Protecting Human Subjects in Research: Are Current Safeguards Adequate?

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AHRP Testimony submitted to Congressional Committee

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- Vera Hassner Sharav, President, and John H. Noble, Jr., Ph.D., steering committee member, The Alliance for Human Research Protection (AHRP), before the Subcommittee on Public Health, Committee on Health, Education, Labor, & Pensions, United States Senate at Hearing, "Protecting Human Subjects in Research: Are Current Safeguards Adequate?" on April 23, 2002.

- Witness Short Title. The Alliance for Human Research Protection (AHRP) is a national network of lay people and professionals dedicated to advancing responsible and ethical medical research practices, to ensure that the human rights, dignity and welfare of human subjects are protected, and to minimize the risks associated with such endeavors.

- We thank the Senate Subcommittee on Public Health for this opportunity to present testimony on current weaknesses and flaws in the regulatory and oversight system for protecting the life safety and human rights of the child subjects of biomedical research. The testimony explains how recent government actions threaten to make a bad system worse.

IV. Minimal Risk for Children.

Current federal regulations set no limits on the level of risk that a competent adult may voluntarily choose to undertake for the sake of science. The regulations require prior approval by a review board (IRB) to ensure the research meets scientific and ethical justification, to ensure that the risks and benefits (if any) are fully disclosed to the subject, and that the subject can exercise the right to give or withhold informed consent. The regulations rely on trust that the research stakeholders - the scientists, sponsors, and institutional review boards - will

comply with the regulations. That trust, however, has been betrayed and even the nation's prestigious research centers were found in violation of ethical standards, including informed consent.

Children present
us with the greatest ethical problem because they are not legally competent to exercise informed consent or to protect themselves from unwanted experiments that put them in harm's way. This status relegates children to the category of involuntary human subjects.

Children's
dependency on others to decide what serves their best interest places them at particular disadvantage. In 1983 special regulations (45 CFR 46 Subpart D, Sections 404-409) were adopted to protect children from harm and to ensure that they will not be exploited in nontherapeutic experiments involving greater than minimal risks or discomfort. Thus, federal regulations protect children by requiring a higher standard of justification for approval of pediatric research by setting limits on the level of risk.

45 CFR 46.102
defines "minimal risk" for adults and children alike:

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.

Regulatory
protections were adopted to ensure that children, who are not volunteers, are protected from undue harm under the provisions of 45 CFR 46.405
- Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

Research under
Section 405 is permissible only if "the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches."

When the research
offers no possibility of a direct benefit, i.e., is nontherapeutic, the regulations restrict such research to "minimal risk." If there is evidence that the research is of "vital importance for the understanding of the subjects' disorder or condition" then the regulations permit children to be subjected to "a minor increase over minimal risk."

45 CFR 46
Section 406 - Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

Under Section
46.406 research could be conducted only if:

- . . . the risk
represents a minor increase over minimal risk; the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;

- . . . the intervention
or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition. [Emphases added]

However, the
1997 FDA Modernization Act (FDAMA) offered the pharmaceutical industry enormous financial incentives - i.e., a six-month patent exclusivity extension - if they tested their patented drugs on children. FDAMA was passed without any risk assessment by the FDA or NIH, and without Congress being informed about the potential unintended consequences that could result unless additional protections were enacted for children. As a result, children who are legally precluded from exercising the right to refuse are being aggressively recruited to bear the burden of testing drugs that may (or may not) be in their best interest. The law, unfortunately, failed to balance financial incentives with new (or improved) safeguards to protect an increased number of young children being exposed to the hazards of research.

In 2001 Alice Dembner
of the Boston Globe examined research conducted since 1994 that involved children. She reported (in a series of articles) that children had suffered and died in clinical trials in which ethical standards had been violated.[1]
Financial incentives for parents, physicians, and researchers are undermining children's welfare. Children are being recruited with Toys 'R Us gift certificates. Parents in need of money are offered as much as $1,000 to "volunteer" their children for drug experiments that involve risks of harm.[2]
The physicians who are engaged in such coercion receive as much as $5,000 referral fees (kickbacks) for the recruitment of children.[3] In the last seven years alone, according to Dembner, at least eight children died in medical experiments and hundreds suffered harmful side effects.

The number of child research subjects has grown from about 16,000 in 1997 to about 45,000 in 2001, and "there is strong reason to believe that deaths and injuries in research involving children are more widespread" than available statistics would indicate. [4]

The FDA acknowledged that before FDAMA the use of children as subjects in phase I safety drug studies "had been primarily limited to life threatening diseases and children who had the disease" in question.[5]
The policy prior to FDAMA protected children from harmful experiments in accord with the 1983 federal regulations (45 CFR 46.404-409). Following passage of FDAMA, however, federal policy broadened the criteria for inclusion of children in research generally and for participation of children entered in high-risk experiments. In 1999 the FDA acknowledged that the post-FDAMA policy change "led to an increasing number of proposals for studies of safety and pharmacokinetics, including those in children who do not have the condition for which the drug is intended."[6]

One can only speculate about the negative impact this policy change had on the healthy children who had been subjected to drug trials before the FDA rescinded the policy. FDA Associate Director of Pediatrics, Dr. Dianne Murphy, was reported to have stated at a conference (April 3, 2001): "FDA will no longer accept information submitted to the agency for pediatric exclusivity if the data is derived from children who are not patients and for whom there is no foreseeable benefit." [7] The same report, however, indicated the FDA was "upset that pharmaceutical companies are continuing to enroll healthy children in clinical trials."

V. Implementation of 45 CFR 46, Section 407

45 CFR 46, Section 407 - Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

Section 407 requires nontherapeutic research involving greater than minimal risk and no potential benefit for the child subjects to be reviewed by the Secretary of Health and Human Services and approved only after consultation with a panel of appropriate experts and "following opportunity for public review and comment." This procedure in many respects parallels the process of initiating or changing regulations that is prescribed by the Administrative Rulemaking Act because of the gravitas of the issue.

The Department of Health and Human Services (DHHS), through its Office of Human Research Protections (OHRP), assisted by the National Human Research Protection Advisory Committee (NHRPAC), and its Food and Drug Administration (FDA) Pediatric Advisory Committee have embarked on initiatives to broaden the recruitment of children - even healthy children - for clinical trials that may undermine their health and welfare.

Indeed, in one 2000 DHHS draft policy and procedure document healthy children who are to be recruited for clinical trials are referred to as "risk-bearing

normal control subjects."[8] The FDA's Pediatric Advisory Subcommittee (PAS) acknowledged: "pediatric studies should be conducted in subjects who may benefit from participation in the trial. Usually this implies the subject has or is susceptible to the disease under study." However, the PAS concluded that by reference to a broad definition of potential benefit, "any child has the potential to benefit from a treatment for otitis media" (middle ear infection).[9]

These OHRP and FDA advisory committees are declaring normal stages of child development as if they were preludes to pathology: "prematurity, infancy, adolescence, poverty, living in a compromised physical environment, and institutionalization" are declared to be "disorders or conditions in children that warrant permissible research that presents greater than minimal risk without a prospect of direct benefit to the child."[10]

The regulatory protections children have had since 1983 are being dismantled one section at a time. Federal policy is overturning regulatory prohibitions without issuing an advanced notice for proposed rulemaking changes (ANPRM) as required under the Administrative Rulemaking Act. Instead, a backdoor strategy is being pursued that redefines regulatory terms and protective restrictions in order to legitimize currently prohibited risky and painful experiments on young children.

Those arguing that all children are potentially "at risk" of a future condition attempt to justify the inclusion of all children - be they healthy or critically ill - in experiments that expose them to pain and risks of harm even when there was no potential for an immediate direct benefit. By applying a broad standard to the definition of "potential benefit" in this way, children are being deprived of existing, more protective federal regulations under 45 CFR 46, Subpart D. The new policy would open access to children who do not have a bone fide condition as research subjects in experiments that would cause them pain and put them at risk of harm without a potential foreseeable benefit. Children are being recruited to test drugs whose safety is uncertain. Small children are subjected to discomfort and foreseeable risks of harm on the basis of a presumed potential risk for which there is no empirical evidence.[11]

Dr. Benedetto Vitiello, NIMH's Director of Child and Adolescent Treatment and Preventive Interventions Research Branch, provided confirmatory evidence in this regard when stating "pediatric psychopharmacology has recently seen an unprecedented expansion . . . NIMH-funded research for clinical trials in youths has more than doubled in the last few years."[12]

At the same time he acknowledges this is happening despite the existence of "diagnostic uncertainty surrounding most manifestations of psychopathology in early childhood." Dr. Vitiello also reveals "only limited data exist on the efficacy and safety of antidepressants and mood stabilizers in school-age prepubertal children. Clinical trials of these agents in preschoolers do not seem possible given the current uncertainties about diagnostic validity of mood disorders in children