

Presidential Commission for the Study of Bioethical Issues: Practical Challenges Posed by Pediatric Research

American Academy
of Pediatrics



DEDICATED TO THE HEALTH OF ALL CHILDREN™

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Historical Context for the Need for Pediatric Research

- Many of the laws which led to the formation of the Food and Drug Administration (FDA) as we know it today came as the result of therapeutic tragedies in children
 - 1902 Biologics Control Act (deaths of 22 children from contaminated vaccine)
 - 1938 Federal Food, Drug, and Cosmetic Act (deaths of 105 patients in 1937, many of whom were children, from a sulfanilamide elixir compounded with diethylene glycol)
 - 1962 Kefauver-Harris Amendments (children born with birth defects after in utero thalidomide exposure)
- As recently as 1997, nearly 80% of drugs used in children were never studied for safety, dosing, or efficacy in children
- Off-label use of drugs - unapproved use of approved drugs - is extremely prevalent among pediatricians
- Absence of pediatric labeling poses significant risks for newborns, infants, and children

American Academy of Pediatrics on Ethical Pediatric Research

- In 1977, the Academy's Committee on Drugs said that it is not only ethical, but also imperative that new drugs to be used in children be studied in children
- In a 2010 revision of the statement, the Academy said that it is unethical to deny children appropriate access to existing and new therapeutic agents
- Further, it is the combined responsibility of the pediatric community, pharmaceutical industry, and regulatory agencies to design, approve, and conduct high-quality studies in children and the responsibility of the public to support the necessary research to ensure that all children will receive treatment at the most appropriate dose in order to maximize efficacy and minimize toxicity
- Performance of research studies to evaluate drugs in children is critical for determining the safety and efficacy of medications in newborns, infants, and children

Special Considerations for Pediatric Research

- **Determination of Benefit and Risk:**
 - *Category 1* No greater than minimal risk
 - *Category 2* Greater than minimal risk but prospect of direct benefit
 - *Category 3* Greater than minimal risk, no prospect of direct benefit but likely to yield generalizable knowledge about disorder or condition
 - *Category 4* Not otherwise approvable but opportunity to understand, prevent or alleviate a serious health problem
- **Institutional Review Boards (IRBs):** Review clinical investigations that involve children and approve based on benefit/risk, protocols should be scrutinized to minimize risks, should include members with pediatric expertise
- **Informed Consent/Pediatric Assent:** Central to all clinical research and ensuring protection of human subjects, wide variation in practice among IRBs, research to define best practices for informed consent needed

Public Policies to Promote Pediatric Research

- In 1997, **Food and Drug Administration Modernization Act (FDAMA)** contained pediatric exclusivity, an incentive to study drugs in children
- Program reauthorized as **Best Pharmaceuticals for Children Act (BPCA)** in 2002
- **Pediatric Research Equity Act (PREA)**, a requirement for pediatric studies, passed in 2003 after the 1998 Pediatric Rule was struck down
- BPCA and PREA were reauthorized together in 2007, creating an integrated system of pediatric research incentives and requirements
- BPCA program at the National Institutes of Health to study off-patent drugs, including medical countermeasures
- BPCA and PREA mandate safety reviews by FDA's Pediatric Advisory Committee
- Pending legislation in both the Senate and House to make pediatric drug testing laws permanent

A Track Record of Successful Pediatric Research

- Since 1997, 438 drug labels updated with pediatric information
- Off-label use of drugs for most pediatric subpopulations reduced to around 50%
- We learned that “we didn’t know what we didn’t know”
- BPCA and PREA studies have revealed safety issues, altered dosing, led to new indications, and shown some drugs to lack efficacy in children
- Since 2007, BPCA and PREA studies have involved 167,382 pediatric patients
- Led to the development of a parallel pediatric program in Europe
- Studies conducted under BPCA and PREA have dramatically improved pediatric practice

Vaccine Research

- Unlike in most drugs, pediatrics drives vaccine research and development
- Vaccines prevent morbidity and mortality and they help to enable children to reach their full potential
- A recent Institute of Medicine (IOM) report on *Safe and Effective Medicines for Children* found that of the 55 vaccines listed by FDA's Center for Biologics Evaluation and Research, only three products (5%) were not labeled for pediatric use
- For most vaccines and drugs, adult safety and immunogenicity data needed before products are studied in children
- Monitor data and usage in broader adult population first for any safety signals

Pediatric Medical Countermeasures (MCM)

- For chemical, biological, radiological, nuclear, and explosive (CBRNE) threats, children have unique vulnerabilities that must be accounted for and they may lack the ability to communicate their needs
 - Higher levels of exposure – Inhale more air, consume more water, aerosolized agents accumulate closer to the ground, thinner skin, larger skin surface-to-body mass ratio than adults
 - Mental health needs – Different from adults and may change over time, varies greatly
 - Separation from parents and caregivers – Parents may not be able to provide consent, orphans, vulnerable to exploitation
- Strategic National Stockpile (SNS) is the national repository of MCMs including medications, vaccines, and medical equipment and products purchased for SNS generally cannot be for off-label uses
- National Commission on Children and Disasters, National Biodefense Science Board, AAP, and other experts found that the SNS is not only under-stocked with formulations of MCMs appropriate for children, but information also lacking on pediatric dosing for MCMs

MCM Research Considerations

- Emergency Use Authorization (EUA) enables the Secretary of Health and Human Services (HHS) to authorize the use of an FDA-approved product for unapproved uses or the use of an unapproved product under certain circumstances *once an emergency has been declared*
- Must have available information on the product's safety and efficacy to allow the Secretary to determine that benefits of use are likely to outweigh potential risks
- Multiple EUAs issued during the H1N1 pandemic including oseltamivir for infants under one year of age
- In the event of an anthrax attack, FDA will not issue an EUA for anthrax vaccine adsorbed (AVA) in children based on existing data
- An investigational new drug (IND) application would apply for AVA in children
- Unlike an EUA which is not considered investigational, an IND requires informed consent and IRB approval

AVA Research Considerations

- Given difficulty of obtaining IRB approval and patient informed consent during an emergency or disaster, collection of data pre-event to support an EUA for pediatric use of AVA is necessary
- Any such research must comply with the 21 CFR 50.54/ 45 CFR 46.407 federal review process which provides the opportunity for public review and comment
- For MCMs like AVA, measuring benefit and risk also involves considerations of national security and threat assessments and while detailed information may be classified, parents and potential enrollees in a research study must be given enough information about the risk of an anthrax attack to assess for themselves the benefits and risks
- Consideration must also be given to the fatality rate of inhalational anthrax (estimated at 75%) and lack of FDA-approval for ciprofloxacin
- Pediatric subject matter experts should be consulted in the design of a pre-event study of AVA in children as well as post-event care, follow-up, and MCM distribution