

Regulatory and Ethical Considerations: Pediatric Oncology Trials

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- 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
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Topics



- Pediatric Regulatory Requirements and Incentives
- Basic Ethical Framework in Pediatrics
- Additional Safeguards for Children
- Considerations for Pediatric Oncology Trials
- Conclusion

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 Pharmaceuticals for Children Act (BPCA) 2002
 - Pediatric Research Equity Act (PREA) 2003
 - Pediatric Rare Disease Voucher 2012
 - Research to Accelerate Cures and Equity for Children Act (RACE) 2017

*Ward, et al., J Pediatr. 2018 Jan;192:13-21.

PREA

- Drugs and biologics
- Mandatory studies
- Required studies only on indication(s) under review*
- Orphan indications exempt from studies*
- Pediatric studies must be labeled

BPCA



- Drugs and biologics
- Voluntary studies with incentives
- Studies relate to entire moiety and may expand indications
- Studies may be requested for orphan indications
- Pediatric studies must be labeled

*Exception under RACE for Children Act



Cancer Drug Development for Children and Adolescents

- Well recognized, long-standing challenges – biologic, clinical, societal, and economic
- Widely leverages adult drug discovery/development – delay in pediatric drug development is inevitable
- Limited opportunities for extrapolation; limited pre-clinical testing in pediatric models; limited access to Precision Medicine
- Impact of legislative initiatives (notably PREA) which support pediatric drug development has been markedly less obvious in oncology than in other clinical areas
- Many targeted agents likely applicable to cancers in children
- RACE for Children Act essentially amends PREA

RACE for Children Act

- Incorporated as Title V Sec. 504 of the FDA Reauthorization Act (FDARA), enacted August 18, 2017
- Requires evaluation of new molecularly targeted drugs and biologics “intended for the treatment of adult cancers and directed at a molecular target substantially relevant to the growth or progression of a pediatric cancer”
- Molecularly targeted pediatric cancer investigation: clinically meaningful study data, “using appropriate formulations, regarding dosing, safety and preliminary efficacy to inform potential pediatric labeling” [FDARA Title V Sec 504 (a)(3)(A) or FD&C Act Sec. 505B (a)(3)(A)]
- Elimination of PREA orphan exemption for pediatric studies for cancer drugs directed at relevant molecular targets

Molecular Target Definition

- A molecule in human cells that is intrinsically associated with a particular disease process such as etiology, progression, and/or drug resistance. To be referred to as a target, there must be evidence that by addressing the target with a small molecule, biologic product, or other intervention, a desired therapeutic effect is produced resulting in the alteration of the disease process

Regulatory Requirements

- Sec 505B(e) of the FD&C Act requires sponsors have an Agreed initial pediatric study plan (iPSP) prior to submission of a new drug or biologic licensing application (NDA/BLA)
- After Aug. 18, 2020, the PREA requirements for applications of NEW active ingredients may change from indication to the molecular mechanism of action (MOA) of an investigational product (including orphan-designated); impact on automatic waivers
- The iPSP must include details of the “molecularly targeted pediatric evaluation”: non-hypothesis testing, dose finding, signal of activity-seeking study or justification for waiver or deferral plan
- FDA, working with the National Cancer Institute (NCI), is required to post on the FDA website, and update regularly, a list of relevant targets and non-relevant targets appropriate for waivers*

* <https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology>

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)” ...

Principle of Scientific Necessity



- Practical application: determine the type and timing of clinical studies required for establishing "safe and effective" pediatric use of FDA-regulated products
 - Using extrapolation of efficacy if appropriate from adults to children
 - Studies may be initiated in children if an appropriate adult population does not exist
- “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*”

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

Additional Safeguards for Children

21 CFR 50 Subpart D



- Research involving children either
 - must be restricted to “minimal” risk or a “minor increase over minimal” risk absent a potential for direct benefit to the enrolled child, or (21 CFR 50.51/53)
 - 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)

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Prospect of Direct Benefit (PDB)*



- A “benefit” is “direct” if it:
 - Accrues to individual subject enrolled in clinical trial
 - Results from research intervention being studied (and not from other clinical interventions included in protocol)
 - Word “benefit” often modified by “clinical” to indicate that “direct benefit” relates to health of enrolled subject
- PDB is based on “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

*National Commission - Report on Research Involving Children (1978)

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Minor Increase over Minimal 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” (absent federal review and approval)
 - May include children “at risk” for a disorder
- Must contribute to generalizable knowledge about the child’s disorder or condition

*National Commission - Report on Research Involving Children (1978)

Component Analysis

- A clinical investigation may include more than one intervention or procedure
- Evaluate each intervention/procedure separately to determine whether it does/does not hold out the prospect of direct benefit to the enrolled child
- Interventions or procedures that hold out the prospect of direct benefit should* be considered under 21 CFR 50.52
- Interventions or procedures that do not hold out the prospect of direct benefit should* be considered under 21 CFR 50.51 or 50.53 (but not 50.52)

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

Component Analysis

- 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)

Considerations for Pediatric Studies in Oncology



- If the disease exists in adults and efficacy can be extrapolated, initial data should be collected in adults first to reduce the burden on children from participation in pediatric trials
 - Enrollment of appropriately selected adolescent patients in relevant adult oncology clinical trials with appropriate dose considerations and adequate safety monitoring is justified given the severe and life-threatening nature of their disease*
- Studies may be initiated in children when the disease is different (but may be linked to the same genetic or molecular defect) in adults or if there are no or limited adults with disease
 - Examples include infantile forms of disease that are fatal in childhood, for targeted therapies where intervention in childhood is critical, or a molecular target that is specific to pediatrics
 - When there are limited or no other treatment options

Considerations for Pediatric Studies in Oncology

- Enrollment of pediatric patients in first in human (FIH) expansion cohorts* may be acceptable after establishing sufficient PDB
 - Generally after a reasonably safe dose and preliminary activity have been established in adults
 - In exceptional circumstances, substantive nonclinical evidence of activity in tumor-derived cell lines or patient-derived xenografts alone may provide sufficient justification to enroll children before full adult data is available (staged enrollment of older children before younger should be considered)
 - For targeted drugs, confirmation of the putative target's presence should be documented and eligibility should be limited to pediatric patients with relapsed or refractory disease for whom no curative treatment exists
 - Detailed toxicity monitoring plans, plans for pharmacokinetic (PK) assessment, and, when appropriate, pharmacodynamic (PD) study objectives should be included to guide further pediatric development

Conclusion



- There are unique regulatory considerations for clinical studies intended for children with cancer
 - RACE for Children Act requires sponsors to study oncology products under PREA based on a molecular target rather than an adult indication
 - PREA orphan exemption no longer applies for these targeted therapies
- There are additional safeguards in place that limit the risk to which children can be exposed without a PDB
- Adolescents may be enrolled in confirmatory adult oncology trials if there is adequate data to support PDB, dosing and safety
- Given the severe and life-threatening nature of many cancers, children may be considered for inclusion in early phase trials, after a reasonably safe dose and preliminary activity to support PDB have been established in adults

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