

**Testimony Before the FDA's
Pediatric Ethics Subcommittee of
the Pediatric Advisory Committee**

**Ethical Issues on Pediatric Product
Development**

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(I have no financial conflicts of interest)

Overview

- **Definition of minimal risk**
- **21 CFR 50.54 requirements**
- **The proposed pre-event anthrax vaccine trial in children**

Minimal Risk

“means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.”

21 CFR 50.3(k); 45 CFR 46.102(i)

Minimal Risk: A Uniform Standard

Public Citizen endorses an interpretation of the regulatory definition of “minimal risk” that uses the uniform-standard framework.

Minimal Risk: A Uniform Standard

IOM Committee on Clinical Research Involving Children:

“On ethical grounds, the committee rejected a ‘relative’ interpretation of minimal risk; that is, an interpretation that allows the application of higher thresholds of minimal risk for children who experience higher risk in their daily lives as a result of their place of residence, family situations, medical condition, or other burdensome circumstances. Instead, the assessment of risk should be indexed to the experiences of average, normal, healthy children.”

Ethical Conduct of Clinical Research Involving Children, Natl Acad Press, 2004

Minimal Risk: A Uniform Standard

IOM Committee on Clinical Research Involving Children:

“Recommendation 4.1: In evaluating the potential harms or discomfort posed by a research protocol that includes children...

- interpret minimal risk in relation to the normal experiences of average, healthy, normal children**
- focus on the equivalence of potential harms or discomfort anticipated in research with the harms or discomfort that average, healthy, normal children may encounter in their daily lives or experience in routine physical or psychological examinations or tests...”**

Minimal Risk: A Uniform Standard

IOM Committee on Clinical Research Involving Children:

“The relative interpretation of the minimal-risk standard is inconsistent both with an ordinary or commonsense understanding of the concept of minimal risk and with the objective of providing special protections to child participants in research.”

Ethical Conduct of Clinical Research Involving Children, Natl Acad Press, 2004

Minimal Risk: A Uniform Standard

IOM Committee on Clinical Research Involving Children's position is similar to that taken by several federal advisory bodies:

- **National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1977 report, *Research Involving Children***
- **National Human Research Protections Advisory Committee, 2002**
- **Secretary's Advisory Committee on Human Research Protections, 2008**

21 CFR 50.54: A Lower Standard?

- **Presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children**
- **Will be conducted in accordance with sound ethical principles***
- **Adequate provisions for soliciting the assent of children and the permission of parents or guardians***

***Apply to all research involving children**

21 CFR 50.54: A Lower Standard?

- **21 CFR 50.54(b)(2)(ii):** Presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children

versus
- **21 CFR 50.53(c):** The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition

21 CFR 50.54: A Lower Standard?

“As described in the 1977 report of the National Commission, the referral of proposed research for ‘national’ review should be reserved for ‘exceptional situations’ and research of ‘major significance.’ Given this context, the committee believed that the criterion for judging the potential contribution of research must, ethically, be as stringent for reviews conducted under Section 407 as for those conducted under Section 406. Thus, although it is not required by the regulations, the standard of ‘vital importance’ should be applied by the panels involved in the review of proposals referred to the Secretary of DHHS or the Commissioner of FDA for approval.”

21 CFR 50.54: Uncertainty and Available Alternatives

- The degree of uncertainty about the need for future use of a product should be taken into consideration when evaluating research involving children under 21 CFR 50.54.
- The availability of existing, FDA-approved products that can be used as countermeasures to exposures in children is also an important consideration.

21 CFR 50.54: Full Transparency

- **All relevant information, including sensitive information that may be classified, should be made publicly available for research studies reviewed under 21 CFR 50.54. Such transparency is essential to allow meaningful, informed input from the public.**

Proposed Anthrax Vaccine Adsorbed (AVA) Study in Children

- **Public Citizen strongly opposes the conduct of pre-event clinical trials of the AVA in children. Such trials would be unethical and are not approvable under the HHS and FDA regulations for the protection of human subjects.**
- **Such research does not present any prospect of direct benefit to the children who would be subjects of the research.**
- **The vaccine poses significant known risks of potentially serious harms, and the research testing the vaccine would involve greater than minimal risk (and greater than a minor increase over minimal risk).**

Known Risks of AVA

- **Anaphylactic shock**
- **Serious allergic reactions, including angioedema, rash, urticaria, pruritus, erythema multiforme, anaphylactoid reaction, and Stevens-Johnson syndrome**
- **Nervous system disorders, including headache, paresthesia, syncope, tremor, and ulnar nerve neuropathy**
- **Musculoskeletal and connective tissue disorders including arthralgia, arthropathy, myalgia, rhabdomyolysis, and alopecia**

Known Risks of AVA

- **General disorders and administration site conditions, including malaise, pain, cellulitis, and flu-like symptoms**
- **Multisystem disorders defined as chronic symptoms involving at least two of the following three categories: fatigue, mood-cognition, and musculoskeletal system**

Proposed AVA Study in Children

- **Such research could only be conducted if the requirements of FDA regulations at 21 CFR 50.54 were satisfied (and 45 CFR 46.407, if the research is HHS-funded):**
 - (a) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious health problem affecting the health or welfare of children;**
 - (b) the research would be conducted in accordance with sound ethical principles.**

Proposed AVA Study in Children

- **Regarding determination (a), anthrax currently is not “a serious health problem affecting the health or welfare of children” in the U.S., and the extremely remote chance of children being exposed to anthrax is not sufficient justification for testing the anthrax vaccine in children, particularly since there are antibiotics approved by the FDA for use in children to treat post-exposure cutaneous or inhalation anthrax, including penicillin and doxycycline.**

Proposed AVA Study in Children

- **Regarding determination (b), the proposed research would not be consistent with sound ethical principles, because exposing vulnerable children, who lack autonomy to make an independent decision about participation in research, to a high-risk experimental intervention is not justified given the lack of any direct benefit to the subjects and the fact that anthrax is not a serious health problem affecting the health and welfare of children.**

Proposed AVA Study in Children

- **Millions of taxpayer dollars currently are being spent to maintain a national stockpile of anthrax vaccine (and other countermeasures).**
- **Exaggerating the risk of an anthrax or other bioterrorism event for both adults and children may help justify such expenditures but should not be used to justify unethical research in children.**

Proposed AVA Study in Children

- **Given the known risks of AVA, Public Citizen disagrees with the proposal by the Presidential Commission for the Study of Bioethical Issues that careful age de-escalation experiments in adults might allow researchers to infer that studies involving children would involve no more than minimal risk.**

Conclusion

Pre-event clinical trials in children testing greater-than-minimal-risk experimental medical countermeasures against unlikely exposures to various biologic or chemical agents, such as the proposed AVA study, should not be permitted by the FDA or HHS.

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