

Risks and Benefits of Inclusion of Foster Children in Pre-Approval Clinical Drug
Trials: How to Protect a Vulnerable Population.

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In 2005, news reports began to emerge describing the policy of the New York City Agency for Children's Services (ACS) to enroll foster children in pre-approval¹ trials of therapies and vaccines for HIV. Many research institutions participated in this consortium of studies, including Columbia University, New York Presbyterian and Johns Hopkins. The *USA Today*, *New York Post*, *New York Times*, *Washington Post* and the BBC all reported the story and in some cases interviewed a few of the foster parents of the children affected.² The BBC report in particular claimed to have interviewed foster parents of the study participants who reported being threatened with loss of custody should they object to the inclusion of their children in the trials. The BBC report indicated that the side effects of the therapies were severe enough in some cases to require the insertion of feeding tubes to administer the investigational therapies.³ Many of these details have not yet been confirmed by ongoing independent investigations, what is undisputed is the fact that these foster children were enrolled in investigational trials (lasting from the early 1990s until 2005) and that many of the therapies or all of the vaccines had not yet been approved in adults. While some of the research universities

¹ Clinical trials are required by the Food and Drug Administration prior to approving a drug for use in the United States, the three phases of these trials are all included in the category of "pre-approval" trials.

² David Seifman, "Panel to Probe Foster Kids HIV-Drug Trials." *New York Post*, April 23, 2005. Mary Otto, "Drugs Tested on HIV-Positive Foster Children." *Washingtonpost.com.*, May 19, 2005.

KaiserNetwork, "Daily Report Across The Nation | *New York Times* Examines Controversy Surrounding, History of AIDS Drug Trials Involving Foster Children" July 18, 2005.

http://kaisernetwork.org/daily_report/rep_index . Accessed 2/10/07.

³ The reporter for this story has been described as believing that HIV is not the cause of AIDS. Such a position represents a potential conflict of interest for that reporter on this matter.

[Http://nature.com/naturemedicine](http://nature.com/naturemedicine). Volume 11:Number1. January 2005

required an independent advocate be appointed to protect the rights of the foster children, others did not. Where an advocate was involved, it is unclear as to whether this person was actually appointed or only consulted. In 2005, an independent advocacy organization, the Alliance for Human Research Protection filed a complaint with the Federal Government.⁴ They managed to generate enough publicity that investigations by the House Ways and Means Committee, the Office of Human Research Protections (OHRP; a department within Health and Human Services) and the City of New York were initiated.⁵

The issue of using children in drug research has long engendered controversy. Some feel that all children are to be protected and that research on children is, in and of itself, unethical. Alternatively, there is a concern on the part of physicians and parents who treat or care for children with devastating illnesses – too little is known about dosages or treatments for children. The FDA has stressed the importance of including children in clinical drug trials.⁶ It is well established that therapies used to treat adults react very differently in the bodies of children and adolescents. Yet the inherent legal and financial risks associated with pediatric research have traditionally made drug

⁴ Vera Hassner Sharav, “Phase I Drug Trials Used Foster Care Children in Violation of 45 CFR 46.409 and 21 CFR 50.56”. Alliance for Human Research Protection. www.ahrp.org. Accessed November 5, 2005.

⁵ House Ways and Means, Subcommittee on Human Research, *Foster Children and Clinical Trials Hearing*. Congressional Quarterly: May 18, 2005.

⁶ Food and Drug Administration. *Guidance For Industry: E11 Clinical Investigation of Medicinal Products in the Pediatric Population*. <http://www.fda.gov/cder/guidance/4099FNL.PDF>. Accessed February 28, 2007.

companies (the dominant sponsors of drug trials) very reluctant to study their drugs or vaccines in pediatric populations. In fact, the legal and financial risks of vaccine manufacturing are so great that very few manufacturers produce vaccines of any sort, as evidenced by the shortage of even flu vaccines in recent years. Pediatricians in community practice are left to guess at the correct dosage of a therapy for their patients, with sparse literature on the side effects that might occur in younger populations. As a result of this quandary, the FDA and NIH have policies which have been designed to allow the participation of pediatric patients under closely supervised conditions. It is the responsibility of the Institutional Review Board of any institution conducting human subject research to ensure these guidelines are followed. These guidelines specify the extra steps needed to protect vulnerable classes of subjects, from prisoners to children. These populations are considered to be at a higher risk of exploitation, resulting in the higher level of protection afforded them.

Between the early nineties and 2005, seven states participated in these HIV drug and vaccine trials, allowing the enrollment of foster children. In New York City alone, over 400 foster children were enrolled. The neighboring state of New Jersey, (whose inner cities were also ravaged by the AIDS epidemic), had a policy that precludes enrollment of any foster children. This paper focuses specifically on the case of the New York City children because of a long history of abuse in this foster care system.⁷

The use of any children, and foster children in particular, has received scrutiny because society believes that children are entitled to special rights as a class and that

⁷ Among others, see Nina Bernstein, *Lost Children of Wilder: The Epic Struggle to Change Foster Care*. (Random House: New York, 2001).

children are not able to speak for themselves. Per FDA policy, Phase 1 trials are ordinarily used to test dosage and effectiveness in a small number of healthy patients. Once a dosage and side effect profile are established, the drug is tested in what are called phase 2 trials with patients who have the condition being studied.⁸ Because Phase I trials involve the greatest level of risk and discomfort, the use of foster children as subjects raises many very troubling questions. Inclusion of these children is in direct opposition to the federal regulation 45 CFR 46.409 (Wards) which forbids participation in experiments involving greater than minimal risk. The Federal Government prevents the states from issuing regulations which reduce the rights of the children, as stated in 45 CFR 46.101 (6)(e)(f).

The foster children included in the New York City trials are not alone. Nationwide, between 1986 and the present day, twelve to thirteen thousand children under the age of 13, who were documented or suspected to be HIV+, participated in drug trials in the United States.⁹ During this time, an Associated Press investigation has shown that 48 AIDS experiments on foster children had occurred in seven states, (Illinois, Louisiana, Maryland, Texas, New York, North Carolina and Colorado), and claims that most violated federal statutes by failing to provide an advocate.¹⁰ Again, the New York City foster children are included in this group. The fact that the vast majority of foster children in the New York City area are Black or Hispanic raises troubling questions as to the concept of equality in the selection of research subjects. This unequal

⁸ http://www.fda.gov/fdac/features/2003/503_trial.html Accessed 2/28/07

⁹ Seifman, 2005

¹⁰ Sharav, 2004

recruitment violates the principle of justice described in the landmark Belmont Report on human experimentation.¹¹ Children of African-American or Hispanic descent were over-represented in the New York City trials; this was a direct result of apparently exclusive recruitment of foster children. Was any attempt made to recruit children who were not in the foster care system? This and other questions concerning recruitment remain unasked and unanswered. The Federal Guidelines protecting human research subjects were adopted after the Tuskegee controversy and are designed to ensure that any one group of people is not disproportionately recruited for human subject experiments.¹² The Belmont Report defines the concept of justice as ensuring a sense of fairness in the recruitment of potential research subjects. To allow recruitment to a drug trial which results in a large percentage of one socioeconomic or racial group can be construed as a violation of this concept of justice.

In a further attempt to protect children, the federal government requires that the risk to the child is to be considered of greater concern than the benefit to society in research programs. If the pediatric study subject was exposed to greater than minimal risk, an independent advocate was specifically required. ACS and the investigators involved in the studies have argued that participation in drug trials was the only way to provide access to therapies which might save these children. However, vaccines and previously unapproved drugs were often studied in these trials. Generally, drugs are

¹¹ Public Law 93-347 established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report was issued by this commission 1979.

¹² National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects Research*. Washington, D.C.:U.S. Government Printing Office, 1979.

studied in pediatric patients only after being established as safe in adults. In its review of the trials using foster children, the Alliance for Human Research Protection claims that in testing the therapies in 52 of these children, half (26) experienced moderate to severe reactions to the therapies. Another trial show a “disturbingly high” death rate in those children who took the drug dapsons.

At the request of the ACS in New York City, the Vera Institute of Justice¹³ has been retained to review both the history of the policy regarding enrollment of foster children and to make recommendations for a future policy. Currently, all participation by New York City foster children is on hold. To date, the Vera Institute has confirmed that over 400 children were in fact enrolled. It will take another year at least to finish interviews of the children and parents involved and to sort out the nature of any informed consent (or assent). The appointment of an independent advocate is also being investigated. This project is unique in seeking input from not only the children affected, their families and the foster care institutions but also from community activists, AIDS research consortiums, and physicians within the community. Although the final report by the Vera Institute will hopefully establish the exact nature of the participation, and confirm or disprove any violation of federal guidelines, it is not necessary to wait for this official (though non-governmental) report to be filed. The issue itself continues nationwide today.

Another area of concern has not been identified in the press, but bears serious consideration. It is traditional for drug companies who are sponsoring phase 1 or 2 trials

¹³ The Vera Institute of Justice is a private New York based research group which specializes in the analysis of governmental programs regarding safety. Their website can be found at www.vera.org.

on their drugs to pay a variety of sources for recruitment of subjects. This has been ethically justified in the past because it can be very difficult to recruit subjects and is very time intensive. There is no public report of the foster care agencies receiving compensation for enrollment of their foster children, however the question needs to be specifically addressed. The issue also needs to be included in a revision of the federal policies concerning enrollment of foster children in clinical drug trials.

Such a revision is urgently needed and can only come from the federal government if protection of foster children is to be comprehensively established. Some of the investigators in the trials in question have indicated that an independent advocate was not technically required according to federal guidelines because there was a possibility of benefit directly to the child. The exact wording of the regulations are as follows:

§46.409 Wards.

(a) Children who are wards of the state or any other agency, institution, or entity can be included in research approved under [§46.406](#) or [§46.407](#) only if such research is:

- (1) Related to their status as wards; or
- (2) Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

(b) If the research is approved under paragraph (a) of this section, the IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

Because the guidelines as written appear to introduce an element of local judgment, those guidelines need to be revised. In contrast to the guidelines covering foster children, the guidelines governing another protected group, prisoners, appear to be more closely followed. Recognizing that incarcerated adults are subject to all forms of subtle pressure, an independent advocate is required in *all* trials when an IRB reviews the protocol. The risk of intimidation or coercion is considered too significant. As a result the local IRB or the investigators, much less a prison official, cannot act on behalf of the inmates without the appointment of an independent advocate for this population. So, if adults who are not completely in control of their destiny (and their bodies for that matter) are required to be represented by an independent advocate, why not children? And especially why not children who statistically tend to be members of minority categories? Abuse of foster children by the agencies responsible for their care has been documented in many cases, but particularly in the case of the New York City program. Foster care programs are neither cheap nor easy to run. Overworked social workers and case workers cannot be expected to anticipate risks associated with inclusion in a clinical trial. While the treating physicians involved often do have the best interests of the children in mind, their sometimes desperate desire to do something for the children endangers any objectivity regarding the risks. The physicians who run the trials are paid by the drug company sponsoring them. All parties can indeed have the best interests of the child in mind and still not be able to focus only on that foster child and that trial risk. The federal guidelines need to be modified to provide foster children with an advocate in all cases where they participate in clinical trials, regardless of the level of risk or benefit anticipated. Due to the history of abuse within the foster care system, no foster children

should be enrolled in phase 1 or phase 2 trials. Finally, extending the protections to all children, no phase 1 trials should include children at all until phase 1 trials have been completed in adults.

In conclusion then, drugs and other therapies do need to be studied in foster children but only with the provision of an independent advocate in every case. U.S. policy should support this. These studies should follow previously established policies and federal regulations designed to protect all children. Significant fines may need to be administered before institutions and drug companies begin to pay attention. Foster children require more protection not less. The only action taken by the FDA to date is to censure the Columbia University IRB and recommend further training. In doing so, the federal government has missed a key opportunity to further clarify its position regarding the checks and balances necessary for ensuring that clinical trials benefit *and* protect pediatric populations. Furthermore, the recruitment methods used by the participating Universities and foster care programs provide undeniable proof that a population of foster children is still too easily abused. Because of the greater inherent risk of improper inclusion in clinical trials, foster children should be prohibited from inclusion in trials of overtly toxic therapies. The U.S. cannot allow the existence of a convenient group of ready made test subjects, whose rights are not honored at least to the extent required by law.