The Need to Conduct Pediatric Clinical Trials

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Historical Perspective on Pediatric Clinical Trials
Historical Perspective

• Descriptions of childhood illnesses are found in ancient Greek, Egyptian and Roman texts
  • Yet, there is no documentation of medical research in children prior to the 18th century

• In the 19th and 20th centuries, pediatric research became a recognized medical specialty
  • Children were often vulnerable to or bore the brunt of experiments involving pain, misery, disability or death (e.g. thalidomide, Tuskegee study, Willowbrook hepatitis study)

• Concerns of pediatric patient vulnerability and risks of exposure to new drugs caused pharmaceutical companies and regulators to avoid pediatric trials
  • Many drugs thus were marketed without evidence of pediatric patient safety and efficacy
  • Pediatricians forced to prescribe based upon extrapolations from adult data
“Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of subjects (e.g. adults before children)…”

“Children are both vulnerable subjects in need of protection from research risks and a neglected class that needs better access to the benefits of research” *

* Eric Kodish, MD, Rainbow Center for Pediatric Ethics
Over the past 20 years, we have evolved from a view that we must protect children from research to a view that we must protect children through research

• Clinicians and regulators have a professional obligation to ensure that there are adequate data to support the safe and effective use of drugs, biologics and devices in infants, children and adolescents
• The critical need for pediatric research on drugs, biologics and devices reinforces our responsibility to assure that children are only enrolled in research that is both scientifically necessary and ethically sound
• Children are widely considered to be vulnerable persons who, as research participants, require additional (or special) protections beyond those afforded to competent adult persons
Current State of Pediatric Trial Regulations
Pediatric Trial Regulations – Europe

• European Regulators enacted several legal provisions to encourage, entice or compel pharmaceutical companies to undertake pediatric trials
  • European Regulation of Pediatric Medicines – 3 Major Initiatives – 2007
    • Incentives for Industry
    • Mandatory Pediatric Investigation Plan (PIP)
      • Waiver from pediatric studies can be obtained for non-applicable drugs / indications
    • Creation of Pediatric Committee (PDCO)

Obligation to submit a PIP for new indications, new routes of administration, new formulation or new medicinal products
• If information submitted after conducting required studies, 6 month extension
• Pediatric Use Marketing Authorization allows 10 year market exclusivity if appropriate studies are conducted on drugs already in use
European Regulators enacted several legal provisions to encourage, entice or compel pharmaceutical companies to undertake pediatric trials (continued)

- Revised European Guideline - 2014
  - Establishes key elements that should be included in a PIP
  - Introduces increased flexibility in the application process
  - Incorporates new study concepts, such as extrapolation of data and modeling
  - Clarifies requirements for the compliance check
US Regulators enacted several legal provisions to encourage, entice or compel pharmaceutical companies to undertake pediatric trials

- Pediatric Rule issued by FDA in December 1998*
  Required the conduct of pediatric studies and development of pediatric formulations. The Pediatric Rule suspended in October 2002.

- Pediatric Research Equity Act (PREA) law in 2003 ** ***

- Pediatric Exclusivity Provision - complementary to the PREA, which provides an incentive for companies who perform clinical trials in the pediatric population ****

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* Pediatric Rule was codified at 21 CFR 314.55 and 601.27 with additional amendments to 21 CFR 201, 312, 314 and 601.


• US Regulators enacted several legal provisions to encourage, entice or compel pharmaceutical companies to undertake pediatric trials (continued)

• Pediatric Study Plan (PSP) required by section 505B(e) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Food and Drug Administration Safety and Innovation Act (FDASIA)
  • Required for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration (i.e., that triggers PREA)
  • Also, long “off-label” use resulting in adequate data can result in pediatric authorization
- **Canada** - Registration of pediatric drug follows normal procedure.

- **Australia** - Market authorisation may be denied / delayed, if clinical pediatric data is not included but is deemed appropriate.

- **India** - If new drug is intended to treat both adults and pediatric patients, the pediatric population should be included in the clinical trials from an early point onwards. If pediatric data is not included, this needs to be justified in detail.

- **China** - Registration of pediatric drug follows normal procedure. Clinical trials on children are discouraged unless the drug-use is limited to only the pediatric population.
- **Japan** - No mandatory pediatric clinical trials. There are however, ongoing projects organized by the MHLW (Ministry of Health, Labour and Welfare), which aim to facilitate an accelerated review of off-label pediatric drugs.

- **South Korea** – No established legislation for pediatric drugs.

- **Switzerland** - Pediatric studies are not mandatory for drug registration, unless the drug has potential pediatric use.
• Regulation of Pediatric Trials has come full circle
  • Studies first conducted in children without much oversight
    • Society then shunned pediatric exposure
  • With no studies in pediatrics, children continued to be exploited through exposure to drugs untested in the pediatric population
  • Regulators now encourage pediatric trials – but with greater oversight that adult trials
Nonclinical Safety Requirements

- Safety data from previous adult human exposure should be available before pediatric clinical trials start.

- Appropriate repeated dose toxicity studies, all reproduction studies and the standard battery of genotoxicity tests should be available prior to the initiation of trials in pediatric populations.

- Juvenile animal studies should be considered on an individual basis when previous animal data and human safety data are insufficient.
Nonclinical Safety Requirements

- Need for non-clinical testing in juvenile animals for pediatric indications
  - Detailed recommendations in a specific FDA guideline
  - Draft CPMP guideline

- Need for carcinogenicity testing should be addressed prior to longterm exposure in pediatric clinical trials considering the length of treatment or cause for concern
Pediatric patients cannot be considered as one homogenous group

Considerable differences in development (e.g. physical, cognitive and psychosocial)

The identification of which ages to study should be medicinal product-specific and be justified

Dividing the pediatric population into many age groups might needlessly increase the number of patients required.
Age Classification for Pediatric Trials

- **Preterm newborn infants**; unique spectrum of diseases, rapid development and differences in their body functions, unique response to treatment, requirements for forms of medications that can be safely administered given their especially small size.

- **Term newborn infants** (0 to 27 days); volumes of distribution may be different than those in older pediatric patients, blood-brain barrier is not fully mature. Oral absorption may be less predictable, hepatic and renal clearance mechanisms are immature and rapidly changing.

- **Infants and toddlers** (28 days to 23 months); rapid mental, physical and immune development. Elimination of drugs from the body may exceed that in adults. Considerable variability in response to medication, because the development does not occur at the same rate in all children.

- **Children** (2 to 11 years); large variation and variability in development. Onset of puberty is highly variable and heralds a time of accelerated growth and marked changes which may alter response to medications and doses required.

- **Adolescents** (12 to 16-18 years (dependent on region)); sexual maturation: medicinal products may intervene with the actions of sex hormones and impede development. Rapid growth and continued neurocognitive development. Increasing independance and responsibility; willingness to take medication may become a problem.
Rationale for Conducting Pediatric Clinical Trials
Rational for Conducting Pediatric Trials

- Children’s right to highest attainable level of health enunciated by Convention of Rights of the Child (1989)
  - Cannot be realized if therapy is based upon evidence generated by adult studies
    - Children and Adults differ in:
      - Physiological capabilities, pharmacokinetic profile and pharmaco-dynamic characteristics
      - Metabolic pathways, organic functions, and metabolic rates
    - Disparities also exist in terms of receptor functions, effector systems and homeostatic mechanisms
    - Additionally, side effects are influenced by age, growth and development

- Extrapolation of adult data is only appropriate in about 6% of drugs
Key Issues in Conducting Pediatric Clinical Trials
When to Begin Pediatric Trials

• Generally, it is not reasonable to enroll pediatric subjects until sufficient proof of safety and significant information about pharmacokinetics and efficacy in adults is available

• Thus, for the most part testing in pediatrics should be delayed until an adult Phase II is completed or a adult Phase III program is underway except for:
  • Diseases that affect children exclusively
  • Diseases that mainly affect children or are of particular gravity in children or have a different natural progression in children
  • Diseases occurring both in children and adults for which there is no current treatment
  • Diseases occurring in adults and children for which a treatment exists, but where there is insufficient efficacy or safety knowledge
Minimizing Risks

- Ethically, we are all obligated to minimize risk in the conduct of clinical trials

U.S. regulations describe four levels of risk for allowing research in pediatric patients:

1. Level of risk is minimal regardless of whether there is prospect for benefit
2. There is prospect of direct benefit as long as the risks are minimized and justified by anticipated benefits
3. Even if there is greater than minimal risk and no prospect of benefit but the intervention or procedure presents experiences that are commensurate with actual expected medical situations and research will yield generalizable information of vital importance to disorder
4. Not otherwise permissible, but presents an opportunity to understand, prevent or alleviate a serious problem (requires DHHS approval)
• Children deserve the highest levels of monitoring safety during a drug study

• Although there is no specific requirement for Data- and Safety-Monitoring Committees (DSMC), trials:
  • Testing new interventions with few safety data available
  • Addressing major morbidity or mortality endpoints
  • Involving high-risk populations
  • Involving large, multi-centered studies should be monitored by a DSMC

• The role of the DSMC is complementary to role of investigators, sponsors and ethics committees
• Informed consent is the cornerstone of protection for human subjects
  • Parents are expected to act in the best interest of their child and thus have been entrusted with the responsibility for providing consent for their child to enter a clinical trial
  • Practitioners concerned that too much information may “over burden” parents or that parents may feel “pressured” to enroll their children in a risky clinical trial

• Researchers also must solicit a child’s assent – “affirmative agreement to participate in research”
  • Typically, children 7-18 years of age
  • Often governed by Ethics committees and may be waived by an IRB
  • No specific guidelines on what information is to be provided to subjects
  • No specific requirement for written documentation
“Special provisions may need to be made when comprehension is severely limited – for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g. infants and young children…) should be considered on its own terms. Even for those persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm.”

Benefits of Assent to Child

• Assent reminds us that children should be treated with dignity and respect

• Permitting children a shared role in decision making benefits their development as autonomous individuals

• Requirement of assent serves to remind parents and investigators that children are persons with interests and not mere vessels for the purpose of research

• An assent requirement offers school-age children the opportunity to learn of respect for others.
Parental Consent

- Generally required for research subjects under 18 in the U.S.

- In the U.S. permission must be obtained from both parents unless:
  - Other parent is deceased
  - Other parent is unknown
  - Other parent is incompetent
  - Other parent is not reasonably available
  - Only one parent has legal custody

IRB may allow permission from only one parent where there is minimal risk and where there is the prospect for direct benefit
Incentives, Compensation, and Payment

Payment is often a contentious issue

Two viewpoints

• Payment should never be made because it creates an undue influence on parents
  • Parents themselves are not subject to any risks
  • Potential bait to overlook potential risks
• Compensation is a must to facilitate enrollment and enhance retention of participants

Possible Reimbursements

• Reimbursements for costs of participation e.g. travel and meals
• Compensation for time spent
• Enticements for recruitment and retention
• Gifts at completion of study enrollment

Any reimbursement must be reasonable and minimal to ensure that the participation remains voluntary, unpressured and not unduly influenced
• Common Difficulties in Enrollment
  • Fear of harming or hurting children – use of children as “guinea pigs”
  • Reluctance to enroll because of lack of assured, immediate benefit
  • Small potential population
  • Greater regulatory oversight
  • Complexity of obtaining a balanced informed consent from parents
Recruitment Issues

• Strategies to Overcome Pediatric Trial Recruitment Issues
  • Assurance that studies are only being carried out when necessary
  • Adequate steps are being taken to minimize risks involved
  • Regulatory Oversight ensures studies are being conducted in a scientific and ethical manner
  • Judicious use of Advertisements
    • Benefits should not be exaggerated or risks downplayed
  • Use of “finders fees” should be minimized

Networking and Use of Newer Geographic areas should be considered
• Patient Advocacy Groups – particularly for rare and orphan diseases
• Multi-national trials
Recruitment Issues

• Industry shifting conduction of clinical trials outside of United States

  • Advantages:
    • Patients are readily available
    • Strong patient-provider relationships
    • Lower cost

  • Disadvantages:
    • Uniformity of regulations, GCP, etc.
    • Logistics (Training at a distance, CROs, supplies)
    • Comparability of study populations
• Bad science is bad ethics - Pediatric trials should depict robust science

• Design needs to be scientifically sound and significant and in most cases with value to children and often the individual participant
  • Unique physiology, pharmacology, psychology, social milieu and special needs of children and their families
  • Need for practical, evidence based standards
    • Quantity, Quality, and Relevance of Data is often less than adults
Emergency Pediatric Research

- Diagnostic and Therapeutic Interventions in Life-Saving and Emergency Situations can provide major improvements in pediatric patient outcomes
  - Patient is in no condition to understand research and provide valid consent and urgent need may not allow adequate time to explain to parents and obtain consent

- U.S. Regulations allow conduct of research studies to test emergency treatments – only if they have the potential for direct benefit to subjects
  - Requires
    - Community Consultation
    - Public Disclosure
    - Mechanism for contacting and providing information to parents at earliest opportunity – to obtain consent
  - Opportunity to object to continued participation
• Newborn babies may have conditions that exclusively occur in them or are rarely seen at other ages
• Neonates are constantly undergoing maturation and differentiation – which can alter pharmacokinetics and drug responses
• Thus, neonatal trials require specific considerations including:
  • Very few drugs are studied in neonates – thus most use is “off label”. Using an existing “off-label” drug as a comparator may result in perpetuating use of the “off-label” or approval of a drug which is “comparable” to an ineffective “off-label” drug
  • Neonatologists often have experience and preference for use of “off-label” drugs. They may be reluctant to explain to parents that their preferred drug does not have adequate evidence of safety and efficacy – in order to allow parents they option for use of an experimental treatment
  • Seeking consent soon after birth can cause parental stress and not allow a fully informed understanding of the risks and potential benefits
Conclusions
Conclusions

- EU and US marketing authorisations for a new drug should contain a pediatric assessment (i.e. data from pediatric studies) if drug is appropriate for pediatric patients.

- Pediatric Study Plans need to be developed and reviewed with Regulators early in the development program.
  - Outline specific pediatric studies in a pediatric Investigational Plan (EU) or a Pediatric Drug Development Plan (US).
  - Submit these plans to regulatory authorities at end-of-phase II (or end-of-phase I in case of serious and life-threatening diseases that lack adequate therapy).
In both EU and US there is an incentive for studying medicines for children. In order to qualify for such a reward, the pediatric study should be agreed upon with regulatory authorities via an agreed Pediatric Investigation Plan (EU) or Written Request (US) prior to carrying out the study. For global development, it is important that the timing of requesting a pediatric incentive should be harmonised in both EU and US, in order to qualify for both the EU and US pediatric incentive.

Clinical efficacy in the pediatric population can be assessed via different approaches, depending on the characteristics of the drug (i.e. PK approach, PK/PD approach, clinical efficacy studies).
Conclusions

- The specific timing of pediatric clinical studies depends on
  - product
  - type of disease
  - safety considerations and
  - efficacy and safety of alternative treatments.

- Safety studies are always necessary in the pediatric population.
Thank You!

Q & A