from baseline to Week 12
  • 24-hour urinary protein
  • Estimated glomerular filtration rate (eGFR)
  • $\Sigma$ protein levels
Questions

• In clinical studies involving pediatric patients with a chronic disease, what study design issues should be considered to ensure the prospect of direct benefit for products that are intended for chronic use?
• Does a change in an exploratory biomarker of a disease constitute benefit in the context of a pediatric clinical trial or should the trial include a change in a clinically meaningful outcome?
• If the biomarker is “reasonably likely” to predict a clinically meaningful outcome based on a strong mechanistic and/or epidemiologic rationale, does a change in the biomarker constitute benefit?
• Is an extension study necessary to allow continued treatment until a validated surrogate or clinically meaningful outcome has been observed?
Case Study 3—Endpoints and Duration of Pediatric Clinical Trials and Prospect of Direct Benefit

**Moderator:** Mark McClellan, Duke-Margolis Center for Health Policy
Prospect of Direct Benefit: A Practical IRB perspective

March 2019
Susan Kornetsky, Senior Director
Clinical Research Compliance
What IRBs Think About

• Will look for potential benefit very concretely in terms of a clinical benefit
  – Will it make patient better, live longer, alleviate or prevent symptom or progression of disease?
  – Will it have less side effects, be more tolerable, change to easier method of administration
  – Will there be better quality of life
IRB Other Considerations

• Is the potential for benefit immediate or in the future?
• How long will the potential benefit last – there is no requirement for the potential benefit to be ongoing?
• Even if some parts of the protocol do not offer a direct benefit, does the protocol design include parts that will
  – Ability to move from one phase perhaps a single dose to ongoing dosing
  – Cross over design
  – Extension after trial
In general

• IRBs will generally accept even a small potential for direct benefit as described
• IRBs do not look at potential benefit in isolation and will consider potential risks side
• IRBs will consider using component analysis for the benefit side as well as risk
Question 1

• What design issues should be considered to ensure the prospect of direct benefit for products that are intended for chronic use?
  – Need to understand what may be of potential benefit when you have a chronic condition: Details of disease matters
    • Could be larger spectrum of potential benefits
    • Now versus later
    • Reverse, prevent or halt
    • Is it quality of life or actual physiological benefit
    • May be different potential benefits for different ages
Question 2

• Does a change in an exploratory biomarker constitute benefit or include change in clinical meaningful outcome
  – “Exploratory” is just that - trying to explore- no evidence
  – Biomarkers in and of themselves may not translate to a potential for benefit for subjects
  – Protocol would need to have some other potential for direct benefit with this goal imbedded
Question 3

• If the biomarker is “reasonably likely” to predict a clinically meaningful outcome, does a change in the biomarker constitute benefit?
  – What is data to suggest “reasonably likely? What is reasonable and how do you measure likely
  – Really does not help because you are still left with needing a basis for a potential for benefit as a clinical outcome; focus cannot be on biomarker alone
  – This just deals with the ability to predict being correct
Question 4

• Is an extension study necessary to allow continued treatment until a validated surrogate or clinically meaningful outcome has been observed?
  – This could be one way to design a trial since you are still aiming for a potential benefit of clinical value or
  – You aiming that the surrogate marker is an indication and therefore there will be a prospect of direct clinical benefit going forward
Some final thoughts

• Educate IRBs that protocol may not be designed to show a potential for benefit but could provide it

• There is increased pressure: IRBS feel it
  – Make it available quicker – One patient advocacy group said “get it on the market first figure out if it works later” (more so in rare and life threatening conditions).
  – Shorten the approval process by using of biomarkers and surrogates as outcomes,

• BUT- Pediatric regulations have not changed:
  – There has been no guidance despite IOM, NRPAC AND SACHRP
  – This creates varying levels of inconsistency and many times overprotection
  – Ethical basis for pediatric regulations continues to be sound
  – We can work within them
Case Study 3—Endpoints and Duration of Pediatric Clinical Trials and Prospect of Direct Benefit

Moderator: Mark McClellan, Duke-Margolis Center for Health Policy
The Prospect of Direct Benefit in Neonatal Clinical Trials

Jonathan Davis, MD
Chief of Newborn Medicine
The Floating Hospital for Children
at Tufts Medical Center
Professor of Pediatrics
Tufts University

Chair, Neonatal Advisory Committee
Office of the Commissioner
FDA
Newborn Intensive Care

- 6% of the 4,000,000 births each year in the US require NICU admission
- Prematurity rates (11%) - highest of any developed country (>29 billion each year)
- Small improvements in survival/outcome in the last 20 years (>90% of drugs not FDA approved)
- Difficulty with study design/outcome measures
- Short-term results may not necessarily correlate with longer-term outcomes
Blood Pressure in Preterm Infants

- How is BP measured? Validated?
- What is “normal BP”?
- What is hypotension?
- What is clinical endpoint for treatment?
- What are the best short and long-term (neurodevelopmental) outcomes?
- How long should we wait to decide?
Blood Pressure in Preterm Infants

[Bar graph showing blood pressure in preterm infants]
Drug Therapy in Preterm Infants

- Caffeine shown to significantly improve apnea, cardiopulmonary complications, CP
- No difference in survival without disability at 5 years of age
- Indomethacin prophylaxis shown to significantly reduce severe IVH
- Head ultrasound and MRI significantly better
- At 8-9 years of age, treated males had improved verbal scores
Drug Therapy in Preterm Infants

- **Dexamethasone** powerful anti-inflammatory
- Improves lung mechanics/gas exchange, less inflammation, facilitates extubation
- Randomized trials – at one year, impaired head growth, more CP, higher mortality rates
- Infants randomized to HFOV vs CMV – no difference in short-term outcomes
- At age 15 years, HFOV associated with better exercise tolerance
The International Neonatal Consortium concentrates its efforts on those conditions most commonly encountered in Neonatal Intensive Care Units (NICUs), and on the prevention of preterm birth.

<table>
<thead>
<tr>
<th>INC AND THE NICU</th>
<th>INC Priority Conditions</th>
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<tr>
<td>The International Neonatal Consortium concentrates its efforts on those conditions most commonly encountered in Neonatal Intensive Care Units (NICUs), and on the prevention of preterm birth.</td>
<td>NEONATAL LUNG INJURY AND CIRCULATORY FAILURE</td>
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<td>PERINATAL/NEONATAL INFECTIONS</td>
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<td>NEONATAL ABSTINENCE SYNDROME (NAS)</td>
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<td>RETINOPATHY OF PREMATURE (ROP)</td>
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<td>NEONATAL GASTROINTESTINAL INJURY</td>
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<td>NEONATAL BRAIN INJURY</td>
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<td>DRUGS TO PREVENT PRETERM LABOR</td>
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<td>HEMODYNAMIC ADAPTATION (HA)</td>
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Members Spanning the Globe

Neonatal Nurses
- NANN
- COINN

Companies
- Baxter
- Bayer
- Chiesi
- Johnson & Johnson
- Lilly
- Novartis
- Pfizer
- Sanofi
- Shire

Families/Advocacy
- Bliss
- Graham’s Foundation
- March of Dimes
- NEC Society
- Preemie Parent Alliance
- EFCNI (Consultants)

*77 Institutions
Success in Improving Design of Neonatal Trials

 ✓ Aligning pharmacologic considerations for neonatal trials

 ✓ Data sharing to generate new drug development tools

 ✓ Innovating the design of neonatal clinical trials
   • Rabe, H., et al. “Proper method of blood pressure measurement is critical in neonates and infants: A systematic review and analysis”, manuscript in preparation.

 ✓ Assessing safety signals in neonatal trials
Conditions Commonly Encountered in NICUs

✓ A master protocol for clinical trials of anti-seizure therapies

✓ Definitions/outcomes for chronic pulmonary insufficiency of prematurity

✓ A scale to define blindness in preterm infants
  • Smith, L. et al. “Considerations for the Development of Therapies to Prevent or Treat Retinopathy of Prematurity (ROP)”. JAMA Ophthalmology, in press.

✓ A framework to identify and treat neonatal gastrointestinal injury

✓ Outcomes measures to assess neurologic development
Success in Building a Global Neonatal Collaboration with Cross-Functional Expertise

 ✓ Establishing a global neonatal community


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Case Study 3 Discussion Questions

1. In clinical studies involving pediatric patients with a chronic disease, what study design issues should be considered to ensure the prospect of direct benefit for products that are intended for chronic use?

2. Does a change in an exploratory biomarker of a disease constitute benefit in the context of a pediatric clinical trial or should the trial include a change in a clinically meaningful outcome?

3. If the biomarker is “reasonably likely” to predict a clinically meaningful outcome based on a strong mechanistic and/or epidemiologic rationale, does a change in the biomarker constitute benefit?

4. Is an extension study necessary to allow continued treatment until a validated surrogate or clinically meaningful outcome has been observed?
Session 3—Synthesis Discussion and Next Steps

Moderator: Mark McClellan, Duke-Margolis Center for Health Policy
Closing Remarks

Moderator: Mark McClellan, Duke-Margolis Center for Health Policy
Adjournment