THE EXPERIENCES OF NEW YORK CITY FOSTER CHILDREN IN HIV/AIDS CLINICAL TRIALS

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with
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Executive Summary

At the request of New York City's Administration for Children's Services, beginning in 2005 the Vera Institute of Justice undertook an in-depth examination of issues related to the enrollment and monitoring of New York City foster children in clinical trials related to the Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS). The request was prompted by allegations that African American and Latino children were inappropriately removed from their families and placed in foster care to facilitate their enrollment in dangerous and unnecessary medical experiments. Other concerns included whether children suffered unnecessarily as a result of their participation, whether children in trials were HIV infected, whether trial researchers properly obtained informed consent, and whether the child welfare system adequately monitored the children in their care.

The Vera Institute agreed to conduct the review under a number of conditions. First, that Children's Services search its files for children who might have participated in the trials and also provide Vera staff complete access to its files and records and the full cooperation of its staff. Second, that Vera retain full editorial control over the final report. Third, that work on the project be overseen by Vera's own advisory board. Dr. Richard G. Dudley, a Vera trustee, a psychiatrist in private practice, and a founding member of the National Black Leadership Commission on AIDS, agreed to chair Vera's Clinical Trials Advisory Board. Children's Services appointed its own advisory board of community advocates and service providers to advise it on issues related to the controversy, to assist the agency in developing a new clinical trial policy, and to facilitate dialogue between Children's Services and the communities it serves.

To conduct the study, Vera reviewers examined the child welfare files of 796 children who might have participated in HIV/AIDS clinical trials. Vera staff also reviewed policy documents and correspondence, clinical trial protocols, published reports about the clinical trials, federal and state regulations, and material from the National Institutes of Health and the federal Office of Human Research Protections obtained through the Freedom of Information Act. Staff also interviewed dozens of people with experience and perspectives on this controversy, including community advocates, clinical trial researchers, foster care agency staff, and child welfare agency personnel.

For each child whose files were reviewed, project staff sought to document the family circumstances that prompted the child to enter and leave foster care, the child's medical problems and medical treatment, and the child's participation in clinical trials. For every child who participated in clinical trials Vera reviewers also documented the consent process, whether the child had adverse consequences or medical benefits from the trial, and the medical care provided throughout the child's stay in foster care.

Vera reviewers found a significant amount of medical information in the child welfare files. However, citing confidentiality laws, the New York State Department of Health (NYSDOH) refused multiple requests from Children's Services that it use its supervisory authority to allow

staff from Vera or Children's Services to review clinical trial research or medical records. This limited Vera's review in several ways, including the ability to fully document the frequency and severity of toxicity (side effects), the individual outcomes of trial participation for the children in the review, and the existence of valid, signed informed consent documents.

Background

The first cases of HIV/AIDS in children were reported in New York City in 1982**.** Between 1977 and 2006, 3,895 children in New York City were born with HIV infection.

Findings

Vera's review of the child welfare files identified 532 New York City foster children who participated in 88 clinical trials and observational studies between 1985 and 2005. Of the 88 clinical trials and observational studies, 65 involved trials of new medications for HIV or its associated conditions. Forty-four of the 65 trials involved antiretroviral drugs.

Vera reviewers found little or no evidence in the information examined for some of the concerns that prompted Children's Services to initiate this study.

1. Many children—inside and outside of foster care and clinical trials—died because of complications of HIV/AIDS during the late 1980s and 1990s. Eighty of the 532 children who participated in clinical trials or observational studies died while in foster care; 25 of them died while enrolled in a medication trial. Vera medical staff did not find, however, that any child's death was caused directly by clinical trial medication.
2. An examination of data from the New York City Department of Health and Mental Hygiene, though not conclusive, suggests that HIV-positive foster children who were enrolled in clinical trials and/or observational research studies did not experience an increased risk of death from their enrollment in clinical trials.
3. The child welfare files contained information indicating that some children experienced serious toxicities, or side effects, from trial medications, such as reduced liver function or severe anemia. These toxicities were consistent with toxicities described in published articles about the trials. Vera reviewers found many instances where a physician made adjustments to a child's treatment in light of these problems as required by the clinical trial protocol.
4. Where documentation allowed reviewers to make a determination, children in foster care met age, HIV status, and disease stage criteria for inclusion in the specific trials in which they were enrolled as described in the trial protocol. Reviewers found that two of the 532 children met exclusion criteria for the medication trials in which they were enrolled.
5. Of the children who participated in trials, Vera identified two who were HIV exposed, but for whom there was evidence suggesting they *might* not have been infected with HIV. Vera project leaders informed Children's Services about these two cases. Children's Services

subsequently responded that inquiries to state and local agencies had confirmed a diagnosis that made it appropriate for one of the children to participate in the clinical trial. Children's Services has not provided additional information on the second child, who died of causes unrelated to clinical trials participation.

6. In 1988, when city officials first considered the participation of foster children in clinical trials, the child welfare agency conducted a lengthy review of state and federal research regulations. The social services commissioner and his staff were aware of concerns about the participation of African American and Latino children in medical research and they consulted with several medical experts, including the National Medical Association (an organization of African American physicians). The standard the agency developed for approving trials—that every child in foster care enrolled in a trial have the possibility of benefiting from that trial—exceeded that of federal regulations. The policy also required that researchers obtain informed consent from a birth parent when parental rights remained intact.
7. In response to physicians' and some advocates' requests for faster trial approvals, the child welfare agency changed its policy in 1991. The new policy called for a medical advisory panel (MAP) of physicians to review and make a recommendation to the commissioner on whether a trial met the agency's standards for approval. Seventy-six percent of foster child enrollments in medication trials that took place after this policy change were in 15 trials recommended by the MAP and approved by the commissioner. Researchers and child welfare staff often followed Children's Services' policy to obtain permission for a child to enroll in a trial.
8. Many files document medical researchers' discussions of the risks and potential benefits of trial enrollment with a birth parent and the parent's subsequent permission to enroll the child. In several cases, parents did not want their children in a clinical trial and the child did not participate in the trial.
9. Children in foster care appeared to participate in trials at rates that suggest they were not specially targeted for enrollment into HIV/AIDS clinical trials. Foster children made up 30 percent of all New York City enrollments in 16 trials of medical interventions for which city-level data were available. Thirteen percent of these enrollments occurred *prior* to the child's entry into foster care, with participation extending into the period they were in foster care.
10. Children in foster care who participated in HIV/AIDS clinical trials were predominantly African American and Latino (64 percent African American and 30 percent Latino). This demographic profile paralleled the demographics of children with HIV infection in New York City (58 percent African American, 35 percent Latino).
11. There was no evidence in the child welfare files of children being removed from their families by Children's Services because a parent refused to consent to a child's participation in a clinical trial. Three-quarters of the children entered foster care before age one year and more than half entered directly from a hospital after birth. Families faced many issues such as substance use, unemployment, and poverty that were exacerbated by the medical needs of children and parents with HIV/AIDS.

12. Several files documented differences of opinion between child welfare staff and both birth and foster parents concerning antiretroviral medications prescribed *outside of clinical trials* and *after the approval* of the medication by the U.S. Food and Drug Administration (FDA). These differences were resolved on a case-by-case basis. Sometimes this involved continued monitoring and alternative treatments; in other cases it resulted in removal from parents or legal guardians or the transfer of a child to a new foster home.
13. Vera reviewers found no evidence in the child welfare files, clinical trial protocols, or interviews that children, parents, foster parents, foster care agencies or staff, or child welfare agencies or staff received incentive payments for children to participate in clinical trials. Vera's study of this issue was limited to information in child welfare, policy files, and public information from the NIH on the funding of their clinical trials.

The Vera review also found evidence that supported some concerns about the participation of foster children and their families in clinical trials. This evidence includes violations of state regulations, Children's Services' own policies for clinical trial review and enrollment, and federal regulations for protecting human subjects.

1. Child welfare agency policy after 1991 called for a review of clinical trials by a Medical Advisory Panel and approval by the commissioner. However,
    - Twenty-one children participated in three medication trials that the MAP reviewed and did *not* recommend and the commissioner did not approve. Thirteen of these enrollments took place before the children entered foster care.
    - Thirteen children participated in four medication trials that the MAP had reviewed but for which no recommendation had been forwarded to the commissioner. Two of these enrollments took place before the children entered foster care.
    - Sixty-four children participated in 30 medication trials that were not reviewed by the MAP. Thirteen of these enrollments took place before the children entered foster care.
2. Regulations and policy required the child welfare agency to retain signed informed consent forms, commissioner approval documents, and other documentation for each trial and each enrollment. For 21 percent of enrollments in medication trials that took place while the children were in foster care, signed informed consent forms were not found in the child welfare files.
3. Trials sponsored by the National Institutes of Health were monitored by an organization charged with ensuring that an informed consent document was present in the research records for each enrolled child. Without access to clinical trial research records, Vera cannot say whether or not a valid informed consent document existed in every case.
4. In at least 16 cases, Vera staff found that children in foster care appeared to have been enrolled in trials prior to the commissioner's approval of the trial. In some instances, HRA/ACS took several months to approve a trial.

5. In at least seven enrollments, the person who signed an informed consent form was not legally authorized to do so. Kinship foster parents, parents without parental rights, and child welfare staff signed the consents in these cases.
6. Federal regulations required informed consent forms to be written in accessible language. Many informed consent forms contained technical language difficult for people without a medical background to understand.
7. The role and requirements of the independent advocate described in federal research regulations were not well understood by clinical trials researchers and, in some cases, child welfare staff. In at least six instances where Vera reviewers found that an independent advocate had been appointed, the person appointed had relationships to the institution conducting the trial or a child welfare agency that the federal regulations specifically bar.
8. In several situations, child welfare files described deviations from the processes required by federal regulations and Children's Services policy. These include handwritten notes for informed consent in lieu of official documents, consent accepted over the phone, and consent sought or obtained from parents who may not have been competent to provide it. In at least two instances, the files indicate that parents' wishes were ignored. In other situations, consent was requested in ways that parents might have perceived as coercive.
9. Although state regulations mandated that Children's Services ensure the retention of most of the child welfare files that Vera was asked to review, for 30 percent of the children, some part of the child welfare file was lost, destroyed, or otherwise unavailable.
10. Available records often did not contain documentation required by state regulations.
11. Though required to collect information related to HIV testing, HIV-related medical care, and clinical trials enrollment, the records of the Pediatric AIDS Unit (PAU) were incomplete, especially after 1995. Problems with the PAU's record keeping after 1995, including defects in the unit's electronic database, were noted in the unit's quarterly reports to supervisors and state officials, including the AIDS Institute.
12. Foster care agency staff approved at least 14 enrollments of children who were in the joint guardianship of the commissioner and the foster care agency. Although conforming to the technical requirements of the policy, this resulted in the enrollment of several foster children in trials the commissioner had not approved. Three of these children were enrolled in a phase I clinical trial even though Children's Services' policy barred participation in phase I trials.

Results of Clinical Trials in which New York City Foster Children Participated. There are presently 15 medications approved by the FDA for the treatment of pediatric HIV. The FDA approved these medications after it reviewed data from clinical trials and determined that the data showed the drugs were safe and effective for widespread use by children living with HIV. Five antiretroviral medications and three HIV vaccines tested in clinical trials in which foster children participated have not been approved by the FDA for pediatric use. All five of the antiretrovirals (but not the vaccines) have been approved by the FDA for use in adults.

Recommendations

There is a continuum of situations in which children might be considered for clinical trials. Each point on this continuum contains a different set of risks and potential benefits. For children in foster care there are additional concerns. These include the effect enrollment in a trial will have on placement stability and how close a child is to entering a permanent home where adoptive parents can assume decision-making responsibility.

Some people feel that child welfare agencies should not allow children in foster care to participate in any clinical trials. In support of their position, they often cite the history of medical research involving African American and Latinos and the vulnerability of foster children. Others feel that children in foster care, including African American and Latino children, should have the same chance to participate in the development of new treatments as other children and that they should not be denied access to a promising new medication because they are no longer in their parents' care. It is not the Vera Institute's role to take a position in this debate: elected and appointed officials, in consultation with community and professional representatives, are charged with making clinical trials policy for foster children.

The knowledge gathered in this study does, however, provide a basis for Vera and its Clinical Trials Advisory Board to make recommendations for those policymakers who do decide to allow foster children to participate in clinical trials. The recommendations presented here are aimed, in part, at remedying the problems that this report identifies. Children's Services has developed a new clinical trials policy. The recommendations below can be seen as a set of benchmarks that child welfare staff, elected representatives, and community advocates can use to measure progress in addressing the concerns this report raises.

1. Respect Parental Decision Making

Concern: Parental rights were not respected in every case.
Recommendation: Only researchers and their staff, not foster care agency staff, should obtain permission for a foster child's participation in a clinical trial.
Recommendation: In cases where the parents cannot be engaged and the child welfare commissioner feels it is imperative that a child enroll in a clinical trial, a person representing the child's interest and not connected to either the foster care agency or the medical institution, such as a law guardian or family court judge, should provide a written determination that participation in the clinical trial is in the child's best interest.

2. Make Detailed Policy

Concern: New York City's clinical trials policy in the 1980s and 1990s did not detail procedures for how to handle many issues. The policy documents Vera reviewed did not anticipate several frequently occurring situations, leaving staff to improvise in a pressured environment that involved legally and ethically complex decisions.
Recommendation: Children's Services should create detailed policy guidelines that can apply across a range of child welfare and medical/public health circumstances.

3. **Ensure That Staff Understand and Agree to Abide by the Rules**

Concern: Vera staff found that not all child welfare and clinical trial research staff knew the regulations and policies regarding the participation of foster children in clinical trials.
Recommendation: Require staff involved in the participation of foster children in clinical trials—within child welfare and at medical institutions—to have a regularly updated certification indicating that they understand and agree to follow the applicable rules and regulations.

4. **Increase Transparency and Community Involvement**

Concern: The policy that allowed the participation of foster children in HIV/AIDS clinical trials was discussed publicly and disseminated to physicians, foster care agency staff, and staff in New York City's child welfare agency. Child welfare officials received input from many medical experts and child welfare professionals. However, there is little evidence that community constituents, including parent and child advocacy organizations, were involved.
Recommendations: Given community concerns about medical research and specifically about the participation of foster children in medical research, Children's Services should take steps to ensure that clinical trials policy development and oversight involve child and community advocates and representatives of African American, Latino, and other constituencies as well as medical and child welfare professionals.

5. **Maintain Commissioner Control of Trial Enrollments for Children in Guardianship**

Concern: For a period in the 1990s, foster care agencies approved enrollments of foster children in joint guardianship.
Recommendation: Only the commissioner of Children's Services should have the right to approve or reject trial enrollments for foster children who are in the sole or joint guardianship of the commissioner.

6. **Document Activities**

Concern: Many of the clinical trials examined in this report were conducted during a difficult period for New York City and its child welfare agency. Nonetheless, the violations of regulations and policy concerning file documentation and retention prevented officials from providing required information about the participation of foster children in HIV/AIDS clinical trials.
Recommendations: Children's Services should provide public reports that demonstrate that the agency is ensuring that regulations regarding record keeping for all foster children are being followed. Government must ensure that child welfare personnel have the resources to adequately staff operations to accomplish this work.

7. **The New York State Department of Health Should Authorize the Review of Medical Records**

Concern: The New York City Law Department determined that only the New York State Department of Health has the right to conduct or authorize a review of medical and clinical trial records of foster children who participated in HIV/AIDS trials—even when hospitals agree to have the files reviewed. Children's Services asked NYSDOH to exercise this supervisory authority on several occasions and in several ways. The NYSDOH declined these requests.
Recommendation: The NYSDOH should either authorize Children's Services to obtain copies of the informed consent forms used to permit children to enroll in the clinical trials and other relevant information that Children's Services may request or conduct its own investigation.

8. Actively Manage Clinical Trials Issues

Concern: In the late 1980s and early 1990s, HRA put considerable resources into increasing the number of employees of the PAU and hired staff with strong credentials. The performance of the PAU declined, however, after 1995.
Recommendations: Children's Services should manage clinical trials issues actively. In addition to providing sufficient staff and resources, Children's Services should also consider conducting regular reviews of clinical trials policy during times of increased participation.

9. Use High Standards for Clinical Trial Enrollment

Concern: Children's Services policy used the standard that a trial must offer a potential treatment benefit to *every* foster child who might enroll in a trial.
Recommendations: For each foster child who might enroll in a clinical trial, Children's Services should ensure that the anticipated benefits outweigh the risks of harm. In addition, Vera urges Children's Services to restrict foster child enrollment to trials in which the individual child has the possibility of receiving a clinical benefit not available outside the clinical trial.

10. Manage Conflicts of Interest

Concern: By relying on external pediatric HIV/AIDS experts to help implement its clinical trials policy and response to the onset of pediatric HIV, Children's Services had little choice but to draw from a small circle of people who shared professional relationships. In some situations, this created real or apparent conflicts of interest.
Recommendations: Children's Services should adopt a conflict of interest policy relating to clinical trials research.

For nearly five decades, the Vera Institute of Justice has provided stakeholders and the general public with information and recommendations aimed at reforming and improving public policy. The authors of this report and their advisors have sought to stay true to this tradition. It is our hope that the information presented here will inform the debates that are sure to follow, and lead ultimately to improvements in the services that people rely on for safety and justice.

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Vera asked for the full cooperation of Children's Services staff before agreeing to conduct this study. Numerous individuals throughout the agency followed through on this condition, which required cooperation from numerous people and divisions, including senior executives, administrators, file warehouse staff, security guards, and facilities staff. The Division of Family Support Services, the Office of Child and Family Health, and the General Counsel's Office in particular enabled this study to take place through the efforts of their directors and staff.

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Table of Contents

Chapter 1: Why Vera Studied the Participation of Foster Children in Clinical Trials 1
- Background 1
- The Vera Study 4
- Outline of the report 6

Chapter 2: How Vera Conducted the Study 8
- Sources of Information 9
- Research Methodology 16
- Strengths and Weaknesses of the Study Methodology 27
- Conclusion 29

Chapter 3: New York City's Child Welfare System, 1985 to 2001 40
- New York City, 1985 to 2001 40
- New York City's Child Welfare System, 1985 to 2001 43
- Summary and Conclusion 54

Chapter 4: Epidemiology and History of Pediatric HIV/AIDS in New York City ... 55
- HIV Epidemic: The Early Years 55
- The Spread of Pediatric HIV in New York City 62
- Children with HIV in Foster Care 66
- How HIV Infection Affects Children 68
- Progress in Preventing and Treating Pediatric HIV 68
- Conclusion 71

Chapter 5: The Child Welfare and Medical Experiences of Children who Participated in Clinical Trials While in Foster Care 72
- How Vera Gathered this Information 72
- Demographics and Family Structure 74
- Pathways into Foster Care 76
- Foster Care Experiences 90
- Pathways Out of Foster Care 100
- Health Status and Medical Care of Children in Vera's Review 105
- Conclusion 114

Chapter 6: The Federal Research Regulations 115
Background: Why Government Regulates Research 116
Regulations for Enrolling Foster Children in Clinical Trials 117
The Challenges of Applying the Federal Regulations to Pediatric HIV/AIDS Clinical Trials 122

Chapter 7: New York City's Policy for Enrolling and Monitoring Foster Children in HIV/AIDS Clinical Trials 131
Background on How the Policy Question Arose 132
Early Steps Toward a Policy 133
Early Implementation Issues 140
Streamlining the Process: Approving Trials 144
Approving Clinical Trials, Not Individual Enrollments 149
1994 Policy Update 153
1998 Clinical Trials Policy 159
Conclusion 161

Chapter 8: The Clinical Trials 163
Federal Regulations for Testing and Marketing New Drugs 163
NIH-Sponsored Clinical Trials of Pediatric HIV Treatment 168
New York City Clinical Trial Sites 171
How Vera Identified Children Participating in Clinical Trials 172
Foster Child Enrollment in Clinical Trials and HIV-Related Observational Research Studies. 174
Medication Clinical Trials 176
Observational Studies 181
Experimental Therapy Outside of a Clinical Trial 183
Where Clinical Trials Were Conducted and Where the Children were Enrolled 183
The Impact of Clinical Trials on Pediatric HIV Treatment 185
Conclusion 186

Chapter 9: Description of Children's Medical Experience in Clinical Trials and Observational Research Studies 187
How Vera Produced this Information 188
Clinical Trial Enrollments 189
How Children Were Selected for Enrollment in Clinical Trials 195

Selection for Entry into "Salvage Protocols" 198
Clinical Trial Eligibility 200
Monitoring, Adverse Events, and Toxicities 209
Deaths of Children while in Clinical Trials 220
Conclusion 225

Chapter 10: Following Child Welfare Policy and Federal Research Regulations 226
Documentation and Record Keeping 227
Adherence to Trial Approval and Enrollment Policy 230
Enrollment Procedures in Medication Trials that Did Not Undergo Standard Trial Review 239
Enrollments in Medical Intervention Trials that Followed the Standard Trial Review Process 240
Enrollments Prior to Obtaining Informed Consent or Approval 244
Compliance with Other Aspects of Trial Policy 245
Elements of Trial Review Policy that Vera Did Not Systematically Review 248
Conclusion 257

Chapter 11: Findings and Recommendations 258
Summary of Findings 258
Discussion and Implications 266
Recommendations 276
Conclusion 278

Sources of Information 279

Appendices 299
Appendix 1: Historical Background: Research on Vulnerable Populations 299
Appendix 2: Conflict of Interest Rules 317
Appendix 3: Description of Children's Services' Efforts to Identify Cases 319
Appendix 4: Children's Services' Screening Tool 322
Appendix 5: Timeline 327
Appendix 6: FDA-approved Antiretroviral Drugs for Adults and Children. 329
Appendix 7: CDC Revised Surveillance Case Definition for HIV Infection 331
Appendix 8: 45 CFR 46 335
Appendix 9: Sample Letter of Agreement 347

Appendix 10: Description of Individual Clinical Trials..... 351
Appendix 11: Peer-reviewed published reports and articles..... 432
Appendix 12: 1994 Revised Classification System for Human Immunodeficiency Virus Infection in Children Less than 13 Years of Age..... 447
Appendix 13: BBC Letter..... 475
Appendix 14: Abbreviations 487

Chapter 1: Why Vera Studied the Participation of Foster Children in Clinical Trials

In 2005, at the request of New York City's child welfare agency, the New York City Administration for Children's Services ("Children's Services"), the Vera Institute of Justice undertook an in-depth examination of issues related to the enrollment and monitoring of New York City foster children in HIV/AIDS clinical trials from the late 1980s through the 1990s. This report describes the results of that examination. It begins by outlining the controversy that led to Vera's study, the questions that Vera staff sought to answer, and the methods used to conduct the inquiry. It also describes the medical, child welfare, and historical contexts in which the clinical trials took place. The results of the study follow. For ease of reading, each substantive chapter begins with a short chapter overview, illuminating highlights of that chapter's contents. The report concludes with a discussion of clinical trials policy for children in foster care and a series of recommendations for Children's Services should officials decide to allow children in foster care to participate in clinical trials in the future.

Background

In January 2004, an independent journalist named Liam Scheff published an article on the web site www.altheal.org.[1] In his article, Scheff alleged that "black, Hispanic, and poor" children in the care of Children's Services had been enrolled without their knowledge and against the wishes of their parents or guardians in HIV/AIDS clinical trials that were "neither safe nor necessary."[2] According to Scheff, these trials involved antiretroviral drugs that were "known to cause disability and death." Scheff reported that the trials took place at the Incarnation Children's Center (ICC) in New York City's Washington Heights neighborhood. From 1988 to 2001, the facility served HIV-positive children in foster care as part of a partnership between Catholic Home Bureau, a foster care agency operating through a contract with Children's Services, and Columbia University Medical Center.[3] Scheff reported that doctors at ICC had coerced and threatened children who refused to take HIV/AIDS clinical trial medications. Approximately one month after Scheff's article appeared the *New York Post* published two articles that repeated many of these allegations.[4]

On March 10, 2004, the Alliance for Human Research Protection (AHRP), an advocacy group "dedicated to advancing responsible and ethical medical research practices," filed a

[1] Liam Scheff, "The House that AIDS Built," http://www.altheal.org/toxicity/house.htm last accessed on January 28, 2008.

[2] This report uses many terms to describe race and ethnicity. We strive to use the most recent categories developed by the U.S. Census Bureau. The material examined for this study, however, often uses different terms that do not correlate with Census Bureau categories. The terms in the source material are used in these instances.

[3] In 2001, ICC converted to a skilled nursing facility for HIV-positive children and is licensed by the New York State Department of Health. As a skilled nursing facility, ICC provides care to children with HIV, regardless of their child welfare status.

[4] Douglas Montero, **"**Shocking Experiments: Aids Tots Used As 'Guinea Pigs,'" *New York Post*, February 29, 2004, p. 5; Montero, "HIV-Baby Probe," *New York Post*, March 1, 2004.

complaint with the U.S. Department of Health and Human Services' Office of Human Research Protections (OHRP), which is responsible for ensuring that federally funded research adheres to federal regulations regarding the ethical treatment of human subjects.[5] AHRP's complaint alleged that Columbia University Medical Center had improperly enrolled foster children in eight clinical trials.[6] On the same day that AHRP filed the complaint, its executive director, Vera Hassner Sharav, discussed the issue on the television program *The O'Reilly Factor*. Sharav was joined on the program by Jacklyn Hoerger, a former pediatric nurse at ICC and former foster parent. Hoerger contended that the health of two HIV-positive foster children in her care in the late 1990s had improved dramatically after she stopped giving them antiretroviral drugs, until they were then removed from her home because she refused to administer the HIV/AIDS medications.[7]

Under pressure to respond to Scheff's allegations, William Bell, who was then commissioner of Children's Services, asked the Pediatric AIDS Unit (PAU), a part of the agency with responsibility for monitoring enrollments in HIV/AIDS clinical trials, to determine how many children had participated in clinical trials and whether the allegations had any merit. The PAU reported back that 76 children had participated in trials while in foster care and that a review conducted of 24 of those children's files had uncovered no evidence to support the allegations. Nevertheless, Children's Services asked seven contract foster care agencies to submit corrective action plans to ensure that they were complying with the city's policies.[8] Children's Services reported their actions to the City Council's General Welfare Committee.[9]

In November 2004, the British Broadcasting Corporation (BBC) aired a television documentary titled *Guinea Pig Kids* that repeated many of Scheff's allegations.[10] The program generated international attention.[11] It also led a Brooklyn-based human rights group called the December 12th Movement, which focuses on issues of concern to the African American community, to organize protests outside of ICC. In a letter to John Mattingly, who succeeded

[5] Quoted material from AHRP mission statement on the organization's web site, www.ahrp.org, last accessed July 27, 2008.
[6] The Vera Institute received a copy of the complaint letter in response to a Freedom of Information Act request to OHRP.
[7] Transcript of *The O'Reilly Factor*, March 10, 2004, provided to the Vera Institute by OHRP in response to a Freedom of Information Act request.
[8] Medical Record Review Report ,"Participation of Children in Foster Care in HIV Clinical Trials," June 8, 2004. The copy we reviewed does not have an author or transmittal information indicating who saw the document. Our interviews confirmed that Children's Services originally reported to the City Council that 76 foster children participated in clinical trials. The seven agencies were Brookwood, Catholic Guardian Society, Catholic Home Bureau, Children's Aid Society, Leake & Watts Services, Seaman's Society for Children and Families, and Sheltering Arms.
[9] See transcript of Democracy Now radio program interview with Vera Sharav and City Councilmember Bill Perkins, May 2, 2005. Available at http://i2.democracynow.org/2005/5/2/hundreds_of_hiv_foster_children_in last accessed on January 29, 2008.
[10] See www.guineapigkids.com, last accessed January 28, 2008. Scheff is listed as a researcher for *Guinea Pig Kids.*
[11] For example, the film prompted the Dutch embassy to send a letter inquiring about its accuracy to the international human research liaison for OHRP. See e-mail from Dirk Ruwaard to Edward E. Bartlett dated February 11, 2005, provided to the Vera Institute by OHRP in response to a Freedom of Information Act request.

William Bell as commissioner of Children's Services in August 2004, members of the December 12th Movement requested that Children's Services respond to the film's allegations.[12] On December 30, 2004, Roger Wareham, a lawyer for the group, sent Commissioner Mattingly a second letter. In it, he asked for an official response that would explain where, when, and under what conditions clinical trials involving HIV-positive foster children took place, who consented to those trials on the children's behalf, and the demographics of the children involved.

In a reply dated January 5, 2005, Commissioner Mattingly denied the allegations in *Guinea Pig Kids* and criticized the film for conveying "a blatantly unfair impression of our policies."[13] Mattingly asserted that the National Institutes of Health and the relevant hospitals' institutional review boards (IRB)—mandatory oversight bodies charged with ensuring the ethical treatment of research involving human subjects—had reviewed the trials prior to enrolling children to ensure that they had complied with federal regulations regarding the ethical treatment of human subjects.[14] He also noted that two of the children featured in the film had never taken part in clinical trials. In February, the New York State Department of Health issued a letter saying in part that "none of the recently published allegations has been substantiated to our knowledge."[15]

That month, representatives of the December 12th Movement met with officials from Children's Services to discuss their concerns in person.[16] Several people who attended the meeting recall that the two groups were unable to resolve their differences.[17] Protests outside ICC resumed.

With increasing attention focused on the clinical trials, senior managers at Children's Services initiated an effort to organize the PAU's files, which were in severe disarray.[18] The PAU used several different filing systems, did not cross reference the filing systems, and files were disorganized within each of the systems. In addition, the PAU's electronic database was unreliable and produced different numbers in response to the same query. Over several months of organizing these files, Children's Services staff identified additional children who might have participated in HIV/AIDS clinical trials while in foster care. By April 2005, 465 foster children had been identified as possible participants in HIV/AIDS clinical trials over a 13-year period. When Children's Services informed the City Council's General Welfare Committee of the

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[12] See Saeed Shabazz, "Advocates Say NYC Child Agency Forcing AIDS Drug Experiments on Children," January 14, 2005, available at http://www.parentsinaction.net/english/Guinea%20Pigs/Advocates_say_NYC_child_agency_forcing_AIDS.htm, last accessed January 28, 2008.

[13] In a response to a complaint by a New York City-based nonprofit, the Center for HIV Law and Policy, the BBC apologized for "significant bias" in parts of *Guinea Pig Kids* while also asserting that its "journalism was vindicated." For the full text of the BBC's letter regarding *Guinea Pig Kids*, see Appendix 13.

[14] The letter cited here is an undated form letter provided by Children's Services drafted to respond to letters the agency received regarding *Guinea Pig Kids* and related issues.

[15] Form letter dated February 2005 (no day) from Guthrie Birkhead, director, New York State Department of Health AIDS Institute to "Colleague."

[16] This information comes from Vera staff interviews with key respondents. See Chapter 2 of this report for a discussion of key respondent interviews conducted for this report.

[17] Vera staff interviewed people who attended the meeting.

[18] Sally Serio, *Information Tracking and Filing System Overhaul*, (Interim Report for the Pediatric AIDS Unit, New York, NY, November 30, 2006): 44-81.

increase from the original 76, committee members expressed concern. Councilmember Bill Perkins, for example, said "ACS grossly misled us in terms of the numbers of children that were participating in these experiments." Perkins went on to question whether the agency had made other misrepresentations as well.[19]

In a response to the controversy, Commissioner Mattingly asserted that there was "no credible evidence…that anything untoward happened" during the trials and that the policies for enrolling foster children seemed "to be thoughtful and to consider the rights of these children and their parents very carefully and to be focused solely on what help the children needed basically to survive the AIDS epidemic."[20] He acknowledged the concerns about the trials and emphasized that Children's Services sought to build a relationship of mutual trust with the community. To that end, he said, he would ask the Vera Institute of Justice to conduct an independent study of issues related to the enrollment of foster children in clinical trials, a decision that would ultimately lead to the publication of this report.[21]

Two days later, on May 4, 2005, a nationally syndicated news article reported that clinical trials involving foster children had occurred in many other large urban jurisdictions as well. John Solomon, the author of the article, cited estimates that between 5 and 10 percent of the approximately 13,000 children who had participated in HIV/AIDS clinical trials nationwide since the mid-1980s had been in foster care at the time of their participation.[22] Solomon noted that many of these children did not have "independent advocates," which are required by federal regulations in some situations.[23]

The controversy surrounding the enrollment of foster children in clinical trials led to a number of legislative hearings on the issue. On May 18, 2005, a subcommittee of the Ways and Means Committee of the U.S. House of Representatives held a hearing entitled "Protections for Foster Children Enrolled in Clinical Trials." Three days later, the General Welfare Committee of the New York City Council held a public hearing on the issue as well. Finally, on September 8, 2005, the New York State Assembly Standing Committees on Health and Children and Families held a joint hearing on the issue.

The Vera Study

After Children's Services asked Vera to study issues in this controversy, Vera staff developed a study plan with a set of questions and the methods Vera would use to examine issues related to enrolling foster children in clinical trials. The following questions were included in the plan:

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[19] Transcript of Democracy Now radio program interview with Vera Sharav and City Councilmember Bill Perkins, May 2, 2005.
[20] Transcript of Democracy Now radio program interview with John Mattingly, May 2, 2005. Available at http://i2.democracynow.org/2005/5/2/hundreds_of_hiv_foster_children_in last accessed on January 29, 2008.
[21] Ibid.
[22] John Solomon, "Researchers Tested AIDS Drugs on Children," *Associated Press*, May 4, 2005.
[23] Chapter 6 of this report discusses the regulations and types of clinical trials that require independent advocates.

1. How many children were enrolled in HIV/AIDS clinical trials, what trials did they participate in, and what kinds of interventions did the trials involve?
2. Did children in foster care who participated in clinical trials experience benefit or harm due to their participation in the clinical trials?
3. What policy did Children's Services and its predecessor agencies have for the participation of foster children in clinical trials?
4. How closely were those policies followed?
5. How did the foster children who participated in clinical trials enter foster care?
6. How did children in foster care come to participate in clinical trials, and did they meet the criteria for enrolling in the trials?
7. Were federal regulations, including regulations related to informed consent, the selection of clinical trial participants, and the appointment of independent advocates, followed?
8. Were children who participated in the trials properly monitored?
9. Did Children's Services, foster care agencies, medical institutions, caregivers, or children receive financial incentives to enroll foster children in clinical trials?
10. How did foster children who participated in clinical trials leave foster care, and how are they doing today?

As part of its request to Vera, Children's Services also asked for policy recommendations to address issues involving foster children and clinical trials in the future.

Vera agreed to conduct the study under a number of conditions. First, Children's Services agreed that Vera has full editorial control over the final report. (Vera agreed to share the final report with Children's Services at least 10 days before its public release.) Second, Vera's work on the project would be overseen by Vera's own advisory board. Dr. Richard G. Dudley, a trustee of Vera and a psychiatrist in private practice who served as the medical director of the Washington Heights-West Harlem Community Mental Health Center and is a founding member of the National Black Leadership Commission on AIDS (NBLCA), agreed to chair Vera's Clinical Trials Advisory Board.[24] Third, Children's Services agreed to continue reviewing its files for additional children who might have participated in clinical trials, with support from Vera on the search process. Finally, Children's Services promised Vera complete access to files and records and the cooperation of its staff.

At the outset of the study, Children's Services created the HIV/AIDS Health Care Advisory Board (HCAB) to advise Children's Services on this project and to use their expertise to guide Children's Services' through the process of formulating a new clinical trials policy. The HCAB comprises a diverse group of community-based service providers and advocates. The co-chairs

[24] The professional backgrounds of Vera's advisory board members appear in the preface to this report.

of the HCAB have included Debra Fraser-Howze, the former chief executive officer and president of the NBLCA; Ana Oliveira, President & CEO of The New York Women's Foundation and past Executive Director of Gay Men's Health Crisis; Gail Nayowith, who served as executive director of the Citizens' Committee for Children, and Ernesto Loperena, the executive director of the New York Council on Adoptable Children, have all served as co-chairs of the HCAB.[25] The HCAB met over a dozen times during the course of the project to review and comment on Children's Services policy, to hear updates on the progress of this study, and to meet with community members and organizations concerned about this issue.[26] Children's Services also asked Dr. Robert Johnson, a pediatrician and now interim dean of the University of Medicine and Dentistry of New Jersey, to provide medical expertise and advice during this project. Children's Services held monthly calls with Dr. Johnson and invited Vera staff to participate in those calls. Neither members of the HCAB nor Dr. Johnson received compensation in these roles.

Vera's project directors screened members of the Vera advisory board and all clinical trials staff for real and apparent conflicts of interest.[27] They developed the screening procedures from guidelines provided by New York City's Conflict of Interest Board. For more on Vera's screening procedures, see Appendix 2. Children's Services developed a similar conflict-of-interest policy for the HCAB and in selecting Dr. Robert Johnson. Vera played no role in their selection or screening.

Outline of the Report

In conducting this study, Vera used a range of methods. These methods and their strengths and weaknesses are described in Chapter 2. In brief, the study is based on many sources, including

- child welfare files kept by Children's Services, its predecessor agencies, and the many organizations that provided foster care under contract with Children's Services;
- policy memoranda, notes, and records from Children's Services' Pediatric AIDS Unit;
- community advocates, people who worked in the child welfare system, and people who funded, conducted and monitored the trials;
- OHRP and National Institutes of Health materials obtained via a Freedom of Information Act request;
- clinical trial protocols; and
- books, articles, periodicals, and other published materials.

[25] Fraser-Howze left NBLCA to become the vice president for government and external affairs at OraSure Technology, a manufacturer of medical diagnostic equipment, in January 2008. Nayowith became the president of the Laurie M. Tisch Foundation, a private New York City-based arts foundation, in September 2007.

[26] Vera staff were invited to some but not all of the HCAB meetings.

[27] Vera's general counsel recused herself from any involvement in this project because of her prior employment at the Human Resources Administration's Office of Legal Affairs in the 1980s. She played no role in this project, Institute staff were instructed not to speak with her about the project, and she left Vera board of trustee meetings when staff provided project updates.

Chapters 3 and 4 of this report place the controversy in its broader historic context. The trials were a response to a new and deadly epidemic which appeared at a time when low-income families and the city's social services were under intense strain. The context also includes an equally relevant history of medical research involving African Americans and other minorities, incarcerated people, and wards of the state (see Appendix 1 for a brief review of this history).

Chapter 5 discusses issues related to the experiences of children who participated in clinical trails while in foster care—topics include their demographics, the different ways in which they entered foster care, their lengths of stay, and how they left foster care. The chapter also discusses their medical conditions, their diagnosis with HIV, the medical services they received outside of clinical trials, and the connections between the medical and child welfare experiences. Chapter 6 summarizes the federal regulations regarding the ethical treatment of children participating in research, including foster children. The chapter also identifies some of the issues encountered in applying these regulations and uses the OHRP investigation as a case study.

Chapter 7 includes a detailed description of the policies that New York City's child welfare officials developed for enrolling foster children in clinical trials, monitoring the children's ongoing participation, and overseeing the trials themselves. Chapter 8 describes the clinical trials in which New York City foster children participated: the different types of trials, who sponsored the trials, and the risks and benefits of participating in these trials. Chapter 9 describes the clinical trial experiences of New York City foster children who participated in trials. The chapter includes a discussion of children's positive and negative experiences in the trials, describes adverse events experienced by children in the trials, and the reaction to those events as identified by Vera's file reviewers. Chapter 10 addresses how closely the experiences of children in foster care complied with child welfare policies and federal research regulations. The report concludes with Chapter 11, a discussion of the findings and recommendations for future policy.

Chapter 2: How Vera Conducted the Study

Chapter Overview

The information available for review was substantial but incomplete. Two teams of document reviewers—child welfare reviewers and medical reviewers—examined all files referred by Children's Services of children who may have participated in clinical trials while in foster care. The process took more than two years and included more than 2,000 child welfare files. Vera staff also reviewed Children's Services' policy documents, clinical trial protocols, reviews of the data safety and monitoring boards, and adverse event reports for some of the clinical trials, as well as a variety of published materials. Staff also conducted interviews with key participants and with two caregivers of children who participated in clinical trials. Not all child welfare files were available for every child and the child welfare files varied in the amount of medical information they contained.

After an extensive legal review, Children's Services and the New York City Law Department determined that only the New York State Department of Health had the legal right to authorize Children's Services or Vera to review clinical trial research files and medical records. The NYSDOH refused Children's Services initial request to grant access to these records, citing confidentiality laws. NYSDOH refused additional requests that attempted to address these concerns. Without access to these files, this report cannot fully answer some questions and provides only limited answers to others as detailed in the limitations section of this chapter.

Information from the available files was recorded on standardized data collection instruments, and document reviewers wrote structured narratives describing the circumstances and experiences of each child. Project supervisors conducted ongoing quality assurance and data security processes. As missing information and the lack of a comparison group did not allow for the use of multivariate modeling techniques, project staff used descriptive statistics to analyze quantitative data. Qualitative data—case narratives and interviews—were coded according to themes identified through a detailed review of a subset of each type of material and analyzed using principles of grounded theory. The Vera Institute retained full editorial control throughout the project and reported to an independent advisory board.

Introduction

This chapter describes the sources of information and the methodology that Vera staff used to carry out this study.[28] The chapter discusses the initial plan Vera staff developed to answer the questions raised in this project, the full range of potential data sources, and the efforts made to access these resources. The chapter then describes the data that Vera staff were able to access and the methods that staff used to organize and analyze that data. The final section of this chapter contains a reflection on the strengths and weaknesses of the study.

[28] Much of this appears in quarterly progress reports written during the project and posted on the Vera Institute of Justice's web site, www.vera.org.

Sources of Information

At the outset of this project, Vera's staff compiled a list of the all of the potential sources that might be used to answer the questions cited in Chapter 1. The entire list of potential sources is listed here.

1. *Children's Services' Documents:* Bulletins, memos, quarterly reports, correspondence, meeting notes, and other documents concerning foster care and HIV-related issues, such as clinical trial enrollment and monitoring, testing, confidentiality, and staff and foster parent training.
2. *Child Welfare Files:* Case management files maintained by Children's Services, information from Children's Services Pediatric AIDS Unit (PAU) that Children's Services provided to Vera, and case planning files maintained by private agencies contracted to provide foster care services.[29]
3. *Child Care Review System (CCRS):* As Children's Services' administrative database, CCRS records children's entry and exit from foster care, as well as movements in custody, such as changes in agency assignments, foster homes, etc.
4. *Medical Records:* Hospital records of the children on Vera's review list. Hospital records contain comprehensive data on an individual treated at a given facility (both inpatient and outpatient), including medical and social histories, birth histories, emergency room visits, illnesses, surgeries, medications, laboratory tests, nurses' notes.
5. *Clinical Trial Research Records:* Each clinical trials investigator maintains research records for each participant in a trial. They contain consent documents, documentation that the child met the criteria to be enrolled in the study, and monitoring information (results of laboratory and physical examinations, x-rays, questionnaires, adverse event reports, etc.).
6. *Key Respondents:* Interviews with child welfare policymakers; contract foster care agency staff; members of advocacy organizations; clinical trial researchers and other physicians who provided medical care for children with HIV/AIDS; nurses and other clinical trials personnel; Institutional Review Board (IRB) members at sites where clinical trials were conducted; and independent advocates appointed to protect the interests of foster children.[30]

[29] With the authorization of the New York State Office of Children and Family Services and the New York City Administration for Children's Services, Vera conducted a management review of these files.

[30] Vera's institutional review board (IRB) reviewed and approved all interview protocols. IRBs comprise people trained in the rules and ethical concerns expressed in federal regulations relating to the participation of people in research (see 45 CFR 46 and Chapter 6 of this report). Dr. Fleda Mask Jackson , senior scientist at the Atlanta Regional Health Forum, who has extensive experience researching issues related to the impact of racism and gender on African American women and families, joined Vera's IRB for this project.

7. *Caregivers:* Interviews with caregivers (biological parents, foster parents, kinship foster parents, and adoptive parents) of the children who participated in clinical trials while in foster care.
8. *Clinical Trials Participants:* Interviews with young adults who participated in clinical trials while they were in foster care.
9. *Clinical Trials Research Protocols:* Clinical trial protocols and protocol summaries of NIH-sponsored and pharmaceutical company sponsored clinical trials in which foster children participated.[31]
10. *Medical Journals:* Published articles from peer-reviewed medical journals on the clinical trials in which foster children participated[32].
11. *Adverse Event Reports* for a selection of NIH-sponsored clinical trials in which foster children participated.[33]
12. *Data and Safety Monitoring Board (DSMB) Reports* from a selection of NIH-sponsored clinical trials.[34]
13. *Office for Human Research Protections (OHRP) Documents* related to the investigation of a complaint against Columbia University Medical Center.[35]
14. *Institutional Review Board (IRB) Minutes* from clinical trials sites. The minutes describe the meeting held by the IRB to determine that a research protocol contains all the protections for research subjects mandated by the federal regulations.[36]

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[31] Protocols from the National Institutes of Health (NIH)-sponsored clinical trials are more than 100 pages long. They address the scientific rationale for the clinical trial, past experience with the medications being tested, the research design of the clinical trial, inclusion and exclusion criteria for enrollment in the trial, monitoring of clinical trials participants, and instructions for handling and dispensing trial medications. Vera obtained the clinical trials protocols from the Pediatric AIDS Clinical Trials Group (PACTG), the consortium of medical institutions, funded by the NIH, that conducted multi-site pediatric HIV clinical trials; from the NIH through the Freedom of Information Act; and from the Children's Services Pediatric AIDS Unit archives. Vera staff were unable to review protocols for clinical trials sponsored by pharmaceutical companies.

[32] Peer review refers to the process used by scientific journals to assure that the research reported is scientifically rigorous. In the peer review process, at least three reviewers, who know the field being researched but not the identity of the author of the article, review the scientific merit of the research.

[6] Adverse events that occur to participants in clinical trials must be reported to the FDA. For NIH-sponsored pediatric HIV clinical trials, adverse events were reported by the site investigator to the PACTG and by the PACTG to the Food and Drug Administration (FDA). Vera obtained the adverse event reports from the NIH through a Freedom of Information Act request.

[34] A data safety monitoring board is a group of scientists not otherwise involved in the research who review data from a trial at regular intervals. Based on the data, they may recommend that the trial be modified or stopped. This is discussed in greater detail in Chapter 8.

[35] The Office for Human Research Protections, a part of the U.S. Department of Health and Human Services, is responsible for ensuring that federally funded research complies with regulations concerning the ethical treatment of human subjects in research. Vera obtained the documents from the OHRP investigation through a Freedom of Information Act request. The documents include correspondence, redacted consent forms, IRB minutes, printouts from Columbia IRB administrative data, and other documents related to OHRP's investigation.

[36] All institutions that conduct federally funded research or research that will be used to support an application to the FDA for approval of a new drug are required to have an Institutional Review Board. The IRB must review and approve all proposed research that involves human subjects to make sure that the research affords all protections required by the regulations. IRBs are required to review ongoing research at regular intervals.

15. *Aggregated data* from the New York City Department of Health and Mental Hygiene's HIV Epidemiology Program on the children in Vera's review, without the identification of individual children.
16. *Other* published material on the history of medical research, the treatment of vulnerable populations in that research, HIV/AIDS, foster care, OHRP investigations, and research ethics.[37]

The following sections describe the project's efforts to access several of the sources of information listed above. Access to child welfare, clinical trial research, and hospital files is restricted by state and federal laws that protect privacy and confidentiality. Vera staff provided advice and information to Children's Services' legal staff in their efforts to facilitate access to this information. Other information sources were not legally protected but were often difficult to access. Vera staff made efforts to speak with children who participated in clinical trials, their caregivers, and a wide range of other people with knowledge about the clinical trials and this controversy. These efforts, which are detailed below, met with mixed success.

Child Welfare Files (2). Vera researchers were granted full access to the child welfare files of the children for the review. The New York State Office of Children and Family Services and Children's Services determined that Vera, as an agent contracted by Children's Services, could conduct an administrative review of the child welfare files. Child welfare files maintain a record of a child and family while the child is in foster care or the family is receiving services from Children's Services or a contract agency.

Vera staff reviewed all of the available case management files, case planning files, and PAU information on individual children.[38] These files included hundreds of thousands of pages of documents. However, some files were destroyed or lost, and thus unavailable for review. For a small number of children, none of the three types of files were available; more commonly, some but not all of the files were available. In many instances, reviewers were unable to collect all of the information Vera staff sought to analyze. Case planning files, in particular, usually contained a significant amount of information. When these files were unavailable, detailed information on a child's medical and child welfare experience was limited. The Vera Institute's efforts to obtain child welfare files and the number of files available for review are described in the following section on research methodology.

Hospital and Clinical Trial Research Records (4, 5). At the urging of its HIV Community Advisory Board and Dr. Robert Johnson, the commissioner's medical advisor for this project, and Vera staff, Children's Services worked throughout this project to make hospital and clinical

[37] See Appendix 1 and 11.
[38] PAU is the Pediatric AIDS Unit of Children's Services. The responsibilities of the PAU are described in Chapter 7. Case management files are the files that Children's Services keeps on each child. Case planning files refers to the files kept by the contract foster care agency.

trial research records available for this review.[39] Children's Services' lawyers requested hospital records, clinical trial research records, and institutional review board minutes from all of the medical centers where children in foster care participated in HIV/AIDS clinical trials. These requests were made on the basis of agreements signed by Children's Services predecessor agencies with the hospitals conducting clinical trials at the time the trials were conducted. The agency sent follow-up letters to the medical centers in February 2007.

Several hospitals subsequently agreed to provide access to some or all of these records. Others, including New York City's Health and Hospitals Corporation, raised issues about the legality of the request, citing strict laws designed to protect the confidentiality of HIV, medical, and foster care status information.[40] Given the legal issues related to accessing medical records and HIV-related information, Children's Services asked for a legal opinion on the issue from the New York City Law Department and informed Vera project staff of these objections. Vera's special counsel agreed with Children's Services' request that Vera project staff suspend review of hospital or clinical trial research records until the Law Department rendered an opinion. Several weeks later, a Law Department attorney with a background in health law determined that applicable federal and state laws did not permit Children's Services or Vera to review hospital or clinical research records of individuals without the consent of the former foster child or his or her parent or legal guardian, if the child is still a minor. The Law Department concluded, however, that the regulations authorized the New York State Department of Health (DOH) to review such records for certain oversight purposes.

Thereafter, Children's Services made three separate requests to the New York State DOH to grant Vera's team access to information contained in hospital and clinical trial research records. Each subsequent request attempted to address the state's confidentiality concerns. The third letter asked for consent information only in aggregate form. The state denied each request, and Vera did not review these records.[41] The end of this chapter contains a document written by Children's Services describing its efforts to make these records available, as well as copies of the correspondence between Children's Services' legal department and the New York State DOH.

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[39] Hospital records contain comprehensive data on an individual treated at a given facility (both inpatient and outpatient), including medical and social histories, illnesses, surgeries, medications, laboratory tests, nurses' notes, and more. Clinical trial research records contain informed consent documents, adverse event reports, changes in clinical trial protocols, and records of laboratory tests and physical examinations conducted for the purpose of monitoring the children in clinical trials. For further information on Children's Services efforts, see the material at the end of this chapter.

[40] New York State Public Health Law Article 27-F protects information related to a person's HIV status (see Legal Action Center, *HIV/AIDS: Testing, Confidentiality & Discrimination* (New York: Legal Action Center, 2001). HIPAA, the Health Insurance Portability and Accountability Act of 1996 (Public Law 104-191), is a federal law that protects personal health information. Under HIPAA, health care providers such as hospitals, physicians, or pharmacies are prohibited from disclosing any personal health information for purposes other than usual hospital business without written consent. This allows hospitals to share information with an insurance company for billing purposes but, for example, not with a researcher. New York State Social Services Law §372(4) protects information related to a person's foster care status.

[41] Vera medical reviewers had started to examine records at one institution. At the request of Vera's counsel, Vera staff destroyed the small amount of information collected at the one institution.

The lack of access to clinical trial research or hospital records resulted in significant limitations to Vera's findings which are detailed at the end of this chapter. Vera researchers relied instead on the medical information available in the child welfare files. Although these files contain some medical information, recording this data is not their primary function. Thus, Vera staff's ability to collect medical data was limited by a reliance on a source that was not designed for this purpose. The amount of medical information found in the case planning files maintained by the contract foster care agencies varied greatly among and within agencies. Some agencies routinely collected and recorded information about each medical visit and kept meticulous records of medications and laboratory results. For children in care with those agencies, Vera medical reviewers had detailed information on the child's medical history and clinical trials participation. For children at other agencies and children whose case planning or case management records were unavailable (see below), the Vera medical review team had very little information to assess clinical trials enrollment, monitoring, and outcomes, or the child's medical history and health status. The data collection instrument that the Vera review team used, which is described in more detail later in this chapter (see Collecting Data), was designed to record the presence or absence of some of this information.

Interviews with Young Adult Participants and Caregivers (7). Vera's original study plan called for conducting interviews with young adults who had participated in clinical trials as children in foster care and their caregivers (foster parents, adoptive parents, biological parents, friends, and family members.)[42] Laws designed to protect personal health information, HIV status, and foster care status prevented Vera staff from approaching any of these individuals directly to request an interview. [43] Instead, Vera staff tried to recruit interviewees through organizations that were most likely to be in contact with this population, such as HIV/AIDS service providers, foster care agencies, clinical trial consumer advisory boards, community advocates, foster parent support groups, and churches. Vera staff presented the project to representatives of these groups and asked them to distribute education material about the project to people they knew who might be eligible to be interviewed or who knew people who might be eligible. A graphic designer created the education materials, available in English and Spanish, in consultation with a group of young people living with HIV. Information on the project and how to request an interview was also posted on Vera's web site.

Vera set up a toll-free number for people interested in participating in these interviews. Callers could learn about the project and the interview process without giving their name. If a caller decided to participate, Vera staff would ask a series of questions intended to verify the

[42] Because of the complexity of the consent process, Vera staff did not try to interview anyone under the age of 18. Children and younger teens with an interest in participating were encouraged by Vera staff to have an adult familiar with their situation speak to Vera on their behalf.

[43] In addition to Vera's IRB, the New York State Office of Children and Family Service (OCFS) reviewed and approved the protocol for conducting these interviews. OCFS routinely reviews interview protocols that may involve the participation of children in foster care or the use information provided by local child welfare agencies.

caller's eligibility. Despite these outreach efforts, Vera staff completed only two interviews with caregivers and none with young adults who participated in clinical trials while in foster care.

The low rate of response prompted project staff to extend the interview period from four months to ten months. During this time, Vera staff contacted key respondents who reported contact with the people Vera hoped to interview, giving them recruitment material and asking them to distribute it to young adults and caregivers with whom they had contact. At the suggestion of the Children's Services Health Care Advisory Board (HCAB) Vera also sent interview recruitment materials for public distribution to all 75 agencies that currently provide contract services (both foster care and preventive services) through Children's Services. A letter from Commissioner John Mattingly urging agency administrators to assist Vera accompanied the materials. In all, Vera distributed 13,000 postcards through community, medical, child welfare, and government and faith-based organizations, and placed advertisements in 48 community newspapers throughout New York's five boroughs.[44] None of these efforts delivered the desired results.

Several factors may account for the lack of interviews. The pool of potential people to interview is limited. The Vera Institute's review confirmed clinical trial participation for 532 of the 796 individuals on the review list. Because of the sensitive nature of the interviews, Vera's IRB approved interviews only for children above age 18, which meant only those children born before 1988 could participate. Like so many others born with HIV infection in the late 1980s and 1990s (in or out of foster care or clinical trials), many of the young people have died, virtually all of HIV-related complications. According to New York City Department of Health and Mental Hygiene (DOHMH) statistics, 156 of the children on Vera's review list have passed away.[45] Some children died while in foster care. Of the 532 children who participated in clinical trials, 129 were 18 years old and did not die while in foster care. Vera staff do not know how many children passed away after leaving foster care, but children born with HIV in the 1980s have higher mortality rates than those born in the 1990s..

Vera's review of files found that on average, foster children who participated in trials entered foster care before the age of one year and left foster care before the age of six years, most of them through adoption. Furthermore, large numbers left foster care more than 10 years ago. Combined, this means that most of the people Vera sought to interview are unlikely to know that they were in a clinical trial in foster care. Some of the young adults who participated in clinical trials as children may no longer live in the New York area. And finally, given the sensitivity of

[44] These activities increased the number of calls to the toll free number; however, none of the callers met the interview criteria, which included being over 18, having been in foster care, having had a child in foster care, or having been a foster parent in New York City.

[45] Of the 531 children from Vera's review list who are in the New York City Department of Health and Mental Hygiene's (DOHMH) pediatric HIV surveillance database, 29 percent have passed away according to the DOHMH's Vital Statistics database, which records births and deaths in all 50 states, the District of Columbia, and Puerto Rico. This report discusses the specifics of this finding and how it compares to HIV-positive children who did not participate in clinical trials in Chapter 5.

the subject, those few who know they participated in trials while in care may be unlikely to want to share such personal information with an unknown interviewer.

The low response rate among former caregivers is likely to have occurred for similar reasons, though available data on this group is limited. The Vera Institute's review of child welfare files found that 232 parents had passed away before their child's discharge from foster care—the majority from HIV-related causes.[46] Other caregivers have moved out of the area. Several people Vera staff spoke to said that caregivers they knew feared disclosing their child's HIV status despite assurances of confidentiality. Virtually all caregivers experienced stressful situations, sometimes including the death of a child and other family members, during or after foster care—and may be unlikely to want to speak about such intimate events with strangers. Because these events occurred a decade or more in the past, many might not recall that a child in their care participated in a clinical trial.

Vera staff's lack of success in speaking directly with the people who experienced the trials as participants or their caregivers—despite substantial outreach efforts—deprives this report of an important perspective. Vera staff, however, read a wide range of material presenting community views of the child welfare system, medical research and institutions, and the experiences of people who either had HIV/AIDS or who cared for them.

Clinical Trials Research Protocols (9). Clinical trials protocols are documents that describe in detail how a clinical trial is to be conducted. Vera accessed protocols of clinical trials sponsored by the National Institutes of Health and hoped to access protocols for trials sponsored by pharmaceutical companies as well. In May 2008, Vera staff requested copies of protocols from six pharmaceutical companies that had sponsored clinical trials in which New York City foster children had been enrolled. Some of the companies did not respond to the request or stated that the protocols were proprietary information that they did not make public. Others responded by sending information about the drugs involved in the trials or referred Vera to published reports or electronic reports of the trial results. None of the companies sent Vera research protocols.

Institutional Review Board Minutes (14). In its July 2006 letter to the medical centers that had conducted HIV/AIDS clinical trials involving children in foster care, Children's Services requested minutes from IRB meetings related to those trials. None of the hospitals or medical centers provided this information. The Office for Human Research Protections' had investigated a complaint against Columbia University, however, and Vera was able to use the Freedom of Information Act to secure minutes from some of the IRB meetings related to the clinical trials mentioned in that complaint.

[46] See Chapter 5.

Research Methodology

The final study plan relied on the following sources of information: child welfare files (including case planning files, case management files, and Pediatric AIDS Unit files), policy documents, interviews with key participants, research protocols for NIH-sponsored clinical trials, published reports of the clinical trials, information obtained through the Freedom of Information Act, and aggregate data on children in New York City with HIV obtained by Children's Services from the DOHMH. The next two sections of this chapter discuss the policies implemented to examine the child welfare files and conduct the key interviews. These are followed by a short discussion of the research methodology's strengths and limitations.

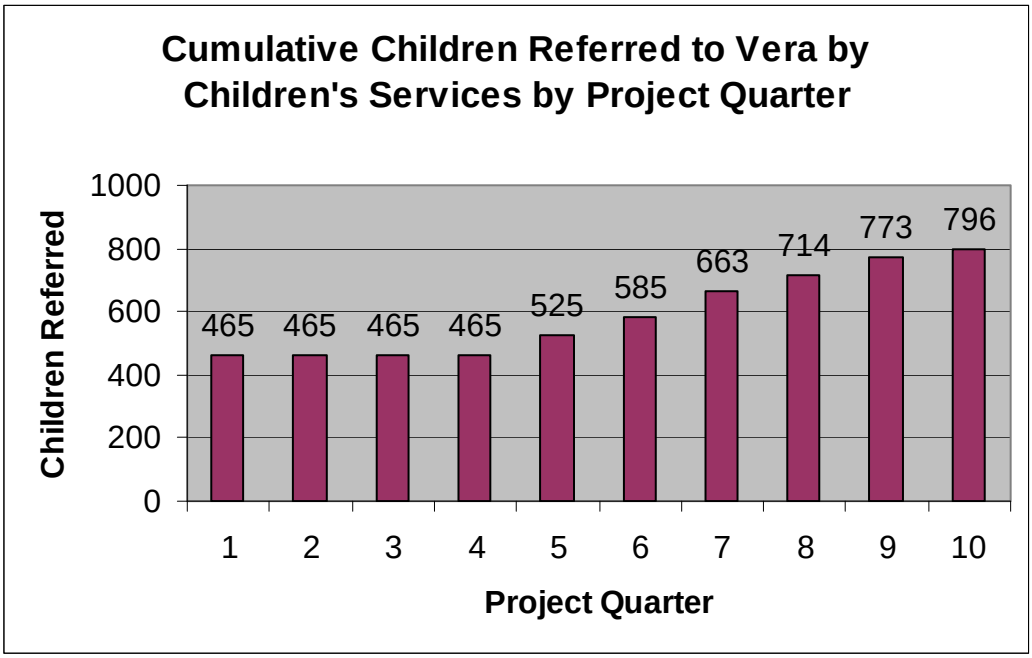
File Review. Vera staff had to identify which cases to review, gain access to the files, and carry out the review itself, taking steps to ensure consistent, high quality findings. Given the sensitivity of and legal protection afforded to the material Vera staff were studying, the process also required that special attention be paid to ensure that the data was secure. Each of these elements of the file review are discussed below.

IDENTIFYING CASES TO REVIEW: Vera's contract called for Children's Services to identify children who *might* have participated in clinical trials and refer those cases to Vera for review. As mentioned in Chapter 1, when this controversy first arose, Children's Services' Pediatric AIDS Unit had neither a coherent paper filing system nor a functioning electronic system.[47] The database that PAU used to track clinical trial enrollments of children in foster care had failed in 1996. Despite efforts to reconstruct that database in 2000 and 2001, the electronic files the PAU maintained did not produce a reliable and complete list of HIV-positive children who participated in clinical trials.[48]

In September 2005 Children's Services gave Vera reviewers a list of 465 children who might have participated in clinical trials. Children's Services continued to identify children who might have been enrolled in clinical trials and add them to the list through November 2007.[49] Figure 2.1 describes the cumulative number of children referred to Vera.

[47] Sally Serio, *Information Tracking and Filing System Overhaul*, Interim Report for the Pediatric AIDS Unit (New York: November 30, 2006): 44-81.
[48] See Chapter 7.
[49] At the beginning of this study, Vera declined Children's Services request to conduct the process of identifying additional children who may have participated in clinical trials for several reasons. Vera did not have expertise in several of the databases used to identify additional children and such expertise was not readily available outside of Children's Services staff. Children's Services staff had already developed expertise in identifying the list of 465 children originally referred to Vera. Furthermore, having Children's Services continue this work limited the distribution of identifying information for HIV-positive children who did not participate in clinical trials and were therefore not relevant to this study.

Figure 2.1: Cumulative Children Referred to Vera by Children's Services by Project Quarter



Children's Services staff searched for children who might have been enrolled in clinical trials.[50] The sources that they examined and the results of their search are as follows:

1. PAU documents, which included lists that had been compiled by PAU staff in the 1990s of children who were enrolled in specific clinical trials or in clinical trials at specific medical centers and correspondence between physicians and the PAU about individual children who were being considered for enrollment or who had been enrolled in clinical trials
2. Files on all children who Children's Services identified as having spent time at the Incarnation Children's Center (ICC) while in foster care
3. Files of children whom ICC staff believed may have been enrolled in clinical trials[51]
4. Files of foster children who were being followed by the PAU, were HIV positive, and who died while in foster care.
5. Foster children who had special or complex medical and mental health needs based on a known diagnosis, disorder, or condition (Children's Services classification as Level of Difficulty Three) and who died while in care.

[50] Memo, June 2008, from Yelena Gladkova (Children's Services), to Dr. Angel Mendoza, assistant commissioner of the Office of Child and Family Health (Children's Services).

[51] During the period that Vera's review covers, ICC was a congregate foster care facility for children with HIV, under the auspices of Catholic Home Bureau. At the present time, ICC is an independent skilled nursing facility for children with HIV, licensed by the New York State Department of Health. The administration changed when ICC made this transition; however, present ICC administration located clinical trials-related files from the previous period and made them available to Children's Services for Vera to review.

6. Children whose HIV status had been tracked by the PAU and recorded in the electronic database as being HIV positive or receiving HIV-related treatment

After referring the initial 465 children, Children's Services reviewers generated a list of additional children from the sources listed above. This list consisted of 821 children whose files Children's Services sought to review for possible referral to Vera. Children's Services reviewers requested 1,018 case planning files from contract foster care agencies for the 821 children and were able to review 757 case files on 682 children.[52] Children's Services was unable to locate files for 139 children and was unable to refer them for review. Vera and Children's Services agreed that establishing a low threshold for adding a child to the list to review would reduce the possibility of accidentally leaving out children who had, in fact, been in clinical trials. If Children's Services reviewers found evidence suggesting that a child *might* have participated in a clinical trial, Children's Services referred the case to the Vera Institute for review.[53]

As Vera's team reviewed files, the reviewers noted names and other information about children who appeared in correspondence, on lists of clinical trial participants, or in case notes that discussed a sibling of a child or a child living in the same foster placement as the child under review. Review supervisors then checked to see if those names were already on the review list. If they were not, Vera reviewers forwarded the name and any other available information about the child to Children's Services. Children's Services would then confirm the identity of the child and make sure he or she was not already on the review list under a different name. This was a difficult process because some children in foster care have more than one name, some children's names and identifying information changed following adoption or reentry into care, several children have similar names, and some are twins and therefore have the same date of birth and case name. Children's Services staff developed detailed procedures to ensure that each name on the list represented one person.[54] Figure 2.2 describes the mechanisms through which names were added to the list. Once Children's Services referred a name, Vera staff used the Child Care Review Service database to identify the agencies where the child had received care and requested the case planning files from those agencies.[55]

[52] There are more files than children because children may have been cared for by more than one agency and would have a case planning file at each agency that cared for them.

[53] For more information on the process for adding children to Vera's case review list, see Progress Report 7, available on Vera's web site, www.vera.org. A description of Children's Services' efforts to identify children to refer to Vera for review is in Appendix 3. Appendix 4 contains a copy of the screening tool used by Children's Services staff during their review. Children's Services staff developed this tool. Vera reviewed the tool and made suggestions for improvement.

[54] This process included a list of aliases for children known by more than one name, a catalog of multiple identifiers if a child had more than one child identification number (CIN) or case number (a number assigned to a family, which often changes after a termination or surrender of parental rights and in other circumstances) and a list of siblings and twins that often had identifiers that made distinguishing the children challenging. Children's Services shared this information with Vera, and Vera confirmed this data in the CCRS database.

[55] In some child welfare paper files, Vera reviewers found periods of time in foster care at agencies not recorded in the Child Care Review Service database. If these spells included time at an agency not recorded in the CCRS, the Vera reviewers forwarded this information to their supervisors so that Vera could request a file from that agency.

Figure 2.2: Composition of the case review list

Source of information	Total
Children on the original review list. (This list was compiled by Children's Services through a preliminary review of Pediatric AIDS Unit files.)	463*
Children identified by Children's Services after reorganizing PAU files and reviewing case management files.	86
Children identified by Vera's document review team. (Many of these children were identified because their siblings were on the original review list.)	41
Children identified by Children's Services as possible participants in clinical trials because of their HIV status or their foster care reimbursement rate/level of difficulty or because they died in care.	184
Children identified by foster care agencies as likely participants in clinical trials.	22
Total number of children on Vera's review list	**796**

* Two names on the original list of 465 children were found to be the same child listed twice under different names. Thus, the number of children originally referred to Vera was 463, not the 465 children listed in Figure 2.1.

ACCESSING CHILD WELFARE FILES: The Vera review team examined case planning and case management files for the children on the review list.[56] In addition, the team reviewed material from the PAU and other sources that Children's Services had organized into child-specific files for 532 children.[57] To provide access to the case management files, Children's Services had to request the files from their storage facilities. If the request did not result in the warehouse shipping a case management file, Children's Services re-sent the request using other identifying information (parents' names, other case numbers associated with the child, possible aliases, etc.). After four requests, Children's Services considered the file missing.

Foster care agencies concerned about file security and the cost of copying the case planning files (many contain thousands of pages for a single child) requested that Vera staff conduct their review at the agencies' offices. Project supervisors responded by asking these agencies to make all files for each child available for review and to provide Vera reviewers with a secure, private space in which to work. Children's Services sent each agency a letter authorizing it to allow the Vera Institute to review the records. Once the agency retrieved the records from storage, Vera staff inventoried the files and conducted a review.

[56] Case management files are the files that Children's Services keeps on each child. Case planning files refers to the files kept by the contract foster care agency.
[57] Most of the information came from Children's Services' organization of the information in the PAU. Some came from the Children's Services' review of case management and case planning files.

The Vera Institute's child welfare review team reviewed 764 case management files (the files maintained at Children's Services) and 659 case planning files (the files usually maintained by contract foster care agencies). Its medical document review team reviewed 764 case management files and 656 case planning files. The number of case planning files only includes those maintained by contract agencies that are still open. An additional 61 files from agencies that are closed were seen as well. As indicated in Figure 2.3, there were 32 case management and 243 case planning files that were either lost or missing and not available for review for various reasons.[58] At least 79 of the 764 case management files reviewed were incomplete.[59]

Figure 2.3: Child Welfare Files Requested & Reviewed

File Type*	Total requested	Not available for review	Reviewed by the child welfare team	Reviewed by the medical team
Case Management	796	32	764	764
Case Planning (open agencies)	902**	243***	659	656****
Total	1,698	275	1,423	1,420

Note: This table does not include the PAU material reviewed. PAU material that Vera reviewed is described in the text.

* Note that the number of case management files corresponds to the number of children on the review list, while the number of case planning files exceeds the number of children on the review list. This "discrepancy" exists because Children's Services maintains one case management file for each family and therefore most children have one case management file. However, it is possible—after a child is freed for adoption, for example—for a child to have more than one case management file. However, for the purposes of this study, each child is considered to have one case management file, since all case management records for a child are reviewed at the same time and in the same place. Each contract agency that provides foster care for that child (some were in the care of more than one agency) maintains a separate case planning file.

** In addition to the 902 case planning files requested for review from open foster care agencies, there were 185 case planning files that pertained to agencies that no longer provide foster care under contract with Children's Services. (As the number of children in foster care in New York City has declined from over 50,000 in the early 1990s to less than 17,000 today, the number of agencies that provide foster care has dropped from 72 to about 40.) These 185 case planning files have not been included in the total number of files reviewed. That is because when an agency closes, its case planning files are often turned over to Children's Services and combined with case management files, with the result that it is rarely possible to distinguish between case planning files that are missing and case planning files that have been incorporated into a child's case management file. Vera reviewed 61 closed agency files that were kept separate from case management files, but it is not possible to determine what portion of the remaining closed agency files were missing and which were seen while reviewing case management files.

*** As described later in this chapter (see File Review Process), Vera asked each contract agency to retrieve the case files from storage. For nine of the 243 children cited here, the contract agency did not have any record of the child in question. These discrepancies may be due to errors in contract agencies' or Children's Services' records. In addition, 32 of the case planning files Vera requested from the Catholic Home Bureau (CHB) were destroyed in a series of warehouse fires in 1997 at a facility maintained by Iron Mountain, the data storage company. The fires destroyed thousands of CHB files as well as nearly 1 million boxes of documents belonging to over 200 organizations. See Michelle Seaton, "For the Record," *NFPA Journal* (March/April 1998); Iron

[58] Vera posted progress reports on www.vera.org throughout this project, which included information on the number of files requested and the number of files made available for review.

[59] A case management file was considered incomplete if reviewers noted that there was no information available for a substantial period of time in which the child was in care.

Mountain's 2001 Annual Report, p. 12; and Pat Moore, "Vital Records Protection Issues," *The Abbey Newsletter* 21, no. 8 (1997). In nine instances, records from the New York Foundling (NYF) were unavailable because one child stayed only in the NYF Hospital (Vera was not authorized to review hospital records), one child entered NYF's care after 2004, a warehouse flood destroyed one file, NYF transferred another file out of state, and in five instances, Vera could not duplicate file materials from microfilm because the microfilm rolls also contained files of children not on the Vera review list and Vera was not authorized to see those files. Vera staff did not inform Children's Services of this problem until after the review.
**** Three case planning files were reviewed by the child welfare team only. In these three cases, Vera reviewers believed that all files at an agency had been reviewed—files were routinely and appropriately placed in locked storage at night at the agencies. Vera staff did not discover that medical reviewers had not reviewed these three files until the reconciliation process, after the review was complete. Vera staff checked child welfare reviewer notes and determined that the missed files did not contain information critical for the review.

Several steps were taken to ensure that Vera had reviewed all possible sources of information about each child on the review list. Once the review team had reviewed all available files, they compared information on the data collection instrument with information on the tools used by the Children's Services reviewers. The results of this comparison raised the possibility that Children's Services may have seen information for some children that the Vera reviewers had not. In response to this situation Children's Services requested that agencies look once again for missing files. Some additional files that were made available are included in the total number of reviewed files (Figure 2.3). Vera also requested that Children's Services allow the review of working PAU files and PAU research files for specific children for whom crucial pieces of information were missing and for children for whom Vera reviewers had not received PAU information.[60] As part of this process, Vera staff reviewed 235 files from the Pediatric AIDS Unit's working files and research files and noted any new information on the data collection instrument.

COLLECTING DATA: To establish a systematic file review process, Vera's team reviewed a random sample of case management files from the original 465 children in order to become familiar with the content and organization of the files. Based on this review, the team developed two standardized data collection forms, or instruments. A child welfare instrument contained questions related to the child's foster care experience, and a medical instrument contained questions related to the child's medical condition and medical experience. Both instruments mainly used closed-ended (multiple choice) questions, in which the reviewer indicated the answer that described the information in the file, and a few open-ended or fill-in-the-blank questions.[61] Both also recorded information about the clinical trials in which the child participated and the consent process used for their enrollment. After piloting drafts of these

[60] At the beginning of the project, Children's Services gave Vera information, organized by child, based on documents and electronic data from the PAU (PAU research files). Children's Services gave Vera additional information for those files during the course of Vera's review. In this final step, the Vera medical review team used the actual PAU working files to search for any additional information about the children in the review.
[61] Closed-ended or multiple choice questions offer the advantage of standardizing the responses so that they can be counted and each case can be compared to all others. If the reviewer found information that did not fit into the closed-ended questions, that information was documented in open-ended questions and in the written narratives prepared about the child.

instruments on 5 percent of the available files, selected at random, and evaluating the questions for reliability and validity, staff adjusted the instrument to improve their accuracy and usefulness. Later, after the review process began, Vera staff re-evaluated the instrument and developed a guide to answer frequently asked questions from reviewers. The topics covered by the review instruments can be found in Figures 2.4 and 2.5.

Figure 2.4: Child Welfare Instrument

Theme	**Number of questions**
Demographic data	16
Family structure and function	9
Family history with Children's Services	7
Circumstances of child's removal(s) from family	45 (for each removal)
Services offered and received by family after child's removal	10
Parents' health status (including HIV/AIDS)	9
Permanency planning for child	32
Child's legal status	29
HIV-related health care and other services	14
Consent for clinical trials enrollment	31 (for each enrollment)

Figure 2.5: Medical Instrument

Theme	**Number of questions**
HIV testing and diagnosis	13
Prenatal, birth, and post-natal medical history	68
Medical care and treatment	13
Admissions to hospitals and skilled nursing facilities	4 (for each admission)
Medical devices (feeding tubes, intravenous catheters) and medical problems	6
Medications used for treating HIV	4 (for each medication)
Medications used to prevent opportunistic infections	4 (for each medication)
Medications used for treating other problems	4 (for each medication)
Consents for general medical care	4
Consents for medical procedures	5 (for each procedure)
Consent for clinical trials enrollment	31 (for each enrollment)
Clinical trial enrollment experience (eligibility, health status at study entry and termination, adverse events, and toxicities)	80 (for each clinical trial)

THE FILE REVIEW PROCESS: To carry out the file review process, Vera project managers recruited and trained a demographically diverse team of child welfare and medical reviewers.[62] The child welfare reviewers were college graduates or had graduate degrees in fields related to child welfare or health. The medical review team consisted of five physicians and a nurse.

[62] All staff were vetted for conflicts of interest. See Appendix 2 for Vera's conflict of interest guidelines.

Cases were assigned to the reviewers by a review coordinator.[63] For each case, the reviewer received a description of the child's movements within the child welfare system generated from the CCRS and the information from Children's Services that prompted the inclusion of the child on the review list. Based on a review of the PAU, the case management files, and the case planning files, a child welfare and a medical instrument were filled out for each child. As the files were not organized in a standard order, reviewers had to read the entire case file for each child on the review list. This required meticulous attention to detail because the files spanned many years, the forms used to collect data changed, and much of the information is handwritten or contained in carbon copies.

To capture the complexity of the child's and the family's experiences, reviewers also wrote narratives about each case they reviewed. The child welfare narratives described how the child entered and left foster care, his or her relationship with the birth family, foster parents, and the foster care agency, and other information. The medical narratives focused on the child's overall health, the signs and symptoms of HIV, and reactions (both positive and negative) to medical treatment within and separate from clinical trials. Both child welfare and medical narratives describe the decisions that led to the child's enrollment in a clinical trial and the process of obtaining permission for that enrollment.

After reviewing the files of approximately 500 children, in November 2007 Vera staff streamlined the file review process. While ensuring that child welfare and medical reviewers examined every piece of available paper in every case, the process sought to speed the review while still collecting all necessary information. Two factors prompted this change. First, reviewers found that some children had evidence that they might have participated in a trial, but closer examination showed no evidence that these children *actually* participated in a trial.[64] Vera project managers instructed the review staff to determine first if a child participated in a trial before filling out a complete instrument and writing a narrative.

Second, as Vera staff learned more about the experiences of the children and the nature of the files, reviewers narrowed their focus to information that could be consistently collected. An analysis of the data and reports of Vera reviewers indicated inconsistent documentation of some information that Vera hoped to collect. For example, Vera initially hoped to document whether a parent developed AIDS, but information in the files did not allow reviewers to answer this question consistently or with confidence.

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[63] This section describes the process Vera sought to follow. The complexity of the project, particularly the incremental referral of files, coordinating reviewer travel with agency space and file availability, the need for complex data protection protocols, and staff turnover, meant that not all elements of this process occurred on every case Vera reviewed.

[64] This might occur for many reasons. For example, a form used by the PAU in the 1990s found in a file may have indicated that the child was enrolled in a clinical trial, which prompted Children's Services or Vera to add a child's name to the list, but a full review found no evidence of participation in the trial. This might have occurred because the design of the form may have increased the chance that a box was checked in error, initial testing may have shown that a child did not meet the criteria for the trial, a child's medical condition might have changed between the signing of the consent form and the start of the trial, or a child may have moved to a new location before the trial started.

Due to this change, the data presented in Chapter 5, which discusses child welfare and medical experiences of children but does not discuss clinical trials participation, reports on 493 children, while data in chapters related to clinical trials reports on 532 children.

Vera staff collected a core of information in every case—such as the names of the trials in which children participated and the presence or absence of a consent form. Reviewers completed full instruments for every instance in which children participated in Phase I trials or when a child died while in foster care. Reviewers were also instructed to write narratives about any unusual events they read and to check with a supervisor before making a decision not to write a narrative.

DATA SECURITY: Because of the sensitivity of this material, several steps were taken to ensure the security of the child-specific information.

1. All children on the review list were assigned a Vera identification number. All instruments and narratives identified the child by this number only.
2. Lists with children's names or other identifiers linking children to their Vera identification number were stored separately from the data collection instruments and were kept in triple locked cabinets.
3. All laptop computers were double password protected and secured so that they could not be connected to the Internet and so that their data could not be accessed by a portable device or copied to a disk.
4. Electronic files with child-identifiable information were stored on Vera's secure network and were accessible only to Vera staff working on this project.
5. Project staff received training in New York State Public Health Law Article 27 and research ethics regulations and signed confidentiality agreements.
6. Laptop computers and confidential documents were transported in locked, secured briefcases. Receipts were obtained when confidential documents were given to foster care agencies or Children's Services.
7. All case management documents were stored and reviewed in a locked room at Children's Services headquarters at 150 William Street, in a room accessible only to Vera staff.

DATA QUALITY ASSURANCE: The nature of the files and the review created many challenges to collecting reliable data. As discussed earlier in this chapter, some child welfare files for some children were not available. Large files and complex cases introduced additional challenges. To address these issues, project staff implemented a variety of data quality assurance strategies.

A child welfare reviewer and medical reviewer read each child's files and filled out their instruments independently. Afterwards, the two reviewers met to reconcile any discrepancies regarding the child's participation in a clinical trial and the informed consent process. These discrepancies, while rare, occurred for many reasons, including conflicting information in the

file, a poorly organized file, large files, reviewer error, and different fields of expertise among individual reviewers.[65] If necessary, the discrepancies were resolved by consulting case notes and, if necessary, reviewing sections of the file.

To minimize reviewer error, a supervisor subsequently conducted a quality assurance process on all child welfare instruments. This included checking dates to make sure they made logical sense, filling in all parts of the instrument to prevent data entry errors, and other checks designed to identify internal inconsistencies.[66] A medical reviewer checked the medical instruments for internal inconsistencies and to determine—based on the research protocols or protocol summaries—whether a child met the criteria to enroll in a specific trial and whether he or she experienced any adverse events or toxicities during the trial.

Initially, a random sample of approximately 10 percent of the cases were selected for an external quality review in which a second team of medical and child welfare reviewers examined the same files. Senior staff compared the two sets of instruments and identified discrepancies, many of which occurred because of different interpretations of questions. Senior staff discussed the cases with the review team and developed a guide to ensure that reviewers collected information in the same way. The guide was loaded electronically onto each reviewer's laptop computer and regularly updated. Over time, the number of discrepancies declined and the quality review process was discontinued.

Vera researchers stored the child welfare and medical data in a Microsoft Access database.[67] To minimize data entry error, the database restricted entries to those with the proper format. To further limit the possibility of data entry errors, staff checked a random sample of approximately 15 percent of the child welfare and 15 percent of the medical instruments against the information entered in the database. As the samples did not overlap, staff checked close to 30 percent of all cases. Staff cross-checked data elements that appeared in both the child welfare and medical instruments to ensure consistency and resolved discrepancies by examining narratives, case notes, case management files, and/or talking to the reviewers involved.[68]

Interviews. Vera staff interviewed people primarily to gain a better understanding of their perceptions and opinions of this controversy and secondarily to record their actual experiences. Because most of the events examined occurred a decade or more in the past, interviews provided a less reliable source to substantiate facts than the contemporaneously written documents.

[65] In general, the medical review team was more familiar with the signs of clinical trial participation than the child welfare team, and the child welfare team became more familiar with the family circumstances and who had consenting authority.

[66] Inconsistencies typically resulted from inconsistent information in the file itself, unclear handwriting in the file, or, in a small number of instances, reviewer error.

[67] Microsoft Access is a relational database program that stored the complex information generated from the review in a format that could be exported to other analytic software programs.

[68] The file review also produced hundreds of narratives. The process used to analyze narratives and interview data is described below.

The Vera Institutional Review Board (IRB) approved two separate interview protocols—one for key respondents and one for clinical trials participants and their caregivers.[69] Vera staff used the term "key respondents" for people who had information, opinions, or experience with the pediatric HIV/AIDS clinical trials or who worked in some aspect of the child welfare or health system. This group included community and advocacy organization staff; medical researchers and medical research staff; independent advocates assigned to some of the clinical trials; members of the Medical Advisory Panel that reviewed the clinical trials and provided recommendations to New York City's child welfare commissioners; past and present employees of nonprofit agencies that provide most foster care in New York City; funding, regulatory, and monitoring staff, including staff at the National Institutes of Health; and past and present Children's Services employees.

Vera staff selected key respondents to interview based on a review of background material on this controversy, the document and child welfare file review, recommendations from Vera's advisory board, and recommendations made by other key respondents during interviews. Members of Vera's staff contacted key respondents by phone and e-mail to request an interview. Interview participants were offered the option of being interviewed for attribution or confidentially.[70] Informed consent was obtained before each interview. If the interviewee agreed, the interview was recorded. Two interview participants opted to provide written responses to the interview questions. Vera staff contacted 86 people altogether, of whom more than half agreed to be interviewed. Some people declined to be interviewed, and others did not respond to repeated requests. Citing the high profile of the project, Vera's IRB required that interviewers contact key respondents who are quoted for attribution in this report to offer them the opportunity to clarify their quotation.

Interview and Narrative Data Analysis. Vera staff systematically analyzed all interview and narrative material.[71] To prepare the key respondent and caregiver interviews for coding, audio

[69] Vera submitted the interview protocols to the IRB, not the child welfare document review. The federal regulations at 45 CFR 46.102(d) define research as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge." The review of child welfare files, while systematic, did not meet that standard as Vera's findings from the review apply only to the children Vera reviewed in New York City. Vera did not collect information on foster children participating in clinical trials for other diseases or in other jurisdictions, or on children who were not in foster care, or employ other research design strategies that would allow the findings from the management review to be generalized. The interviews, conversely, aimed to produce generalizable knowledge in a way that the management review did not. Vera staff used a sampling design for the interviews that included purposively selected groups of people and attempted to have some representation from each group in our key respondent pool. Vera's counsel recognized that experts might have different views on whether the interviews met the federal definition of research and determined that IRB review provided a conservative approach that best insured the protection of human subjects.

[70] Vera also applied for and received a Certificate of Confidentiality from the federal Department of Health and Human Services (DHHS). DHHS routinely provides such certificates to researchers when confidentiality of data may be important. The certificate shields research data from court orders and investigations.

[71] The analysis of this data uses an approach known as "grounded theory," which involves systematic collection and analysis of data without any pre-conceived ideas or hypotheses of what the data will show. See A. Strauss, and J.

recordings were transcribed verbatim. The transcripts were then checked against the recording for accuracy. Staff then read a subset of this material to identify common topics and develop a list of codes to allow the interview material to be sorted by topic. Specially trained Vera staff coded each interview and narrative. QSR N-6 software was used to organize and store the data by code.[72] All the data for each topic or code was then reviewed again, and common themes were identified. Theme tables were constructed for each topic, and salient quotes that illustrated the theme were identified.

To minimize the potential bias of staff, the 46 key respondent and caregiver interviews were coded separately by two members of Vera staff. The two coders then reconciled the differences in their coding. Vera staff also coded narratives for 572 children.[73] The volume of narratives did not allow for two people to code each narrative. Instead, two staff coded 10 percent of these narratives separately and then reconciled the differences. The 10 percent sample came primarily from the first sets of narratives coded so that coders learned to identify and eliminate potential bias and improve the accuracy of the coding.

Quantitative Data Analysis. Vera project managers developed a relational Access database using Structured Query Language (SQL).[74] The structure of the database allowed Vera staff to cross reference and analyze the medical and child welfare data. The database also allowed for multiple entries into foster care, enrollments in clinical trials, and other events that might be experienced more than once by children. Vera staff analyzed the data using standard statistical software packages. The analysis consisted of descriptive statistics, as missing data and the lack of a comparison group limited the utility of multivariate modeling techniques.

Strengths and Weaknesses of the Study Methodology

This study has many strengths. Vera staff accessed a broad range of materials not available to anyone else writing on this topic. Few reports include information based on unfettered access to child welfare case files. Vera staff know of no other studies that contain information from foster care case records of HIV-affected and -infected children. This report also includes analyses of the electronic administrative data of cases provided by Children's Services to Vera. Access to electronic records by those outside of child welfare staff is unusual, and Vera staff did not discover any other study that includes analysis of the electronic foster care records of HIV-exposed and HIV-positive children. Vera also received unprecedented access to policy files and

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Corbin, *Basics of Qualitative Research: Techniques and Procedures for Developing Grounded Theory* (Thousand Oaks, CA: Sage Publications, 1998).

[72] QSR N6, QSR International Pty. Ltd.

[73] The total number of narratives is less than the 796 children referred to Vera for review because reviewers did not write narratives for every child. In instances with little information due to missing or unavailable files, instances in which the child did not participate in a clinical trial, or certain situations in which reviewers conducted streamlined reviews, reviewers did not write narratives.

[74] K. Kline, L. Gould, and A. Zanevsky, *Transact-SQL Programming* (Sebastopol, CA: O'Reilly, 1999).

correspondence related to the participation of foster children in clinical trials. No previous study on this topic includes information from these resources.

Vera project managers know of no other study that includes the material Vera received from the Office for Human Research Protections and the National Institutes of Health. While this material is publicly available through the Freedom of Information Act, accessing the information cost several thousand dollars. This cost includes only fees paid to OHRP and NIH, not the staff time to read and analyze the information.

In addition to the unique access to materials, the volume of material Vera staff reviewed is another strength of the study. Vera staff reviewed all available child welfare files of children on the list, a process that took more than two years. The case management files filled over 100 lateral filing cabinet drawers, and case planning files were often double or even triple the length of the case management file. Vera staff reviewed several boxes of clinical trials policy documents, notes, and correspondence. Staff reviewed thousands of pages of OHRP investigative material and dozens of clinical trial protocols—many of which exceeded 100 pages. Vera staff also read dozens of articles and numerous books dealing with medical research, AIDS, child welfare, and related topics.

The formal and informal access to staff at Children's Services, staff at the Vera Institute, nonprofit service providers, and advocates constitutes another strength of the report. Many of these contacts came through interactions with the Vera's Institute's Clinical Trials Advisory Board, the commissioner's HIV/AIDS Healthcare Community Advisory Board, Dr. Robert Johnson, and key respondents. Vera staff called upon people with experience or expertise in numerous fields, from the intricacies of family law to the experiences of particular communities with HIV, medical institutions, and the child welfare system.

Vera and its Clinical Trials Advisory Board retained full editorial control throughout the project Vera reported to its own independent advisory board, not Children's Services. As called for in Vera's contract, Children's Services received a substantively complete draft of this report prior to its publication. Vera staff kept a record of the comments received from Children's Services and the impact of individual comments on the report, if any. Vera shared those comments with the chair of its advisory board.

The methods used for this report also have limitations. Although Vera staff had access to large quantities of information, there were critical sources of information, as described earlier in this chapter, that were unavailable. Most notably, Vera could not review clinical trial research or hospital medical records. When medical and clinical trial information was missing or incomplete in the child welfare files, Vera staff had no alternate source of information.

The lack of access to these records significantly limited the analysis and findings of this report as described in detail in several of the chapters that follow. With regard to the medical questions this study sought to answer, the lack of access to clinical trial and hospital records meant that in *some* situations Vera reviewers could not verify trial participation; trial enrollment and exit dates; a child's HIV status, the reason for a child's exit from a trial; a child's medical condition throughout their participation in clinical trials, and/or the extent of toxicities

experienced while participating in clinical trials. In a small number of trials, the lack of access to medical records prevented Vera staff from knowing the type of interventions that clinical trials tested.

The lack of access to clinical trial research and hospital records also affected some parts of the analysis of the adherence to child welfare policy and federal research regulations. In the substantial proportion of cases where the child welfare files did not contain a signed informed consent form, the lack of access to clinical trial research and hospital records prevented Vera staff from confirming the existence of signed and valid informed consent forms. In *some* instances, Vera reviewers could not determine if an enrollment took place, if it took place while a child was in foster care, or if it took place while a parent retained their parental rights. In a few instances, the lack of an enrollment date prevented Vera staff from knowing which child welfare agency policy applied to a particular enrollment or if a child enrolled in a clinical trial prior to the commissioner approving a trial.

Though not as significant as the limitations noted above, three other methodological issues are worth noting. Despite significant effort, Vera staff were unsuccessful at recruiting clinical trials participants for interviews and spoke with only two caregivers. Also, as described earlier in this chapter, some of the files were incomplete, destroyed, or missing. Finally, Vera project staff did not review the out-of-state files of children placed outside of New York State via the Interstate Compact.[75]

Conclusion

This report contains a wealth of information not previously available for the public's consideration. The report provides the most comprehensive answers yet available to many of the questions concerning the participation of foster children in HIV/AIDS clinical trials. Before reporting those answers, the report examines the medical and child welfare context in which the clinical trials took place.

[75] The Interstate Compact for the Placement of Children (ICPC) is an agreement regulating the placement of children across state lines. All 50 states, the District of Columbia, and the U.S. Virgin Islands are part of the ICPC. Out-of-state placements occur for many instances, including situations where members of a child's family live outside the state and become kinship foster parents, because a prospective adoptive foster parents move and the child moves with them, or because the child has specific medical or other needs that cannot be met by available placements in New York.

Correspondence: Children's Services Efforts to Arrange Access to Clinical Trials Research and Hospital Medical Records

The City of New York

ADMINISTRATION FOR CHILDREN'S SERVICES
Office of the General Counsel
150 William Street, 18th Floor
New York, New York 10038

JOHN B. MATTINGLY
Commissioner

JOSEPH CARDIERI
General Counsel &
Deputy Commissioner

September 21, 2007

Thomas Conway, Esq.
General Counsel
New York State Department of Health
Division of Legal Affairs
Corning Tower
Empire State Plaza
Albany, New York 12237

Dear Mr. Conway:

I am writing on behalf of the New York City Administration for Children's Services (ACS) regarding an issue of great importance to the City of New York and I am hoping you can assist us in addressing this issue. Deputy General Counsel Martin Baron recently spoke with Janet Cohen and then with Jean Quarrier of your office, and Ms. Quarrier suggested that ACS write to you concerning this matter.

ACS has contracted with the Vera Institute of Justice (Vera) to conduct a comprehensive review of issues related to the enrollment of foster children in clinical trials of HIV and AIDS treatment from 1988 to 2001. As part of this review, Vera will be identifying the processes established to enroll and monitor these children, determine whether those procedures were followed, and report on the condition of those children today.

Pursuant to discussion with the New York State Office of Children and Family Services (OCFS), in consultation with the New York State Department of Health (SDOH), ACS has shared information from its own records about children who participated in the trials with Vera. ACS is now attempting to obtain from hospitals the records of children who are no longer in the custody of ACS, with the goal that these records will be shared with Vera for purposes of this investigation. It is in this endeavor that I hope to obtain your assistance.

We believe it is critically important that Vera have an opportunity to review the hospital records of these children, as including such information would provide a clear picture of the health of these children and the progress they made while participating in the clinical trials. These records would help us answer critical questions that have been raised in

legislative hearings concerning consent procedures, quality of care, and clinical outcomes for this group of children. We feel that without this information, Vera's final analysis will be incomplete.

ACS is seeking SDOH's assistance in its efforts in obtaining these hospital records. Such assistance is warranted pursuant to SDOH's supervisory powers regarding the provision of health services to State residents, as well as SDOH's power to investigate the appropriateness of care and services provided to patients receiving Medicaid. We believe that SDOH has a legitimate interest, pursuant to the provisions of Public Health Law section 2803(1), in determining the quality and adequacy, as well as the necessity and appropriateness, of care received by participants in clinical trials and whether the clinical trials were conducted in such a way as to be beneficial to the participants, particularly when the participants were children with serious health conditions.

Assuming your agency is supportive of Vera's investigation and our efforts to obtain the hospital records of children formerly in foster children, we feel there are several potential means of succeeding here. Each of the following potential methods would require the assistance of SDOH.

The first approach would be for SDOH to "designate" ACS and/or Vera pursuant to Public Health Law §2803(1) to conduct a public health investigation on its behalf. The second approach would be for SDOH to make ACS and/or Vera its "authorized representative" pursuant to Public Health Law §2803(1)(d)(i) to determine the necessity and appropriateness of care and services provided by hospitals to patients eligible for medical assistance.

Under either of these approaches, a hospital could, consistent with the HIPAA rules permitting disclosure for "public health activities" (45 CFR 164.512(b)(1)) and for "health oversight activities" (45 CFR 164.512(d)(1)), disclose protected health information to ACS and/or Vera. Such disclosure would be consistent with Public Health Law §18, as being "for purposes of facility inspections or professional conduct investigations. They would also be consistent with the specific protections afforded HIV information under Public Health Law §2785, as subdivision 6 of that section permits disclosure to an "agent" of a state agency where "reasonably necessary" for the purpose of supervision by a state agency.

Should you wish to discuss any of the above with me or should you have any questions regarding this, please feel free to contact me at 212-341-0927.

Very truly yours,

Joseph Cardieri

STATE OF NEW YORK
DEPARTMENT OF HEALTH
Corning Tower The Governor Nelson A. Rockefeller Empire State Plaza Albany, New York 12237

Richard F. Daines, M.D.
Commissioner

Wendy E. Saunders
Chief of Staff

November 21, 2007

Joseph Cardieri, Esq.
Administration for Children's Services
Office of the General Counsel
150 William Street, 18th Floor
New York, New York 10038

Dear Mr. Cardieri:

This is in reply to your September 21st letter requesting State Department of Health (Department) assistance with a review currently being conducted by the Vera Institute of Justice (Vera).

The New York City Administration for Children's Services (ACS) has contracted with Vera to review issues related to the enrollment of foster children in clinical trials involving HIV/AIDS treatment from 1988-2001. Vera's goal is to identify the process established to enroll and monitor HIV infected foster children, determine whether the procedures were followed and report on the current condition of the children. As part of this investigation, Vera desires to access the confidential hospital records of such children, pursuant to a designation by the Department to be its agent or representative under Public Health Law §§ 2803(1) or 2803(1)(d)(1).

Although we support ACS's investigation, the Department is constrained to deny Vera's request. The Department cannot confer its statutory authority to investigate hospitals on a private (or public) entity in order to enable such an entity, in furtherance of its own investigation, to obtain the confidential medical records of patients. Any such attempt to utilize the Department's statutory authority in such a manner would be particularly inappropriate here in light of the fact that the medical records sought contain HIV/AIDS diagnoses, which are afforded special protections under PHL Article 27-F.

I trust you understand our constraints.

Sincerely,

Thomas Conway
General Counsel

cc: G. Birkhead, M.D.
B. Warren, R.N.

NYC Children's Services

New York City Children's Services
Office of the General Counsel
150 William Street, 18th Floor
New York, NY 10038

John B. Mattingly
Commissioner

Joseph Cardieri
Deputy Commissioner & General Counsel

April 7, 2008

Thomas Conway, Esq.
General Counsel
New York State Department of Health
Division of Legal Affairs
Corning Tower
Empire State Plaza
Albany, New York 12237

Dear Mr. Conway:

On September 21, 2007, I sent a letter to your office on behalf of the Administration for Children's Services (ACS) requesting State Department of Health (Department) assistance with a review being conducted by the Vera Institute of Justice (Vera) of issues related to the enrollment of foster children in clinical trials of HIV and AIDS treatment from 1988 to 2001. We indicated that we believe that it is critically important that Vera have the opportunity to review the hospital records of these children, as such information would provide a clear picture of the health of these children and the progress they made while participating in the clinical trials, as well as helping to answer critical questions that have been raised in legislative hearings concerning consent procedures, quality of care, and clinical outcomes for this group of children. Your reply, by letter dated November 21, 2007, indicated that while the Department supports ACS's investigation into these issues, you were constrained to deny Vera's request for access to these records, and noted that PHL Article 27-F afforded special protections to medical records that contain HIV/AIDS diagnoses.

At a recent meeting of the HIV/AIDS Community Advisory Board which advises ACS concerning issues related to HIV and AIDS, the group again expressed their belief that it was critically important for Vera to have access to this information. It was proposed that confidentiality concerns could be adequately dealt with by providing the information to Vera replacing any personal identifiers with coded data, essentially excluding all information that would identify an individual patient.

We ask that the Department reconsider the position that was expressed in your November 21, 2007 letter, with the understanding that ACS is now requesting that the records be provided to Vera without child identifying information, but with the substitution of coded data instead of the identifying information. We thank you in advance for your consideration of this request.

Should you wish to discuss any of the above with me or should you have any questions regarding this, please feel free to contact me at 212-341-0927.

Very truly yours,

Joseph Cardieri

STATE OF NEW YORK
DEPARTMENT OF HEALTH
Corning Tower The Governor Nelson A. Rockefeller Empire State Plaza Albany, New York 12237

Richard F. Daines, M.D.
Commissioner

Wendy E. Saunders
Chief of Staff

May 1, 2008

Joseph Cardieri, Esq.
Deputy Commissioner and General Counsel
Administration for Children's Services
150 William Street, 18th Floor
New York, New York 10038

Dear Mr. Cardieri:

This is in reply to your April 7th letter requesting that the NYS Department of Health reconsider its determination, as set forth in my letter to you dated November 21, 2007, that the Department cannot confer its statutory authority to investigate hospitals on the Vera Institute of Justice to assist Vera in its review, on behalf of ACS, of issues related to the enrollment of foster children in clinical trials involving HIV/AIDS treatment from 1988-2001. After further reviewing the issue, the Department is constrained to adhere to its initial determination.

As I pointed out in my earlier letter, the Vera review is not part of the Department's on-going monitoring or enforcement activities. Instead, it is part of a study undertaken by ACS, which has contracted with Vera for assistance. Although the purpose of the study may be laudable, DOH cannot confer its statutory authority to investigate hospitals on a private, or public, entity to assist that entity in its own investigation. I also noted that any attempt to confer the Department's authority would be particularly inappropriate in this case where the medical records sought contain HIV/AIDS diagnoses, which are afforded special protections under PHL Article 27-F.

In your letter, you indicate that confidentiality concerns could be adequately dealt with by providing patient records with patient identifying information redacted. However, even if specific enrollee names were deleted, identifying characteristics such as date of admission and discharge, age, diagnosis, drug regimen, facility name or provider name could reasonably lead to identification of the child, given the limited number of children involved. In any event, however, the Department simply cannot confer its statutory authority upon an outside entity to assist in that entity's investigation.

I hope this helps clarify our position.

Sincerely,

Thomas Conway
General Counsel

TC/JQ

NYC Children's Services

New York City Children's Services
Office of the General Counsel
150 William Street, 18th Floor
New York, NY 10038

John B. Mattingly
Commissioner

Joseph Cardieri
Deputy Commissioner & General Counsel

June 9, 2008

Thomas Conway, Esq.
General Counsel
State of New York
Department of Health
Corning Tower
The Governor Nelson A. Rockefeller Empire State Plaza
Albany, New York 12247

Dear Mr. Conway:

I am in receipt of your May 1, 2008 correspondence clarifying the New York State Department of Health's ("SDOH") position with regard to its determination that it cannot confer its statutory authority to the Vera Institute of Justice ("Vera") on behalf of the Administration for Children's Services ("ACS"). Please disregard my June 5th, 2008 response letter to you on this subject – as this present letter, while substantively similar, modifies (and thus moots) that June 5th letter.

While we understand your stated position in the earlier correspondence, we are hoping SDOH would be willing to consider offering assistance in another way, particularly since SDOH is in support of ACS's investigation, as noted in your November 21, 2007 letter. It would be of tremendous value to ACS, Vera, the private and public hospitals who were involved in the clinical trials being reviewed, as well as the children and families who participated in the trials, if SDOH would exercise its statutory authority and conduct its own investigation and/or monitoring, in particular by requesting the participants' consent forms from the hospitals that administered the HIV clinical trials. We are seeking only aggregate information which indicates the number of children in foster care who enrolled in clinical trials for whom consent forms had been obtained and retained in records maintained by the hospitals. We currently have a record of consents received, but it is incomplete because – as you know -- we cannot access the hospital records, wherein we expect most of the consents should be. If you agree to this approach, we would reduce the total number of consents to be searched for by the number of consent forms that are now in Vera's possession.

In seeking only aggregate information about consent forms from SDOH, the issue of confidentiality of child specific records, underscored in all of your responses to ACS, would not be at issue. If this is something that SDOH would do to assist us, the names of the children would be obtained from the Vera review and provided to you.

Please let me know whether SDOH would consider providing this assistance at your earliest convenience.

Sincerely,

Joseph Cardieri

STATE OF NEW YORK
DEPARTMENT OF HEALTH
Corning Tower The Governor Nelson A. Rockefeller Empire State Plaza Albany, New York 12237

Richard F. Daines, M.D.
Commissioner

Wendy E. Saunders
Chief of Staff

July 31, 2008

Joseph Cardieri, Esq.
Deputy Commissioner and General Counsel
Administration for Children's Services
150 William Street, 18th Floor
New York, New York 10038

Dear Mr. Cardieri:

I am replying to your June 9, 2008 letter.

As you know, in earlier correspondence I advised that the Department of Health could not comply with your request to confer the Department's statutory authority to investigate hospitals upon the Vera Institute of Justice to assist Vera in its review, on behalf of ACS, of issues related to the enrollment of foster children in clinical trials involving HIV/AIDS treatment from 1988-2001. In your June 9, 2008 letter, you request that the Department open its own investigation of these issues, and then share information obtained from that investigation with Vera in order to assist it in its inquiry.

The Department does not have any basis for opening an investigation of the issues being reviewed by Vera, and it would be inappropriate for the Department to open an investigation for the sole purpose of sharing information with a private entity.

Accordingly, we cannot comply with your most recent request.

Sincerely,

Thomas Conway
General Counsel

cc: G. Birkhead, M.D.
B. Warren

Chapter 3: New York City's Child Welfare System, 1985 to 2001

Chapter Overview

During much of the period that Vera studied, New York City's families, communities, and government grappled with a range of economic and social issues that influenced the demands placed on the child welfare system and other human service systems. In the late 1980s and early 1990s in particular, a severe recession, the onset of the widespread use of "crack" cocaine, and increases in crime and homelessness contributed to a tripling in the number of children in foster care—to close to 50,000 children in care at a time. Throughout this period, reports by city and state officials, nonprofits, court appointed panels, and academics found shortcomings in the provision of child welfare services in New York City. The child welfare agency had three different names and administrative structures during the time this report covers. It was confronted with numerous lawsuits and faced withering criticism in the wake of tragedies in child protection.

A reorganization in 1996 combined with an increased budget and oversight by a court-appointed special panel resulted in what many observers described as improved services and greater accountability. Changes in policy and practice combined with an improved economy, decreases in crime, and changes in drug use patterns to reduce the number of New York City children in foster care to fewer than 20,000 since 2005. Although many observers acknowledged improvements, many also contended that underlying problems remain in the child welfare system, including high staff turnover and strained community relations.

Introduction

Even in ordinary times, there is a contentious dimension to child welfare services in most large U.S. cities. Child welfare agencies contend with some of the most challenging aspects of modern American society: poverty, domestic violence, addiction, mental illness, race and class divides, and the vulnerability of children. This chapter provides the context in which New York City's child welfare agency created and implemented clinical trials policy. The HIV/AIDS epidemic merits a discussion of its own and is the subject of Chapter 4.

New York City, 1985 to 2001

More than 7 million people, including more than 1.5 million children, lived within New York City's five boroughs in 1985. That year voters re-elected Edward I. Koch to his third term as mayor, the number of children in foster care started to climb, and the federal drug enforcement officials made their first crack cocaine arrest in New York.[76]

[76] New York City demographic data come from the New York City Department of City Planning web site and are derived primarily from the decennial U.S. Census. See http://www.nyc.gov/html/dcp/pdf/census/demonyc.pdf , last accessed September 2, 2008. For racial and ethnic characteristics of children, see http://www.nyc.gov/html/dcp/pdf/census/pl3b.pdf. For a discussion of the onset of crack cocaine use and policy, see

Although the total number of people living in New York City did not change much in the ensuing decade, dramatic changes took place in the city's demographic composition. By the end of the decade, New York became a "majority minority" city, as the number of older white ethnic residents declined, replaced by newer, younger immigrants from the Caribbean, Central America, and Asia. By 1990 there were roughly equal numbers of Hispanic, black, and white children under age 18—about 30 percent each of the total number of children living in New York City, with most of the remainder of Asian descent.[77] By the turn of the millennium, when New York had gained 1 million more residents, 29 percent of the city's children were African American, 34 percent were Hispanic, less than a quarter were white, and 9 percent were Asian.[78] Each of these broad categories contained people with many different ethnic and national identities.

The period was also a time of marked economic change. After its near-bankruptcy in 1975, New York City began to experience an economic resurgence. By 1985, unemployment had declined and the city's tax revenues had climbed in step with a stock market rally and a construction boom.[79] The market's crash in October 1987, however, preceded a recession beginning in 1989 that contributed to the flight of middle class residents and further polarized the income distribution in the city.[80] Private sector employment, especially in manufacturing, plummeted. Unemployment rose from a 1988 low of 5 percent to more than 11 percent in 1992.[81] It would not drop below 8 percent again until 1998.

As the economy stagnated, New York City's crime rate—especially the rate of violent crime—surged. Homicides in the city went from slightly more than 1,300 in 1985 to 2,245 in 1990.[82] The increase affected low-income neighborhoods hardest. The south Bronx, central Brooklyn, northern Manhattan, and southern Queens led the city in both crime victims and incarceration rates.[83] Areas suffering from high rates of crime and victimization were also areas with high rates of unemployment, foster care placements, AIDS deaths, and new HIV infections.[84]

Chapter 4 of Henry H. Brownstein, *The Rise and Fall of a Violent Crime Wave* (Monsey, New York: Criminal Justice Press, 1996).

[77] The census data we looked at used Hispanic as an exclusive category. Today, most writers use the term Latino and understand that Latinos may be of any racial category.

[78] 2000 U.S. Census.

[79] For a discussion of politics and economics in New York City in the 1980s, see John Mollenkopf, *A Phoenix in the Ashes* (Princeton, NJ: Princeton University Press, 1994), and John Mollenkopf and Manuel Castells, *Dual City: Restructuring New York* (New York: Russell Sage Press, 1991).

[80] See John Mollenkopf, *Hollow in the Middle* (New York: City Council Finance Division, 1996) and Timothy Ross, *Still Hollow in the Middle* (New York: City Council Finance Division, 1997).

[81] The unemployment rate source is the *Local Area Unemployment Statistics Program*. See http://www.labor.state.ny.us/workforceindustrydata/laus.asp

[82] For New York City homicide rates, see http://bjsdata.ojp.usdoj.gov/dataonline.

[83] See Jeffrey Fagan, Valerie West, and Jan Holland, "Reciprocal Effects of Crime and Incarceration in New York City Neighborhoods" *Fordham Urban Law Journal*, 2003.

[84] *New York City HIV/AIDS Annual Surveillance Statistics* (New York: New York City Department of Health and Mental Hygiene, 2007), updated November 27, 2007, accessed April 24, 2008 at http://www.nyc.gov/html/doh/html/ah/hivtables.shtml*; Psychiatric News* 36 no. 10 (May 18, 2001): p. 16;

Homelessness increased in the late 1980s as well. The number of homeless single adults in New York quintupled, from 2,000 in 1980 to 10,000 in 1988.[85] During that same period, the number of families that were homeless also rose five-fold, from 1,000 to 5,000. The average daily census of homeless people in 1982 included 2,507 children. Five years later, more than 11,000 children lived in the homeless shelter system, including in "welfare hotels" known for their unhealthy and chaotic conditions.[86]

The growing use of crack cocaine added to the sense of crisis. An inexpensive and highly addictive derivative of powder cocaine, crack became available in New York City in the early 1980s. Although it peaked in the late 1980s, crack use continued at high rates through the mid-1990s. Because of its low cost, crack became prevalent in low-income communities, where it had destabilizing effects.[87] Studies have linked crack with increases in violent crime, premature birth, and high-risk sex.[88] Public and official concern about the drug led to harsh sentences for its possession and distribution. Coupled with increased enforcement as a consequence of the "war on drugs," this led to large increases in incarceration rates among many of the same communities.[89]

Concerns about the negative impact of crack addiction on parenting contributed to an increase in the number of children in foster care.[90] Media coverage of crack use also generated apprehension about "crack babies"—children exposed to cocaine *in utero* who allegedly had severe neurological damage as a result and therefore little chance of a productive life.[91] Although many have subsequently questioned research on this connection, fears of their behavioral problems and allegedly diminished potential made crack-exposed infants harder to place in foster care if they were removed from their parents.[92] Media coverage also focused on crack cocaine

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[85] Data are from the New York City Department of Homeless Services, see http://www.nyc.gov/html/dhs/downloads/pdf/histdata.pdf, last accessed April 24, 2008.

[86] For a description of conditions in the welfare motels, see Jonathan Kozol, *Rachel and Her Children* (New York: Fawcett Books, 1989).

[87] For a discussion of crack's origins and connection to HIV/AIDS in urban, low income, African American communities, see Jacob Levenson, *The Secret Epidemic: The Story of AIDS and Black America* (New York: Pantheon Books, 2004), p. 79-95.

[88] See Jeffrey T. Grogger and Mike Willis, "The Introduction of Crack Cocaine and the Rise in Urban Crime Rates" NBER Working Paper No. W6353 (January 1998), available at http://ssrn.com/abstract=226104; Mitchell S. Ratner, *Crack Pipe as Pimp* (Lanham, MD: Lexington Books, 1992).

[89] See Michael Jacobson *Downsizing Prisons* (New York: The Free Press, 2005).

[90] See M.H. Kearney, S. Murphy, and M. Rosenbaum, "Mothering on Crack Cocaine: A Grounded Theory Analysis." *Social Science and Medicine* 38 no. 2 (January 1994):351-61, who found that cocaine-addicted mothers cared deeply about their children and used several strategies to compensate for the challenges of parenting while combating an active addition—with mixed success. See also Dorothy Roberts, *Killing the Black Body* (New York: Vintage, 1998), which describes how media and child welfare responses to crack addiction often demonized African American mothers.

[91] More recent research shows that the dire predictions about the developmental issues caused by *in utero* cocaine exposure have not come true and raises questions about the methodology of the early studies of crack-exposed infants. See Deborah A. Frank, Marilyn Augustyn, Wanda Grant Knight, Tripler Pell, and Barry Zuckerman, "Growth, Development, and Behavior in Early Childhood Following Prenatal Cocaine Exposure: A Systematic Review," in *JAMA* 285 (March 28, 2001): 1613.

[92] Chapter 5 of this report discusses results from Vera's review of child welfare files that show the impact of stigma and fear on placements decisions.

use in communities of color. There is debate concerning the relative concentration of crack cocaine use among different racial groups. That crack use increased in lower income neighborhoods of color, had a destructive impact, and led to birth complications associated with foster care placements is well established.[93]

It was not until the mid-1990s that circumstances began to improve. New York City's economy rebounded as financial markets rallied and unemployment dropped. After 1992 crime declined steeply and continued falling throughout the decade.[94] The spike in homelessness leveled off as well—although many more people were homeless in New York throughout the 1990s than before 1985.[95] New immigrants helped to revitalize many neighborhoods throughout the city.[96]

All of these trends affected New York's child welfare system. Changes in the economy, for example, are often associated with changes in the number of children entering foster care—and with a city's financial resources to provide services to families.[97] Similarly, substance abuse patterns and the policies that respond to them are also thought to be associated with changes in the foster care census.[98] As these factors fluctuated over the period Vera studied, so did conditions in the city's child welfare system.

New York City's Child Welfare System, 1985-2001

New York City's child welfare system experienced many changes from 1985 to 2001.[99] These included a tripling of the number of children in foster care from approximately 16,000 children to 50,000 children between 1985 and 1990, the creation of the Administration for Children's Services in 1996, and the institution of a special panel to oversee the child welfare system in

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[93] For an empirical discussion of the impact of crack cocaine on low-income neighborhoods, see Roland G. Fryer, Jr., Paul S. Heaton, Steven D. Levitt, and Kevin M. Murphy, "Measuring the Impact of Crack Cocaine," National Bureau Of Economic Research, Working Paper 11318, Cambridge, MA, 2005, available at http://www.nber.org/papers/w11318, last accessed December 4, 2008.

[94] See Eli Silverman, *The NYPD Battles Crime* (Boston, MA: Northeastern University Press, 1999).

[95] After peaking in 1988 at over 27,000, the number of people in the homeless system dropped below 25,000 in 1989 and stayed below that threshold throughout the 1990s. See New York City Department of Homeless Services web page, http://www.nyc.gov/html/dhs/downloads/pdf/histdata.pdf, last accessed May 30, 2008.

[96] The city's population rose by 9 percent in the 1990s, largely due to immigration by Latino and Asian groups. See New York City Department of City Planning web page, http://www.nyc.gov/html/dcp/pdf/census/demonyc.pdf, last accessed May 30, 2008. See also Philip Kasinitz, John H. Mollenkopf, Mary C. Waters, and Jennifer Holdaway, *Inheriting the City: The Children of Immigrants Come of Age* (Cambridge: Harvard University Press, 2008).

[97] Statistically sophisticated studies of long-term causes of change in the foster care population are rare. For an argument that poverty influences entries into foster care, see Richard Wexler, *Wounded Innocence* (Amherst, NY: Prometheus Books, 1995). For a recent discussion of the relationship between methamphetamine and child welfare involvement, see Mary Bissell and Jennifer Miller, *Meth And Child Welfare: Promising Solutions For Children, Their Parents, And Grandparents* (Washington DC: Generations United, 2006).

[98] See R.P. Barth, C. Gibbons, and S. Guo, "Substance Abuse Treatment and the Recurrence of Maltreatment Among Caregivers with Children Living at Home: A Propensity Score Analysis," *Journal of Substance Abuse Treatment* 30 (2006): 93-104; J. Semidei, L. Feig-Radel, and C. Nolan, "Substance Abuse and Child Welfare: Clear Linkages and Promising Responses," *Child Welfare* 80 (2001): 109-128.

[99] Vera's contract called for the Institute to examine the period between 1988 and 2001, as the issue of foster children participating in clinical trials first arose in 1988 and their participation largely ended in 2001. We expanded the time period to 1985 in this discussion because that year marked the start of the increase in the foster care census.

1998. The remainder of this chapter describes the administrative structure of the city's child welfare system during this time and significant events that provide context for understanding both how the agency developed and how it implemented clinical trials policy. It begins with a general overview, followed by sections covering three distinct periods: 1985 through 1989, 1990 through 1995, and 1996 through 2001.

General Overview. New York is one of the few states that operates a state-supervised, rather than a state-administered, child welfare system. This means that the state's social service agency sets policy guidelines for local child welfare agencies, but it does not hire local staff. Instead, local agencies are led by commissioners who report to locally elected leaders, usually mayors or county executives. The local commissioner of social services operates the child welfare agency, and the city or county supplies part of its budget.[100]

New York City's child welfare agency conducts child protective investigations, files petitions in the family court (including petitions seeking the placement of children in foster care), and provides family support services aimed at keeping children safe. Children removed from their parents in New York City are usually placed in foster homes that are recruited and monitored by private, nonprofit foster care agencies. (These agencies are also commonly referred to as "contract agencies" or "voluntary agencies.") Contract agencies in New York City also arrange and supervise visits between children and their biological families and make recommendations that help determine whether children will return to their birth parents, stay in foster care, or be adopted. Although many contract agencies have religious origins, as city contractors they are required to follow nonsectarian rules.[101]

Like most urban child welfare systems, New York City's child welfare system has a history that includes high profiles cases, tense community relations, and stressful working conditions. Whenever the agency investigates the safety of a child, the experience is likely to be traumatic for parents, children, and child protective workers. Often, these investigations focus on families that are struggling to survive, or in communities that lack access to high quality education, employment, health care, and other services which child welfare agencies have a limited capacity to provide. These tensions have been exacerbated in recent decades as the foster care population has been increasingly—and eventually almost exclusively—comprised of children of color.[102]

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[100] In state-administered systems, local child welfare administrators are state employees and report to a state commissioner appointed by the governor.

[101] See Nina Bernstein, *The Lost Children of Wilder* (New York: Vintage, 2002).

[102] See Dorothy Roberts, *Shattered Bonds* (New York: Basic Civitas Books, 2007); Annie E. Casey Foundation (AECF), *Race Matters* (Baltimore: AECF, 2006); and Government Accountability Office (GAO), *African American Children in Foster Care* (Washington, DC: GAO, 2007), GAO-07-816, available at http://www.gao.gov/new.items/d07816.pdf last accessed June 5, 2008. Children of color and African American children in particular are more likely to enter foster care, to experience more placements, and to stay longer in care. They are also less likely to return to their parents than white children who enter care. Concerns about the treatment of children of color in child welfare cases predate the time period discussed here; see Andrew Billingsley *Children of the Storm: Black Children and American Child Welfare* (New York: Harcourt College Publishing, 1972). The change in the racial and ethnic background of children in foster care is linked with shifts in the composition of New York City's low income population. Bernstein notes that the decline in the proportion of white children in foster

Conflict over nearly every aspect of the system—the availability and quality of services, government funding, policies for removing children from their families, and the role of the nonprofits that provide foster care—is a staple of New York City politics.[103] Nevertheless, the late 1980s stand apart as an especially volatile time for the city's child welfare system.

1985-1989: Special Services for Children and the Child Welfare Crisis. From 1974 to 1989, New York City's child welfare agency was known as Special Services for Children (SSC), operating as a division of the Human Resources Administration (HRA), which also ran many other social service programs, including those that provided income assistance, food stamps, homeless shelters, adult protective services and, starting in 1985, the Division of AIDS Services.[104] In 1986, Mayor Koch appointed William Grinker to be commissioner of HRA.[105] As a measure of the system's volatility in that period, Grinker's team included Executive Deputy Commissioner Eric Brettschneider and SSC Deputy Commissioner Brooke Trent, both of whom were the seventh person to hold their positions in the previous nine years.

The number of children in foster care, a figure commonly referred to as the "foster care census," had declined in the early 1980s, reaching a floor of 16,230 in 1984.[106] The census started to climb in 1985, although it was still low by historical standards. Nevertheless, by September 1, after a 10-month increase in the foster care census to slightly more than 18,000 children (see Figure 3.1), the city experienced a "bed shortage"—a lack of available foster homes—so severe that some children stayed in temporary, overnight placements while city workers searched for more permanent homes.[107] One-third of all children in care at the time were adolescents aged 13 to 17— about the same proportion as children in care up to five years old.

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care accelerated in the late 1970s, a time when many white families moved out of New York City. See Bernstein, *The Lost Children of Wilder*. We do not provide exact numbers because the Child Care Review Services data on race and ethnicity during much of this time period are incomplete.

[103] See Bernstein, *The Lost Children of Wilder*.

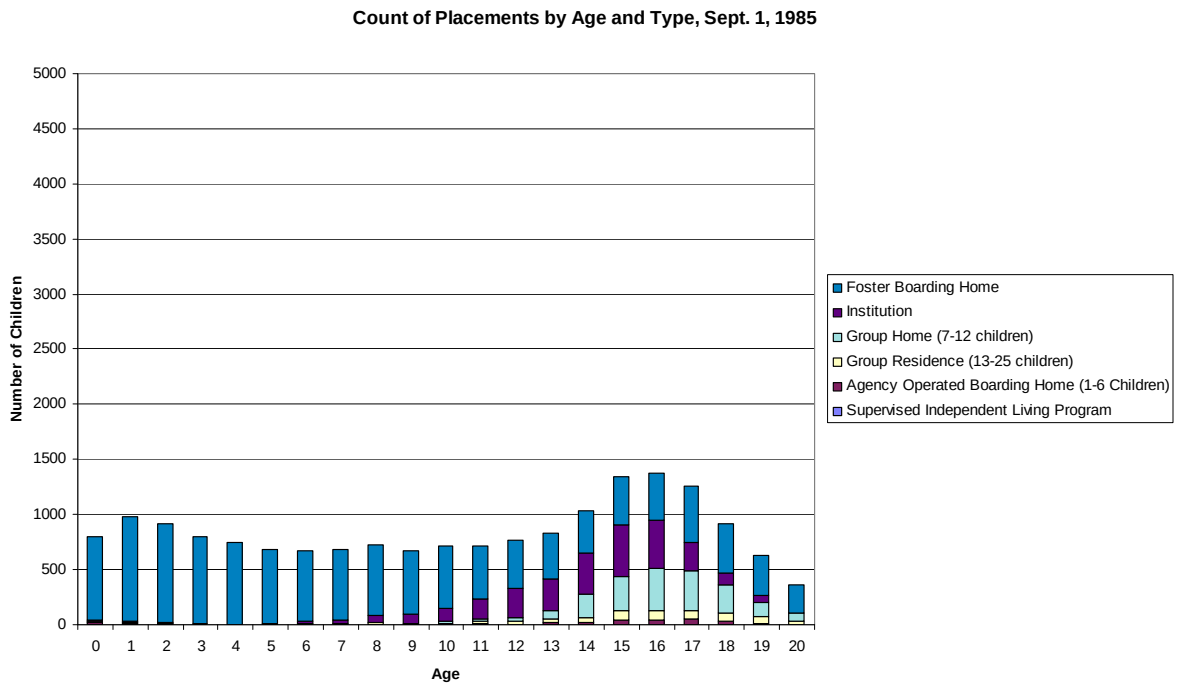
[104] In December 1992, responsibility for the shelter system was transferred to the new Department of Homeless Services. See Celia W. Dugger, "Feud Between Top Dinkins Aides Is Seen Hurting Social Programs," *New York Times.* January 1, 1993. For a description of the origins of the Division of AIDS Services, see Anita Vitale, "The New York City Division of AIDS Services" in *A History of AIDS Social Work in Hospitals* edited by Barbara I. Willinger and Alan Rice (New York: Haworth Press, 2003). The Division of AIDS Services is now known as the HIV/AIDS Service Administration (HASA) and is housed within HRA.

[105] See Appendix 5 for a timeline of key leaders at HRA and Children's Services.

[106] Bernstein, *The Lost Children of Wilder*, p. 357.

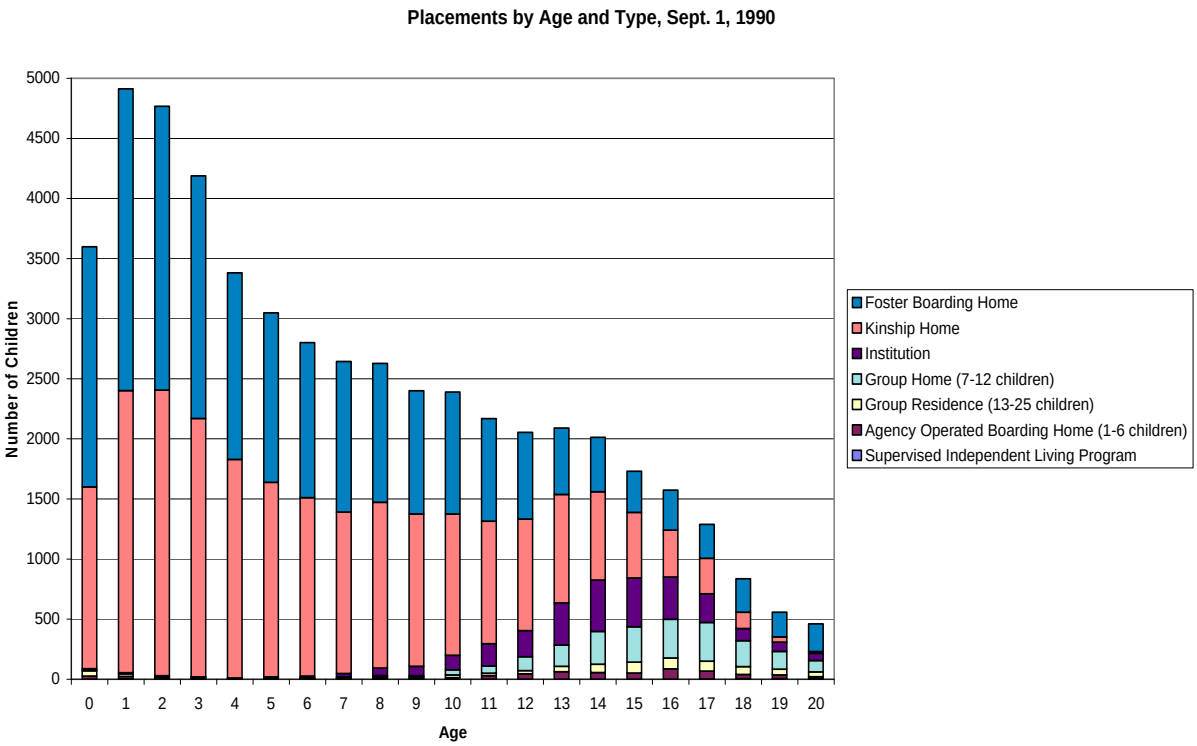
[107] See Timothy Ross, *A System in Transition: An Analysis of New York City's Foster Care System at the Year 2000* (New York: Vera Institute of Justice, 2001); Bernstein, *The Lost Children of Wilder*, p. 357.

Figure 3.1: Children in New York City Foster Care by Age and Placement Type, September 1, 1985



Five years later, the number of kids in care had multiplied three fold, with more than 48,000 children living in foster care (see Figure 3.2). Children under five accounted for the vast majority of the increase. The average age of children entering care had dropped from about nine years old in 1985 to six-and-a-half years old in 1990. Twice as many children entered care in 1989 as in 1985, yielding a net increase in the foster care census of more than 11,000 children in one year.

Figure 3.2: Children in New York City Foster Care by Age and Placement Type, September 1, 1990



Several factors contributed to this increase. These include influential lawsuits, more infants exposed to drugs, especially crack cocaine, and a rise in the number of "AIDS orphans"—children whose parents had died of AIDS. Each of these factors is addressed below.

Lawsuits led New York City to convert thousands of informal kinship arrangements into full foster care placements.[108] Prior to 1985, children who lived with relatives as the result of child protective investigations were not formally in foster care. Thus, their caretakers did not receive foster care payments and were not supervised by any contract agency. Converting these informal arrangements into formal foster care placements remedied what many perceived as a longstanding injustice: in some cases the lack of payment had led children to be placed with foster parents instead of family members who were willing to provide care but financially unable to do so. Now, relatives caring for children qualified to receive direct payments and be reimbursed for furniture, clothing, and other expenses. They also had to comply with the same rules as foster parents regarding a child's medical care, education, and contact with birth parents. The changes required kinship homes to be supervised regularly by caseworkers from the city or contract foster care agencies.

[108] A Supreme Court ruling in 1979 and two lawsuits involving New York City's child welfare agency in 1985—*Eugene F. v. Gross* in state court and *Jesse E. v. New York City Department of Social Services* in federal court—led to the conversion of informal kinship placements into formal foster care placements. See Administration for Children's Services, *Protecting the Children of New York: A Plan of Action for the Administration for Children's Services* (New York: Administration for Children's Services, 1996).

Meanwhile, the number of infants and newborns entering the system independent of the new kinship policy continued to increase. Even four years after the start of kinship foster care, relatives who provided care were facing long delays in receiving payments or having their homes formally licensed, visits by caseworkers often did not take place, and individual caseworkers faced caseloads of up to 200 families.[109]

Exposure to drugs accounted for a growing percentage of the infants coming into the foster care system. Between 1986 and 1989 reports of child maltreatment to the State Central Register based on "positive toxicology," or positive drug tests of newborn infants, rose from 1,325 to 4,875.[110] A government report found similar increases in the number of drug-exposed infants nationally during this time.[111] Many of these children had health issues that required additional services and were hard to place into foster boarding homes.[112]

By 1986, the increase in the number of infants removed from their parents at birth and a dearth of available foster homes had led to thousands of babies remaining in hospitals not for medical reasons, but because there were no foster homes available.[113] The number of "boarder babies" climbed from 3,805 in 1987 to 5,182 in 1988 and again to 5,810 in 1989.[114] Many of these infants' mothers had received no prenatal care. Some were homeless and many suffered from substance abuse, poverty, and associated problems. Among the children there were high rates of *in utero* cocaine exposure, and many were born prematurely, at low birth weight, and suffered developmental delays. A significant number suffered from HIV infection and showed symptoms of AIDS. Some doctors cited fear of the disease as a reason why the children could not be placed in foster care or returned home to their families.[115]

In December 1986—when the average boarder baby spent 36 days in the hospital waiting for a placement—the Association to Benefit Children, a children's advocacy group and service provider, sued the city to force it to find placements for infants more quickly.[116] In settling the suit, the city agreed to move all children out of hospitals within seven days of their being medically ready for discharge. To meet this obligation, contract agencies created special boarder

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[109] Suzanne Daley, "Agency Said to Fail Children Placed in Relatives' Care," *New York Times*, February 23, 1989.[110] Letter, February 22, 1990, from Amy Van Dorfy, executive assistant to the assistant deputy commissioner for policy and planning, Child Welfare Administration, New York City Human Resources Administration, to Amy Collier, United States General Accounting Office.

[111] See *Drug-Exposed Infants: A Generation at Risk* (Washington, DC: Government Accounting Office, June 1990), GAO/HRD-90-138.

[112] Chapter 5 of this report contains more information on the types of medical issues faced by drug- and HIV-exposed children.

[113] See *Protecting the Children of New York: A Plan of Action for the Administration for Children's Services*, 1996, p. 34. This report discusses the link between boarder babies and HIV in more detail in Chapter 4.

[114] Letter, February 22, 1990, from Dorfy to Collier.

[115] Associated Press, "High Costs Cited for AIDS 'Boarder Babies,'" *New York Times*, October 9, 1988.

[116] "Human Resources, Still Reeling," (editorial page) *New York Times*, October 6, 1989.

baby units and new programs to recruit foster parents.[117] For medically fragile foster children, including those who were HIV positive, the city and the state created a "special needs" rate that paid foster parents more money.[118] To speed the placement of boarder babies to any available, certified home, in 1987 the city rescinded a policy of placing children with foster families of similar ethnic or racial background.[119] Despite increases in capacity generated by these steps, the boarder baby crisis persisted through the end of the decade and into the 1990s.

While the boarder baby crisis attracted much attention, these infants represented only a portion of the influx of new children into foster care. By 1989, the number of abuse and neglect reports that the city needed to investigate had approached 60,000, an increase of almost 24,000 in five years.[120] In 1985, divisions of the city's child welfare agency and contract foster care agencies had struggled with an increase of fewer than 2,000 foster children; they now faced increases fives times as large two years in a row. To cope with the huge numbers, child welfare officials and contract foster care agencies hired hundreds of new staff—most with little or no experience in child protection, foster care, or other complex child welfare issues.[121] With an inexperienced staff and increasing caseloads, administrators created standard procedures and "check off" lists instead of relying on the more nuanced judgment of senior child protective staff.

The strain on the system showed: a state report issued in 1989 said that more than half of the city's child protective investigations contained serious flaws, though HRA contested the report's results.[122] Experts described record keeping as sloppy and noted a lack of basic supplies.[123] The child welfare budget doubled in the late 1980s. Still, the city's first deputy mayor, Stanley Brezenoff, told reporters that New York's social problems were "outstripping the city's ability to meet [them]. We don't have enough resources to cope adequately with all these issues."[124]

Following the election of Mayor David Dinkins in November 1989, HRA Commissioner Grinker resigned. At the time, New York City counted approximately 813,000 welfare recipients, about 28,000 homeless people, and 35,000 children in foster care.[125]

1990-1995: The Child Welfare Administration. As Manhattan borough president, David Dinkins had criticized the city's child welfare policy; he ran for mayor on a platform that emphasized

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[117] Incarnation Children's Center, the focus of the article that spurred concerns about the enrollment of foster children in HIV/AIDS clinical trials, opened in 1988 to address the needs of HIV-positive boarder babies. For more information on Incarnation Children's Center, see Chapter 5.
[118] Protecting the Children of New York, 1996.
[119] Joyce Purnick, "Foster Children to Be Assigned Regardless Of Race," *New York Times*, February 5, 1987. Unlike foster homes, kinship homes were usually certified after placement.
[120] See Suzanne Daley, "For Child Welfare Agency, Small Gains and Big Flaws," *New York Times*, July 3, 1989. The city is required to investigate all reports of abuse or neglect forwarded by the New York State Central Register (commonly referred to as "the child abuse and neglect hotline").
[121] This information comes from Vera staff interviews conducted as part of this project. See also Bernstein, *The Lost Children of Wilder*.
[122] Richard Levine, "H.R.A. Chief Is Indignant On State Study," *New York Times,* May 13, 1989.
[123] Suzanne Daley, "For Child Welfare Agency, Small Gains and Big Flaws," *New York Times*, July 3, 1989.
[124] Michel Marriott, "Needs Strain Social Services and Budgets," *New York Times*, September 14, 1988.
[125] "Human Resources, Still Reeling," *New York Times*,1989.

preserving families over removing children into foster care.[126] Following his election in November 1989, Dinkins installed a new leadership team at HRA: a trained nurse, Barbara Sabol, became commissioner of HRA, and Robert Little, a child welfare administrator from Washington, DC, became executive deputy commissioner of the city's child welfare agency, which was now known as the Child Welfare Administration (CWA).[127] Sabol and Little shared the new mayor's commitment to doing more to keep families intact.[128]

The foster care census continued to increase in the first two years of the Dinkins administration but at a slower rate as the number of entries into foster care started to decline. Whereas more than 21,000 children had entered foster care in 1989, fewer than 12,000 children entered three years later (see Figure 3.3). In 1992, for the first time in seven years, the census contracted.

Figure 3.3: Entries, discharges, and changes in the foster care census, 1985-2002

Year	Entries	Discharges	Net change
1985	10,794	10,283	511
1986	11,803	9,885	1,918
1987	16,167	8,498	7,669
1988	18,415	8,334	10,081
1989	21,885	10,517	11,368
1990	16,373	12,032	4,341
1991	13,890	12,449	1,441
1992	11,923	13,052	-1,129
1993	11,584	12,874	-1,290
1994	10,757	12,490	-1,733
1995	9,330	13,364	-4,034
1996	12,295	12,109	186
1997	13,207	13,036	171
1998	12,186	12,330	-144
1999	10,646	13,551	-2,905
2000	9,583	13,771	-4,188
2001	8,729	11,494	-2,765
2002	8,106	10,302	-2,196

Note: Entries include both first-time entries and reentries.
Source: The data from 1985 to 1998 come from Ross, *A System in Transition*. These numbers are for calendar years. The data from 1999-2002 are for the city's fiscal year (July 1 to June 30) and come from http://www.nyc.gov/html/acs/html/statistics/statistics_links.shtml, last accessed June 4, 2008. Though not strictly comparable, the data are sufficient for the trend analysis discussed here

[126] See Josh Barbanel, "Mayoral Aspirants Address Ideas for Helping Children," *New York Times*, August 28, 1989; Manhattan Borough President's Advisory Council on Child Welfare, *Failed Promises: Child Welfare in New York City* (New York: Manhattan Borough President's Office, 1989).
[127] In 1989, Special Services for Children became the Child Welfare Administration (CWA).
[128] "Who Killed Jeffrey Harden?" (editorial page) *New York Times*, January 2, 1993. Heather MacDonald cites Robert Little as a voice for family preservation. See MacDonald, "The Ideology of 'Family Preservation,'" *Public Interest* (Spring 1994).

Many factors have been cited for this decrease. The child welfare system began focusing on improving services to preserve families. Child protective workers and other staff may have responded to the agency leaders' new emphasis on keeping families together.[129] The use of crack cocaine leveled off, and state officials announced that *in utero* drug exposure alone did not constitute grounds for placing a child in foster care.[130] More resources were devoted to child welfare as foster care agencies and communities mobilized against the crisis of the late 1980s.

The impact of budget cuts during the recession of the early 1990s may also help explain the decline: the number of caseworkers who investigated child abuse reports declined by a quarter from 1990 to 1993.[131] Removals require more paperwork and time from child protective workers than other types of case closures. With fewer staff, limited placement resources, and a management emphasis on family preservation, child protective workers may have changed their standard for removing children from their families.[132] In 1993, following the death of a child under CWA supervision, the city announced plans to hire 300 new child protective staff after years of recession-driven budget cuts.[133] The mayor's office and HRA publicly argued about who should take responsibility for declines in child protective workers.[134]

In 1994, newly elected mayor Rudolph Giuliani appointed Marva Livingston Hammons as commissioner of HRA and Kathryn Kroft to lead CWA. Giuliani favored a more conservative approach to child welfare issues that emphasized child safety, but he paid comparatively little attention to child welfare issues during the first two years of his administration.[135] Nonetheless, the foster care census plummeted by more than 4,000 children in 1995, as entries into foster care dropped below 10,000.

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[129] One study showed that messages sent by child welfare managers altered child protective decisions. See Jeffrey Leiter, Kristen Myers, and Matthew Zingraff, "Substantiated and Unsubstantiated Cases of Child Maltreatment: Do their Consequences Differ?" *Social Work Research* 18 (1994): 67-82.

[130] See *Protecting the Children of New York*, 1996, p. 35: "In l990, the State clarified its policy to provide that positive toxicology newborns should not be held in protective custody without additional evidence of neglect…The decline in reports, and the prohibition on holding these infants without additional signs of neglect, served to reduce the backlog of infants in maternity wards." Another source indicates that prior to 1991, a positive toxicology report indicating drug use during pregnancy alone was sufficient grounds for establishing neglect. See *Secrets That Can Kill: Child Abuse Investigations in New York State.* A report of the Temporary Commission of Investigation of the State of New York (December 1995/January 1996), Chapter 2, available at http://www.nysl.nysed.gov/edocs/investigation/secrets.htm#Footref102, last accessed October 6, 2008. See also "*Nassau County Department of Social Services v. Denise J.*" *New York Law Journal* (Dec. 1, 1995): 27.

[131] See Celia W. Dugger, "Feud Between Top Dinkins Aides Is Seen Hurting Social Programs," *New York Times,* January 1, 1993.

[132] See Bob Herbert, "In America; See-No-Evil Mayors," *New York Times,* January 8, 1996. Herbert quotes Public Advocate Mark Green and lawyer Marcia Lowry as asserting that "the child protection system is currently in such shambles that it can give the erroneous impression that child abuse is going down. Telephone lines are overloaded and understaffed. Fewer complaints are being investigated, and caseworkers, overwhelmed, are making fewer placements. 'I think there has been a real concerted effort to not open cases," said Ms. Lowry. "It's been clear for at least the last couple of years that there has been a decision to cut the population.'"

[133] "Lingering Questions about Child Abuse," (editorial) *New York Times,* January 16, 1993.

[134] Dugger, "Feud Between Top Dinkins Aides Is Seen Hurting Social Programs."

[135] This characterization is Giuliani's, not the authors. See Steven Lee Myers, "His Child Welfare Response Was Too Slow, Mayor Says," *New York Times,* December 30, 1995.

On November 21, 1995, a six-year-old girl named Elisa Izquierdo died after a series of beatings by her mother.[136] Although the city had investigated seven reports made to the State Central Register concerning Elisa's family in the 18 months prior to her death, the child had remained in the custody of her mother.[137] The young girl's death generated substantial media coverage and sharp criticism of the child protection system. A month later, an advocacy group named Children's Rights filed a federal class action lawsuit, *Marisol v. Giuliani*, charging New York City with failing to protect children. Over the next year removals increased by one-third, and the foster care census's decline ended.

The Administration for Children's Services and the Marisol Panel: 1996-2001. In December 1996, the city released *Protecting the Children of New York: A Plan of Action for the Administration for Children's Services*.[138] The report described "a long, unbroken record of failure" in the city's child welfare system that included inadequate staffing and training, insufficient basic supplies, a history of violations of state regulations, poor data, inadequate communication about policies and procedures, and a failure to hold contract agencies responsible for the services they provide.[139] The report argued that having many complex and lengthy policies helped to create a dysfunctional organizational culture in which workers struggled to meet regulations without adequate resources. To remedy the situation, the report outlined a major restructuring of the child welfare system that emphasized accountability, neighborhood-based services, enhanced training, and lower caseloads.

Instead of structuring child welfare as one of many services under the direction of the HRA commissioner, the city created the Administration for Children's Services (Children's Services), whose commissioner reported directly to the mayor. Children's Services sought to implement neighborhood-based services that emphasized local services and kept children who entered foster care in their communities. Reversing previous budget cuts, the Giuliani administration added child protective workers, raised senior management and other salaries, increased training for child protective investigators, and developed accountability systems for contract agencies, among other reforms. The new agency moved into a renovated office building and, shortly after its creation, received new leadership when Mayor Giuliani asked Nicholas Scoppetta to replace Kathryn Kroft as commissioner. Scoppetta's team included William Bell, who succeeded Scoppetta as commissioner in 2002.

The reforms did not end criticism of the child welfare system, however. In 1997, a judicially appointed panel that reviewed child welfare practice as part of the *Marisol v. Giuliani* litigation

136 Joe Sexton, "Mother of Elisa Izquierdo Pleads Guilty to Murder in a Pivotal Child-Abuse Case," *New York Times*, June 25, 1996.
137 Nina Bernstein and Frank Bruni, "Seven Warnings: A Special Report," *New York Times*, December 24, 1995.
138 The report is available at http://www.nyc.gov/html/acs/html/about/history.shtml, last accessed June 3, 2008.
139 *Protecting the Children of New York*, p. 20.

found "staggering deficiencies" in the system.[140] The panel reported that even though state law required caseworkers to meet with children and parents twice a month, they failed to do so 97 percent of the time. It also reported that child protective workers routinely failed to fulfill basic requirements of investigations mandated by state law.[141] Also, new abuse or neglect occurred in 43 percent of the homes that Children's Services monitored, and one-quarter of the children in foster care received inadequate medical, dental, or psychological treatment, including almost half of those in group homes.[142]

A settlement of the *Marisol* lawsuit in September 1998 led to the appointment of a Special Child Welfare Advisory Panel to advise Children's Services as it implemented reforms.[143] The settlement required Children's Services to make good faith efforts to follow the panel's advice or face reinstatement of the *Marisol* suit—which asked that the city's child welfare system be placed in federal receivership. To facilitate implementation of the panel's recommendations, the settlement barred litigation against New York City's child welfare system for two years.

From 1995 to 1998, the foster care census stayed level, at approximately 40,000 children. Then, in 1999, the census started to drop almost as precipitously as it rose in the late 1980s. Meanwhile, unemployment, crime, crack use, and the number of people incarcerated were also declining from peaks in the early 1990s, and a surging stock market was increasing city tax receipts and the budget for child welfare services. City hospitals no longer housed boarder babies, and earlier predictions of a foster care system overwhelmed by tens of thousands of "AIDS orphans" and children at risk due to welfare reform did not materialize, in part because of new treatments that reduced the transmission of HIV from mother to child and a strong economy.[144]

The *Marisol* panel and other observers lauded improvements in the city's child welfare system.[145] The Children's Services budget surpassed $2 billion for the first time in 1999, and the new money funded more staff and increased salary levels, as well as new equipment, computerized accountability systems, and more family preservation services.[146] Lengths of stay in foster care declined, adoptions rose, and child protective caseloads fell. Although state case

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[140] Wendy Davis, "Marcia's Law," *City Limits,* December 1999, available at http://www.citylimits.org/content/articles/viewarticle.cfm?article_id=2431, last accessed June 3, 2008. The quote is Davis's characterization of the panel's findings.

[141] Rachel L. Swarns, "Panel Faults Caseworkers in Child Abuse," *New York Times*. August 14, 1997.

[142] Davis, "Marcia's Law."

[143] Douglas Nelson, president of the Annie E. Casey Foundation, chaired the panel, which included current Children's Services commissioner John Mattingly.

[144]A 1996 study estimated that AIDS deaths would create an additional 30,000 New York City "AIDS orphans" by 2001. See *Families in Crisis: A Report of the Working Committee on HIV, Children and Families*. Megan McLaughlin of the Federation of Protestant Welfare Agencies chaired the working committee, which received funding from the New York State Legislature.

[145] See "Saving the Children," *New York Daily News* (editorial), December 7, 1999; Somini Sengupta, "Number of Foster Children in City at Lowest Level Since the 1980's," *New York Times*, December 6, 1999.

[146] See *A Renewed Plan of Action for the Administration of Children's Services* (New York: Administration for Children's Services, 2001), available at http://www.nyc.gov/html/acs/html/about/history.shtml, last accessed June 5, 2008.

file reviews still found issues with practice and documentation, compliance with state and federal mandates improved.[147]

Yet even as many observers acknowledged improvements at Children's Services, experts noted that significant problems remained. Five years into neighborhood-based services, only 10 percent of foster children lived in placements in their neighborhoods and half lived outside their borough.[148] Lengths of stay in foster care remained above national averages, many felt that services for families needed to be strengthened, and the agency missed some reform timelines. In its fourth and final report, the *Marisol* panel harshly criticized the family court, which must review and approve many child welfare actions such as foster care placement, mandated services, and supervision. The panel said that in some instances the court's "practice comes frighteningly close to abdicating the court's basic responsibility to protect the rights of children and families."[149] The city's most prominent child welfare advocacy publication, *Child Welfare Watch*, praised reforms but raised a series of outstanding issues and asserted that Children's Services needed to pay more attention to the voices of parents and communities.[150]

Summary and Conclusion

Child welfare is a policy area characterized by crisis, conflict, and instability. During the period this report examines, New York City's child welfare agency had three different names and underwent several restructurings, large and small. Driven by a host of social problems, the census rose dramatically in the late 1980s. As these problems leveled off, the census stayed at high levels throughout most of the 1990s. Only at the end of the decade, as the economy grew and many social problems waned, did the census begin a dramatic decline. Throughout all of this time, stakeholders—parents, children, foster parents, contract agencies, city officials and line staff, advocates, and elected officials—faced enormous challenges and rarely felt that the system operated in a satisfactory manner.

In this context, the child welfare system was faced with another challenge: hundreds of children entering foster care who suffered from a new and lethal disease. The next chapter describes the evolution of the HIV/AIDS epidemic and its impact on the city's child welfare system.

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[147] Ibid.
[148] Nina Bernstein, "Effort to Fix Child Welfare Draws Praise," *New York Times*, December 8, 2000.
[149] Somini Sengupta, "Bleak Assessment Offered on City's Child Welfare System," *New York Times*, March 10, 2000.
[150] David Fischer, Jessica Green, David Kihara, Glenn Thrush, and Jennifer Warren, **"**Unfinished Business: Analyzing NYC's Foster Care Reforms," *Child Welfare Watch*, January 12, 2001, available at http://www.nycfuture.org/content/articles/article_view.cfm?article_id=1020, last accessed June 5, 2008.

Chapter 4: Epidemiology and History of Pediatric HIV/AIDS in New York City

Chapter Overview

The first cases of adults with acquired immune deficiency were reported in the medical journals in 1981. One year later, acquired immune deficiency was reported in children. Although the cause of the illness was not yet known, by 1982 epidemiologists were sure that it was transmitted through sex or through blood. In 1984 HIV, was identified.

Early challenges to providing medical care for children with known or suspected HIV infection included the difficulty of distinguishing between infected infants and infants carrying maternal antibody, a lack of available treatment options, rapid progression of the illness, and high death rate. The child welfare system faced its own set of challenges in caring for these children, including the stigma and fear associated with HIV/AIDS, the children's complex medical needs, and the need for strict confidentiality.

The number of children in New York City with HIV climbed until the mid-1990s, when AZT treatment of mother and baby was found to decrease the transmission of the virus from mother to child from approximately 30 percent to 8 percent, resulting in a rapid drop in the number of new cases of pediatric HIV infection.

The first antiretroviral medication, AZT, was approved for treating adults in 1987, and for treating children in 1990. By the mid-1990s, the recommended treatment for both adults and children became a combination of different types of medications known as HAART (Highly Active Antiretroviral Treatment). By 2007there were 15 antiretroviral medications available by prescription for the treatment of children with HIV.

Introduction

This chapter provides the medical context in which the pediatric HIV/AIDS clinical trials took place. It starts with a description of the onset of the AIDS epidemic in the United States and the realization that HIV affected children as well as adults. Next, it describes the development of tests and treatment for HIV/AIDS in children. Finally, the chapter discusses the spread of pediatric HIV/AIDS in urban communities and the impact of the epidemic on hospitals, child welfare agencies, and the community.

HIV Epidemic: The Early Years

During the summer of 1981, medical journals and the popular press carried reports of a strange new illness that destroyed the immune systems of previously healthy people.[151] Doctors were

[151] M.S. Gottlieb et al. "*Pneumocystis carinii* Pneumonia and Mucosal Candidiasis in Previously Healthy Homosexual Men: Evidence of a New Acquired Cellular Immunodeficiency," *New England Journal of Medicine* 305 (June 14, 1981): 1425-31; and Centers for Disease Control and Prevention, "Kaposi's Sarcoma and

seeing young, previously healthy adults with rare and serious infections such as *pneumocystis carinii pneumonia* (PCP) and *cytomegalovirus* (CMV) that previously had only affected the few people with congenital problems of the immune system or who were receiving chemotherapy for cancer.[152] While the initial reports of cases of this new illness were in gay men (in fact the illness was first named Gay-Related Immune Deficiency), other reports soon described the same occurrences among injection drug users and their partners.[153] The first cases in New York City were reported to the Centers for Disease Control in 1981.[154] Almost all of the people diagnosed with this new syndrome died. Specific infections such as PCP sometimes responded to treatment with antibiotics, but there was no identified cause or treatment for patients' deteriorating immune systems.

The first report of children with an acquired immune deficiency appeared in the Centers for Disease Control's weekly publication in December 1982.[155] The article described four infants with severe immunodeficiency, opportunistic infections, poor growth, and abnormal immunoglobulins.[156] The mothers of two children were injection drug users; the two other children were of Haitian descent. In May 1983, a report appeared in the *Journal of the American Medical Association* describing a group of seven children who had been evaluated at the Albert Einstein College of Medicine in the Bronx. [157]

At the time, no one knew the cause of the new illness. Without a known causal agent such as a virus or bacteria or toxin, a diagnostic test for the new illness could not be developed. The children, however, shared some common characteristics: an abnormally low number of T lymphocytes—a type of white blood cell that plays a crucial role in defending the body against certain infections, an unusual distribution of the different sub-types of T-cells (reversed T4/T8 ratio), and abnormalities in a type of protein called immunoglobulins that help the body fight infections. To learn more, public health officials interviewed the mothers of children with this new immune system disease. Pauline Thomas, a pediatrician and epidemiologist, described to Vera researchers how public health workers studied the new illness:

Pneumocystis Pneumonia among Homosexual Men—New York City and California," *Morbidity and Mortality Weekly Report* 30, No. 4: 305-08.

[152] R. Bayer and G. Oppenheimer, *AIDS Doctors, Voices from the Epidemic* (New York: Oxford University Press, 2000).

[153] Centers for Disease Control and Prevention, "Current Trends Update on Acquired Immune Deficiency Syndrome (AIDS)—United States," *Morbidity and Mortality Weekly Report* 31, no. 37: 507-08,513-14; Centers for Disease Control and Prevention, "Epidemiologic Notes and Reports Immunodeficiency among Female Sexual Partners of Males with Acquired Immune Deficiency Syndrome (AIDS)—New York," *Morbidity and Mortality Weekly Report* 31, no. 52 (January 07, 1983): 697-98.

[154] NYC Department of Health and Mental Hygiene, "NYC HIV Surveillance Slide Sets 2007," http://www.nyc.gov/html/doh/downloads/ppt/dires/epi-surveillance-aids1981-2006.ppt, accessed July 28, 2008..

[155] Centers for Disease Control, "Unexplained Immunodeficiency and Opportunistic Infections in Infants—New York, New Jersey, California," *Morbidity and Mortality Weekly Report* 31 no. 49 (December 17, 1982): 665-67.

[156] Immunoglobulin is a type of protein that helps the body fight infections.

[157] A. Rubinstein , M. Sicklick M, A. Gupta , et al. "Acquired Immunodeficiency with Reversed T4/T8 Ratios in Infants Born to Promiscuous and Drug-addicted Mothers," *Journal of the American Medical Association* 249 (1983): 2350-56.

> *[A]t first we were interviewing drug addicts, and then we realized, "Oh it's transmitted through contaminated needles probably, so we don't need to keep interviewing all the drug addicts." But we started interviewing only the adults who had no identified risk. And every single one of them—every single one—you could map them to a sexual encounter, or a needle encounter, or a transfusion, you know. So by the end of [19]82, I was really convinced—I think all the epidemiologists were convinced—that this was spread pretty similar to Hepatitis B,…you needed blood or sex exposure.*[158]

By 1984, researchers in the United States and France identified the Human Immunodeficiency Virus (HIV) as the cause of the new condition, named Acquired Immunodeficiency Syndrome (AIDS). In New York City, 1,841 people had died of AIDS.[159]

Children and HIV Testing. Soon after HIV was identified, researchers developed a test for antibodies to the virus. The first antibody tests for HIV were licensed in the United States in 1985.[160] When a person is exposed to a virus, their immune system makes proteins called antibodies. Antibodies help the body recognize and fight most viruses. They remain present in the person's body and serve to prevent the person from becoming ill if he or she is exposed to the same virus again. Mothers pass antibodies to their babies in the uterus and during breast feeding, having the effect of protecting the newborn while the immune system develops.

The presence of HIV antibodies in an infant indicates, therefore, that the mother is HIV positive.[161] But it does not necessarily mean that the child has the virus. Virtually all children born to mothers who are HIV positive will be HIV-antibody positive at birth, although only 15 to 30 percent of them are actually infected with HIV. Most of those who are not infected will have lost maternal HIV antibody by the time they are nine months old, although a few will carry it until age 18 months.[162] Children who are born HIV positive, but are not actually infected with the virus, are called seroreverters, because their serum (blood) goes from being positive to being negative for the HIV antibody.

The HIV antibody test has two steps. An initial screening test called an EIA (Enzyme Immunoassay) or ELISA (Enzyme-Linked Immunosorbent Assay) is performed first. If the EIA or ELISA test is positive, a second, more specific, confirmatory test called the Western Blot is performed. If both tests are positive, the person is considered to be HIV positive. If the ELISA is positive and the Western Blot is negative, the test is considered to be indeterminate and must be

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[158] This and other quotes in this report come from a series of interviews that Vera staff conducted with key participants including physicians, nurses, child welfare staff, community advocates, and parents of children with HIV. For more information on the interview methods, please see Chapter 2.
[159] W. Armstrong., B. Kachka., D. Kirby, Y. Kohen., "AIDS in New York: A Biography," *New York Magazine* 39, no. 20 (June 5, 2006): 46.
[160] U.S. Food and Drug Administration, "HIV AIDS Historical Time Line," http://www.fda.gov/oashi/aids/miles81.html#1985, accessed January 7, 2009.
[161] S. Zeichner and J. Read, *Textbook of Pediatric HIV Care*, (New York: Cambridge University Press, 2005), 106.
[162] Centers for Disease Control, "1994 Revised Classification System for Human Immunodeficiency Virus Infection in Children Less than 13 Years of Age," *Morbidity and Mortality Weekly Report* 43, no. RR-12 (September 30, 1994).

repeated. The two-step process is necessary because the ELISA, though easier and less expensive to perform than the Western Blot, can give a false positive result in a small number of circumstances.[163]

The antibody test, though effective in diagnosing adults and older children, could not accurately diagnose HIV infection in babies younger than 18 months.[164] Finding abnormalities in the child's immune system served as an *indirect* indicator of HIV infection in young infants who were HIV positive. In an HIV-antibody positive child who suffered from an opportunistic infection or had other AIDS-associated medical problems, the finding of abnormal T4/T8 cell ratios and abnormally high or low amounts of immunoglobulins allowed doctors to make a presumptive HIV/AIDS diagnosis.[165] When the antibody test is the only diagnostic test available, children must be tested repeatedly until they are 18 months old before it can be determined if they are infected or only carrying the maternal antibody.

Testing newborns, however, raised complex issues for mothers, physicians, the child's family, and the child welfare system. Since the antibody test measures the presence of maternal antibody, children born to mothers with HIV would all test positive. Yet, less than one-third of them are actually infected with the virus.[166] Being labeled HIV positive could have significant consequences for the child, including stigma, isolation, and abandonment. The policy and child welfare documents that Vera reviewed, published legislative documents, and state law contain much discussion about how to handle questions of recording test results in medical and child welfare records and who could or should be informed of the results of a child's HIV test.[167]

Testing infants also meant discovering the mother's status. Some mothers refused to allow their children to be tested because they feared learning or disclosing their own status. Dr. Leslie Gulick, a pediatrician who worked with HIV-positive children and families at Kings County Hospital, recalled the ambivalence that some high-risk mothers had when deciding whether they and their children should be tested:

> *We'd have people coming into the clinic…[a] mom finally admitting that she's HIV positive and wondering which of her children would turn out to be HIV positive, or a mother afraid to be tested herself but wanting testing for her children.*

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[163]Mayo Clinic, "HIV testing: What Tests and When to Get Tested," http://www.mayoclinic.com/health/hiv-testing/ID00050, accessed January 7, 2009.

[164] Centers for Disease Control, "1994 Revised Classification System for Human Immunodeficiency Virus Infection in Children Less than 13 Years of Age," *Morbidity and Mortality Weekly Report* 43, no. RR-12 (September 30, 1994).

[165] AIDS program, Centers for Disease Control, "Revision of the CDC Surveillance Case Definition for Acquired Immunodeficiency Syndrome," *Morbidity and Mortality Weekly Report* 36, no. 1S (August 14, 1987).

[166] Centers for Disease Control, "1994 Revised Classification System for Human Immunodeficiency Virus Infection in Children Less than 13 Years of Age," *Morbidity and Mortality Weekly Report* 43, no. RR-12 (September 30, 1994).

[167] For an example from the child welfare policy files, see letter dated December 4, 1989, from Anne Dede Hoerning, director of foster care and adoption, New Alternatives for Children, to Nancy Arroyo; New York State HIV testing and medical consent policy bulletins; and New York State Public Health Law Article 27-F.

Obtaining consent to test children in foster care for HIV created additional challenges. New York City's child welfare agency modified its testing policy several times in response to changes in state regulations and in response to recommendations by medical and child advocacy organizations.[168] Child welfare officials and legislators addressed issues of who could consent for testing, how to proceed if the parent refused to allow the child to be tested, whether consent for testing could be given by child welfare officials or contract foster care agencies, who was responsible for counseling the mother if the child tested positive, and who, including foster parents, could be informed about the test results.[169]

Determining how to handle positive test results of children in foster care presented legal and ethical dilemmas. Informing a mother of her child's status was, in effect, telling her that she was positive. Informing a father of his child's HIV-positive status meant disclosing the mother's status as well, which might also put her at increased risk for domestic violence and abandonment. Failing to inform the father meant leaving him unaware of his own risk and of his child's medical needs. Similarly, informing law guardians, family court judges, and other child welfare officials of a child's status also meant informing them of the mother's status, which could affect perceptions of the mother and decisions made in a child welfare case.

The controversy about HIV testing often pitted children's advocates, including child welfare agencies and pediatricians, who argued that early testing offered life-saving or life-extending benefits, against women's advocates, who felt that testing of newborns violated the mothers' rights and scared women away from prenatal care and other medical services.[170]

Progress in Diagnosing Pediatric HIV. By 1987 the CDC had developed a set of criteria that could be used to define whether an adult or child had AIDS.[171] Because people can be infected with HIV for years before showing symptoms of AIDS, the CDC definition made a distinction

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[168] Mireya Navarro, "HIV Testing for Children in Foster Care," *New York Times* June 7, 1994 reports on the adoption of a new policy and discusses the reasons for the new policy and the impact of the change. She notes that one effect of the new policy was avoidance of a threatened lawsuit by the Association to Benefit Children, an advocacy group that took the position that early testing and treatment to prevent opportunistic infections would save lives. In 2000, the American Academy of Pediatrics recommended HIV testing for foster children with risk factors for HIV and recommended that foster care agencies and pediatricians should be jointly responsible. See American Academy of pediatrics, Committee on pediatric AIDS, "Identification and Care of HIV-Exposed and HIV-Infected Infants, Children, and Adolescents in Foster Care," *Pediatrics* 106, no. 1 (July 2000).

[169] This is discussed in greater detail in Chapter 7 of this report, in the context of Children's Services policies concerning HIV-related care, including clinical trials enrollment.

[170] In 1991 the Institute of Medicine (IOM), recommended routine HIV-counseling and offering testing to all pregnant women. In 1999, based on evidence that treatment of HIV-positive pregnant women and their babies could reduce mother to infant transmission, the IOM recommended universal HIV testing of all pregnant women, with notification of the patient that they are being tested for HIV. The IOM recommendation was supported by the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists. ("American Academy of Pediatrics, American College of Obstetricians and Gynecologists, Human Immunodeficiency Virus Screening," *Pediatrics* 104, no. 1 (July 1999)). For an analysis of the debate over testing pregnant women and newborns in the context of race, gender and HIV, see Karen Booth, "Just Testing": Race, Sex, and the Media in New York's "Baby AIDS" Debate," *Gender and Society* 14, no. 5 (Oct., 2000):.644-61.

[171] Centers for Disease Control and Prevention, "Revision of the CDC Surveillance Case Definition for Acquired Immune Deficiency", *Morbidity and Mortality Weekly Report* 36, Suppl. 1 (1987): 1-15.

between HIV infection and AIDS in adults and older children. For infants younger than 18 months, the CDC definition also provided a basis for making a definitive diagnosis of HIV infection for a child who was antibody positive and had an AIDS-defining condition.

Developing tests that could make the diagnosis of HIV infection in newborns and young infants became a research priority. This would require a test that could directly test for the presence of the virus (and not just the antibody). The first of these direct tests was the viral culture, which involves taking a blood sample and incubating the white blood cells, called lymphocytes, to see if the virus is reproducing. This process, however, is time-consuming and expensive.

In the mid-1990s, two other direct viral tests became available. The P24 antigen test measures the presence of P24 antigen, the core structural protein of HIV. Its primary use is to screen the blood supply. It was not considered sensitive enough to use in children under three months of age. [172] Another direct viral technique called polymerase chain reaction (PCR) was developed. PCR amplifies genetic material in a blood specimen and measures the presence of minute quantities of the genetic material found in the HIV virus. Because it is more accurate and less complicated than viral culture, the PCR test became the preferred test for diagnosing HIV infection in infants. Based on the availability of new testing techniques, the CDC issued guidelines in 1994 for classifying HIV infection in children (see Figure 4.1).[173]

[172] Centers for Disease Control and Prevention, "Revised Guidelines for HIV Counseling, Testing, and Referral," *Morbidity and Mortality Weekly Report* 50, no. RR19 (November 9, 2001): 1-58; and S. Zeichner, S. and J. Reid, *Textbook of Pediatric HIV Care* (New York: Cambridge University Press, 2005), 106.
[173] Centers for Disease Control and Prevention, "1994 Revised Classification System for Human Immunodeficiency Virus Infection in Children Less Than 13 Years of Age," *Morbidity and Mortality Weekly Report* 43, no. RR-12 (1994).

Figure 4.1

DIAGNOSIS: HIV INFECTED

a) A child <18 months of age who is known to be HIV seropositive or born to an HIV-infected mother and:
- has positive results on two separate determinations (excluding cord blood) from one or more of the following HIV detection tests:
  - -- HIV culture,
  - -- HIV polymerase chain reaction,
  - -- HIV antigen (p24),

  or
- meets criteria for acquired immunodeficiency syndrome (AIDS) diagnosis based on the 1987 AIDS surveillance case definition (10).

b) A child >=18 months of age born to an HIV-infected mother or any child infected by blood, blood products, or other known modes of transmission (e.g., sexual contact) who:
- is HIV-antibody positive by repeatedly reactive enzyme immunoassay (EIA) and confirmatory test (e.g., Western blot or immunofluorescence assay {IFA});

  or
- meets any of the criteria in a) above.

DIAGNOSIS: PERINATALLY EXPOSED (PREFIX E)

A child who does not meet the criteria above who:
- is HIV seropositive by EIA and confirmatory test (e.g., Western blot or IFA) and is <18 months of age at the time of test;

  or
- has unknown antibody status, but was born to a mother known to be infected with HIV.

DIAGNOSIS: SEROREVERTER (SR)

A child who is born to an HIV-infected mother and who:
- has been documented as HIV-antibody negative (i.e., two or more negative EIA tests performed at 6-18 months of age or one negative EIA test after 18 months of age);

  and
- has had no other laboratory evidence of infection (has not had two positive viral detection tests, if performed);

  and
- has not had an AIDS-defining condition.

* This definition of HIV infection replaces the definition published in the 1987AIDS surveillance case definition (10).

PCR testing can diagnose HIV infection in some infants as early as one day after birth and by 28 days of age in 96 percent of infants with HIV.[174] Because in a small percentage of cases PCR testing can produce both false positive tests and false negative tests in infants less than one month of age, two positive tests performed on blood samples drawn at different times are

[174] L. Mofenson and the Committee on Pediatric AIDS American Academy of Pediatrics, "Technical Report: Perinatal Human Immunodeficiency Virus Testing and Prevention of Transmission," *Pediatrics* 106, no. 6 (December 2000).

required to make the diagnosis of HIV in a child less than 18 months old.[175] Current recommendations are initial testing of HIV-exposed infants at 14 to 21 days, one to two months, and four to six months. Some experts recommend testing at birth.[176]

The Spread of Pediatric HIV in New York City

Between 1977 and 2006, 3,895 children in New York City were born with HIV infection, and 9,094 children with AIDS were reported in the United States.[177] From the early 1980s on, the number of children born with HIV in the city increased steadily each year. Then, after peaking in 1990, it gradually began to decline, due primarily to the development of interventions that decreased transmission from mother to infant.

As in other urban areas, drug use played a pivotal role in the spread of HIV/AIDS in New York City, particularly among women. In 1983, injection use of heroin, cocaine, or other drugs that involved shared needles and syringes was the risk factor for HIV infection in 70 percent of mothers of babies born with AIDS, nationwide.[178] By 1987 the Centers for Disease Control reported that 50 to 60 percent of injection drug users in New York City, northern New Jersey, and Puerto Rico were HIV-positive and that partners and children of injection drug users were at risk for HIV.[179]

Crack, an inexpensive, highly addictive form of cocaine that is smoked, was introduced on the streets of New York City around 1985 and soon replaced heroin as the drug of choice among many users.[180] With the rise of crack cocaine, the proportion of new HIV infections due to

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[175] In assessing the accuracy of a diagnostic test, two measures are considered: sensitivity and specificity. Sensitivity measures the possibility that a negative test is really negative and is not a false negative. Specificity measures the possibility that a positive test is really positive and not a false positive. At age 28 days, PCR testing for HIV is 96 percent sensitive and 99 percent specific. See Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection*, February 28, 2008.

[176] Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection*, February 28, 2008

[177] The Centers for Disease Control (CDC) collects data from states and territories that have mandatory confidential name-based reporting of HIV infection. The state and territorial health departments send data to the CDC that includes the number of people infected and their characteristics, but does not include names or other identifying information. Data from the New York City Department of Health and Mental Hygiene comes from several sources, including New York State Health Department Newborn HIV Testing, New York City Department of Vital Statistics, Pediatric Spectrum of Disease Project, Expanded Pediatric HIV/AIDS Surveillance, and routine New York State HIV and AIDS Surveillance. Centers for Disease Control, *Reported AIDS Cases and Annual Rates (per 100,000 population), by Area of Residence, 2005, 2006, and Cumulative—United States and Dependent Areas.* from http://www.cdc.gov/hiv/topics/surveillance/resources/reports/2006report/table14.htm (accessed July 28, 2008); and NYC DOHMH, *Pediatric Semiannual Report*, December 2007, http://www.nyc.gov/html/doh/downloads/pdf/dires/epi-surveillance-pedhivaids77-06.pdf (accessed July 28, 2008).

[178] Centers for Disease Control and Prevention, "HIV Surveillance Slide Sets," http://www.cdc.gov/hiv/topics/surveillance/resources/slides/pediatric/slides/pediatric.ppt (accessed July 20, 2007).

[179] Centers for Disease Control, "Human Immunodeficiency Virus Infection in the United States: A review of Current Knowledge," *Morbidity and Mortality Weekly Report* 36 (December 18, 1987); 1-20.

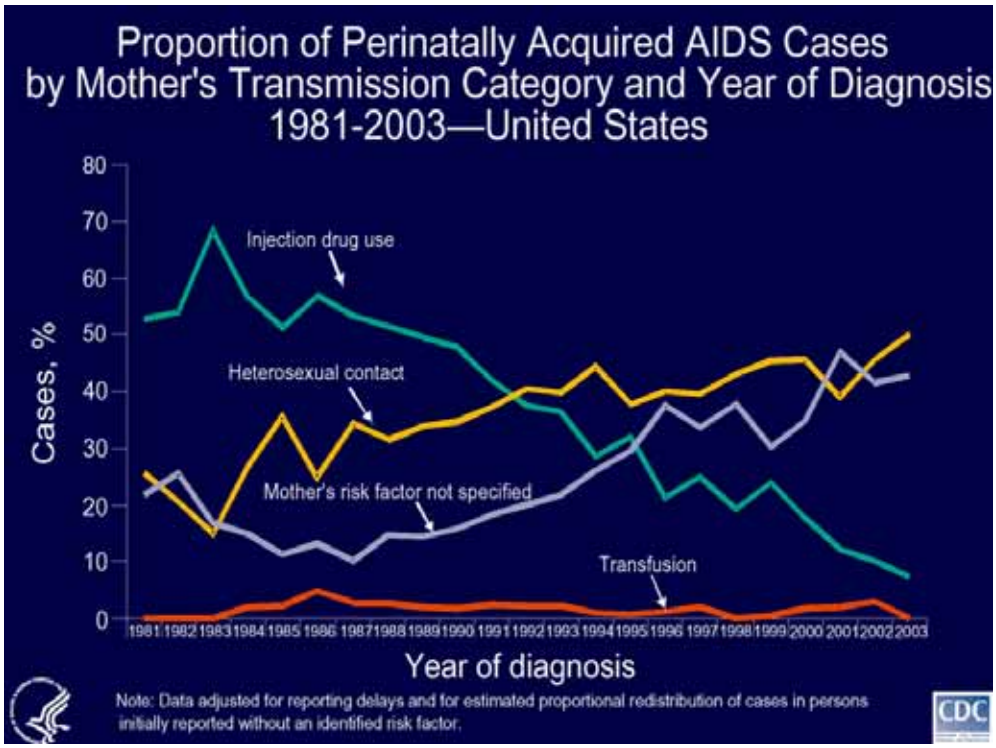
[180] "The AIDS Plague Spreads," *The Economist* 312 no. 7611(July 15, 1989): p23.

injection drug use decreased, even as the overall number of HIV infections continued to grow.[181] The accelerating rate of HIV in black and Latino communities alarmed some African American and Latino public health practitioners examining the relationship between crack use, sexually transmitted infections, and HIV.[182] Their extensive interviews and focus groups with crack cocaine users documented the addictive properties of crack, the effect of crack smoking on sexual behavior, including trading sex for drugs, and the ways in which the effects of crack use put users at high risk for acquiring HIV.[183]

Several characteristics of the drug increased users' vulnerability to HIV infection. Cocaine stimulates the desire for sex and also makes the user feel invincible and therefore less likely to use protection.[184] The risk of HIV spreading from one group of drug users to another also occurs because some crack users used small amounts of injected heroin to "come down" after heavy crack use. Some heroin users, in turn, became aware of their increased risk for HIV and switched to crack, believing it to be safer.[185] As Figure 4.2 shows, by 1992 injection drug use as the maternal risk factor for babies born with AIDS had decreased to about 35 percent and high-risk heterosexual contact became the leading maternal risk factor.[186]

[181] Centers for Disease Control and Prevention, "HIV Surveillance Slide Sets," http://www.cdc.gov/hiv/topics/surveillance/resources/slides/pediatric/slides/pediatric.ppt (accessed July 20, 2007).
[182] Jacob Levenson, *The Secret Epidemic: The Story of AIDS and Black America* (Random House: New York, 2004).
[183] See also Mitchell Ratner, ed., *Crack Pipe as Pimp* (Lanham, MD: Lexington Books, 1992); Tanya Sharpe, *Behind The Eight Ball: Sex For Crack Cocaine Exchange And Poor Black Women* (New York: Haworth Press, 2005).
[184] Academy for Educational Development, *HIV Prevention Among Drug Users: A Resource Book for Community Planners and Program Managers*, June 1997.
[185] Jacob Levenson, *The Secret Epidemic: The Story of AIDS and Black America* (Random House: New York, 2004).
[186] "High risk heterosexual contact" is defined as heterosexual contact with a person known to have HIV or be at high risk for HIV infection. The fact cited in this sentence comes from Centers for Disease Control and Prevention, "HIV Surveillance Slide Sets," http://www.cdc.gov/hiv/topics/surveillance/resources/slides/pediatric/slides/pediatric.ppt (accessed July 20, 2007).

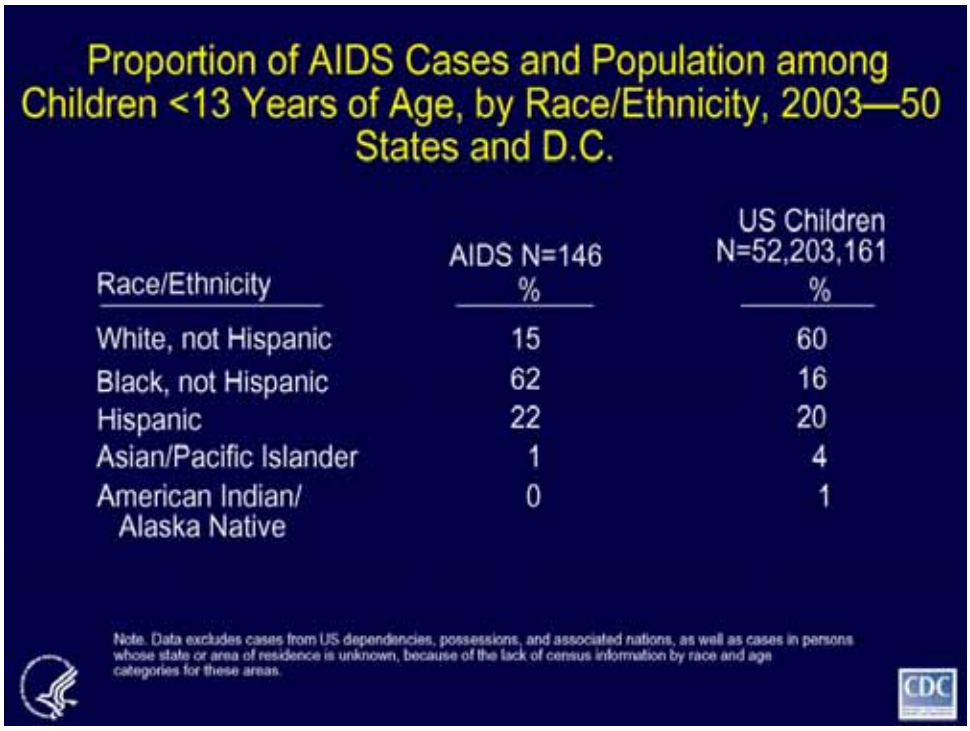
Figure 4.2



Both in New York City and in the country as a whole, pediatric HIV and AIDS disproportionately affect children who are black. As shown in Figure 4.3, black children are 16 percent of the U.S. population under the age of 13, but account for 62 percent of all U.S. children with AIDS.[187] In New York City, 58 percent of children with HIV infection acquired through mother-infant transmission are black, 35 percent are Hispanic, and six percent are white.[188]

[187] CDC Surveillance slide, http://www.cdc.gov/hiv/topics/surveillance/resources/slides/pediatric/slides/pediatrics.
[188] NYCDOHMH, HIV Epidemiology and Field services Program, "Pediatric HIV/AIDS in New York City, 1977-2006," http://www.nyc.gov/html/doh/downloads/pdf/dires/epi-surveillance-pedhivaids77-06.pdf, accessed July 28, 2008.

Figure 4.3



Early in the HIV epidemic, doctors at Harlem Hospital, which serves a predominantly African American community, reported on the high rate of HIV infection in the community and the association of HIV with race and drug use. In 1989, the hospital tested anonymously all babies born there and collected data from their medical records about maternal drug use.[189] Out of approximately 3,000 infants, 3.3 percent were HIV positive, indicating that roughly three out of every 100 women who had their babies at Harlem Hospital that year were infected with HIV. Subsequent research has shown that children born to women who used injection drugs or cocaine during pregnancy were more likely to be born with antibodies to HIV, as were babies whose mothers had syphilis.[190] The same 1989 study documented the relationship between maternal drug use, the child welfare system, and pediatric HIV. Researchers documented that 364 of the mothers in the study, or one in every eight, were reported to Children's Services that year because of drug use during pregnancy. Of these women, 245 had their babies placed into foster care directly from the hospital after birth. Thirty-nine of these discharged children were HIV positive.

[189] This type of testing is called surveillance testing and is used to establish the rate at which a condition or disease is present in a specific population. Blood samples are tested anonymously, which means they are not used to make an individual diagnosis. Surveillance testing is a tool used by public health officials to determine the extent of a problem and to guide them in developing future interventions.

[190] S. Nicholas, D. Bateman, S. Ng, T. Dedyo, M. Heagarty, "Maternal-Newborn Human Immunodeficiency Virus Infection in Harlem," *Archives of Pediatric and Adolescent Medicine* 148 (1994):813-19.

Pediatric HIV's Impact on Health Services and the Child Welfare System. New York City's public hospital and child welfare systems were both severely affected by the HIV epidemic and maternal cocaine use. The average occupancy rate of neo-natal intensive care units (NICU) at city public hospitals increased from 103.4 percent in fiscal year 1987 to 108.6 percent in fiscal year 1988.[191] Cocaine use by women during pregnancy increased greatly between 1980 to 1988.[192] Hospitals routinely reported maternal cocaine use to child welfare authorities, which often led to removals from their parent's care, and as noted above, some of these infants had HIV. Many infants had prolonged hospital stays due to a combination of medical problems and the difficulty of the child welfare system finding foster homes. As noted in Chapter 3, this led to the boarder baby crisis of infants who continued to receive room and board at the hospital after they were medically cleared for discharge because they had no homes to go to. The Department of Pediatrics at Harlem Hospital reported in 1988 that babies born with HIV infection who had families to care for them stayed in the hospital for an average of 89 days, but those discharged to foster care stayed for an average of 339 days.[193] Other hospitals in areas with concentrated crack cocaine use reported similar problems. The Yale-New Haven Hospital in Connecticut, for example, found that more than half of the days (54 percent) that children with HIV spent in the hospital were due to the fact that the children had no place to go.[194]

The hospital crisis in New York City contributed to the child welfare system problems discussed in Chapter 3. Between 1985 and 1990, the number of children in foster care tripled, from roughly 17,000 to 50,000 children in care on any given day. Both HIV and maternal drug use contributed to this crisis. Maternal cocaine use was the most frequent reason for children to be removed from their mothers in New York City.[195] Children were also entering the foster care system because their parents were sick or dying from AIDS and were unable to care for them.[196]

Children with HIV in Foster Care

Definitive numbers of children with HIV who entered foster care nationally and in New York City are not available, as rates of testing, the sensitivity and specificity of testing, and the consistency of recording test results by child welfare systems all vary over time. Several studies, however, indicate that substantial numbers of children with HIV entered foster care.

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[191] Testimony, October 5, 1989, James Brenner (representing the City of New York), at a hearing of the State Senate's Investigations, Taxation and Government Operations Committee.
[192] Ibid.
[193] JD Hegarty, E. Abrams, VE Hutchinson, SW Nicholas, MS Suarez, and MC Heagarty, "The Medical Care Cost of Human Immunodeficiency Virus-Infected Children in Harlem," *Journal of the American Medical Association* 260, no. 13 (October 7, 1988).
[194] K. Kemper and B. Forsyth, "Medically Unnecessary Hospital Use in Children Seropositive for Human Immunodeficiency Virus,"*Journal of the American Medical Association* 260, no. 13 (October 7, 1988).
[195] D. Neuspiel, T. Zingman, V. Templeton, P. DiStabile, E. Drucker, et al., "Custody of Cocaine-Exposed Newborns: Determinants of Discharge Decisions," *American Journal of Public Health*, 83, no. 12 (December 1993).
[196] F. Cohen, "Foster Care of HIV-positive Children in the United States," *Public Health Reports* (January 1, 1994).

In 1989, Congress asked the federal Department of Health and Human Services (DHHS) to report on the number of HIV-positive children entering foster care and the types of services they required. DHHS reported that New York, Florida, and New Jersey ranked first, second, and third respectively in both the number of children with AIDS (as reported to the CDC) and the number of children with HIV in foster care. New York State had 476 children with AIDS and 301 HIV-positive children in foster care. Ninety percent of New York State children with AIDS lived in New York City, which was also home to 92 percent of the state's children in foster care. The study estimated that between 16 and 21 percent of HIV-positive children in New York City were in foster care.[197]

Two other research studies also document the impact of pediatric HIV on the foster care system. Both studies found the percentage of HIV-positive children in foster care to be even higher than the 1989 DHHS report had estimated. The Pediatric Spectrum of Disease project at the Centers for Disease Control and Prevention found that 45 percent of children born to women with HIV infection did not live with a biological parent.[198] Similarly, a report by the New York City Perinatal HIV Transmission Collaborative Study Group found that 31 percent of children born to HIV-positive mothers were discharged to foster care.[199]

To help track the foster care and medical needs of children with HIV, New York City Children's Services established the Pediatric AIDS Unit (PAU).[200] In 1987 the PAU reported 79 children in care who were HIV positive. Six years later, in 1993, the number had risen to 618 (representing all children who had had a positive HIV-antibody test, including some who would later sero-revert).[201] The PAU tracked children with positive HIV tests until they either were discharged from the foster care system or found to be not infected. In 1994, the PAU reported that it was following 601 HIV-positive children in care, and that 757 children had already been discharged from the PAU tracking system. Of the discharged children, 55 percent were reported as seroreverted (HIV negative), 17 percent had been adopted, 10 percent had returned home, 5 percent were living with a relative, and 14 percent had died.[202]

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[197] These data, from the CDC, included children with AIDS. The number of children with HIV infection was estimated to be two to three times the number of reported AIDS cases. The number of children in foster care with HIV also includes some children carrying maternal antibody who would sero-revert. See U.S. Department of Health and Human Services, Assistant Secretary for Planning and Evaluation, *A Report on Infants and Children with HIV Infection in Foster Car*,(November 1989).

[198] M.B. Caldwell, L. Mascola, and W. Smith, "Biologic, Foster, and Adoptive Parents: Caregivers of Children Exposed Perinatally to Human Immunodeficiency Virus in the United States," *Pediatrics* 90 (1992):603-07.

[199] E. Abrams, P. Matheson, P. Thomas, D. Thea, K. Krasinski, G. Lambert, et al., "Neonatal Predictors of Infection Status and Early Death Among 332 Infants at Risk for HIV-1 Infection Monitored Prospectively from Birth," *Pediatrics* 96, no.3 (September 1995).

[200] For a fuller description of Children's Services Pediatric AIDS Unit, see Chapter 7.

[201] Human Resources Administration (HRA)/Child Welfare Administration (CWA), *Early Clinical Monitoring of HIV Positive Infants/Children in Foster Care*. Fifth Quarterly Progress Report (For quarter October 1 through December 31, 1993).

[202] We believe that the statistics from the PAU, though not as high quality as surveillance data, provide a good estimate through 1996. See Chapter 7 for more information on the PAU's data quality.

How HIV Infection Affects Children

The task of taking care of children with HIV became more complex as it became apparent that there is a spectrum of ways that HIV infection affects children. Some HIV-infected children are "rapid progressors" while others are "slow progressors." Rapid progressors were identified in the early days of the epidemic. These children became extremely sick at a very young age. They suffered from *pneumocystis carinii* pneumonia (PCP), brain involvement (encephalopathy) causing severe developmental delays, and serious and often fatal bacterial and viral infections.[203] After direct testing methods became available in the mid-1990s, researchers found that about one quarter of babies who were ultimately found to be infected with HIV had positive PCR tests for HIV during the first two days after birth. They inferred from this that babies who had early positive PCR or viral cultures had been infected in the uterus and were the rapid progressors, while babies whose PCR tests became positive after several weeks had been infected during birthing and were late progressors.[204] Without treatment with antiretroviral medication and prophylaxis for opportunistic infections, rapid progressors usually have multiple admissions to the hospital, often require prolonged hospital stays and treatment in the intensive care unit, and have a life expectancy of about two years. They have high levels of HIV and develop symptoms by around four months of age. Between 10 and 25 percent of children born with HIV infection are rapid progressors.[205]

Symptoms in slow progressors often do not appear for several years. For this group, which comprises the majority of children with HIV, the disease progression occurs in six to nine years.[206] Before 1997, when New York State law mandated testing of newborns, many slow progressors were not diagnosed until unexplained medical problems later in life prompted their physicians to test them for HIV. Often, this happened after they had been placed in foster homes. Here is how a nurse described the diagnosis of two siblings she cared for:

> *We had a set of siblings, an 18-month old and a three-year old…they were in [foster] care for six months, the 18-month old kept on getting thrush and Candida diaper rash…the three-year old in a routine blood work showed a very low white [blood cell] count. So we sent him to hematology. And from hematology, it came back that he was HIV infected.* [207]

Progress in Preventing and Treating Pediatric HIV

In the late 1980's and early 1990s there were few treatment options for children with HIV/AIDS. In 1989 the median survival for HIV-infected children was 38 months from the time of

[203] S. Zeichner and J. Read, *Textbook of Pediatric HIV Care* (New York: Cambridge University Press, 2005).
[204] L. Kuhn, E. Abrams, P. Matheson, P. Thomas, G. Lambert, and M. Bamji, "Timing of Maternal-Infant HIV Transmission: Associations between Polymerase Chain Reaction Results," *AIDS* 11, no. 4 (1997): 429-35.
[205] Zeichner & Read, *Textbook of Pediatric HIV Care*.
[206] Ibid.
[207] Interview with nurse at a foster care agency.

diagnosis. Mortality was highest in the first year of life (17 percent).[208] Before 1990, when AZT was approved by the Food and Drug Administration for children, there was no treatment for children with HIV other than preventing PCP pneumonia and treating opportunistic infections and serious bacterial infections as they occurred. AZT was the first antiretroviral treatment for children, followed by Didanosine (ddI) in 1991.[209]

As the 1990s progressed, more became known about both the treatment and prevention of pediatric HIV/AIDS. In 1993, a clinical trial called PACTG 076 found that treating pregnant women and newborn babies with zidovudine (ZDV, AZT, or brand name Retrovir)—which the FDA had approved for treating adults with HIV in 1987 and children in 1990—decreased the transmission of HIV infection from mother to baby from approximately 25 percent to 8.3 percent.[210] Shortly thereafter, New York State and the U.S. Public Health Service published guidelines recommending HIV counseling and testing for all pregnant women and treatment of all HIV-positive pregnant women and their babies. The addition of other interventions, including treatment of mother and baby with different combinations of antiretroviral medications and use of elective caesarean delivery, decreased the rate of mother-to-baby transmission in the United States to two percent.[211]

Two additional antiretroviral medications—lamivudine and stavudine—became available for treating children in 1995 and 1996, respectively.[212] Initial treatment of HIV in children and adults involved the use of single drugs (monotherapy) or two-drug combinations.[213] Experience in treating adults with ZDV alone had shown that patients treated with more than one antiretroviral drug have increased survival compared with those treated with a single drug.[214] In the mid- 1990s, the group of antiretrovirals known as protease inhibitors (PIs) became available and the recommended treatment for both adults and children became a "cocktail" or combination of different types of medications, known as HAART (Highly Active Antiretroviral Treatment).

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[208] G.B. Scott, C. Hutto, R.W. Makuch, M.T. Mastrucci, T. O'Connor, C.D. Mitchell, E.J. Trapido, and W.P. Parks, "Survival in Children with Perinatally Acquired Human Immunodeficiency Virus Type 1 Infection," *New England Journal of Medicine* 321, no. 26 (December 28, 1989):1791-96.

[209] U.S. Food and Drug Administration, "Drugs Used in the Treatment of Pediatric HIV Infection," http://www.fda.gov/oashi/aids/pedlbl.html (accessed May 9, 2006). This is no longer posted on the FDA web site.

[210] E. Conner, R. Sperling, R. Gelber, P. Kiselev, G. Scott, and M. O'Sullivan, "Reduction in Maternal-Infant Transmission of Human Immunodeficiency Virus Type 1 with Zidovudine Treatment," *New England Journal of Medicine* 331 (November 3, 1994):1173-80.

[211] Centers for Disease Control and Prevention, *Morbidity and Mortality Weekly Report* 55, no. 21 (June 2, 2006): 592-97.

[212] U.S. Food and Drug Administration, "Drugs Used in the Treatment of Pediatric HIV Infection," http://www.fda.gov/oashi/aids/pedlbl.html (accessed May 9, 2006). This is no longer posted on the FDA web site.

[213] HIV drugs are classified by the mechanism that they use to stop the HIV virus from multiplying inside the cells of an infected person. The classes of drugs available today are NRTIs (Nucleoside/nucleotide Reverse Transcriptase Inhibitors, NNRTIs (Non-Nucleoside Reverse Transcriptase Inhibitors), Protease Inhibitors (PIs), Fusion Inhibitors, Entry Inhibitors, and HIV Integrase strand transfer inhibitors. Appendix 6 lists all available drugs in each class and the year they became available for adult and pediatric use.

[214] S. Schwarcz, L. Hsu, E, Vittinghoff, M. Katz, "Impact of Protease Inhibitors and Other Antiretroviral Treatments on Acquired Immunodeficiency Syndrome Survival in San Francisco, California, 1987–1996," *American Journal of Epidemiology* 152, no. 2: 178-85.

By 2007 there were 15antiretroviral medications available by prescription for the treatment of children with HIV (see Appendix 6 for a list of available drugs for adults and children).[215] These medications went through a process of clinical trials testing for safety and for efficacy before being approved by the Food and Drug Administration for prescription use. HIV-positive foster children in New York City participated in some of those trials, which were conducted at multiple medical centers around the United States and Puerto Rico. The clinical trials and their results will be described in Chapter 8 and the experience of the New York City foster children will be described in detail in Chapter 9.

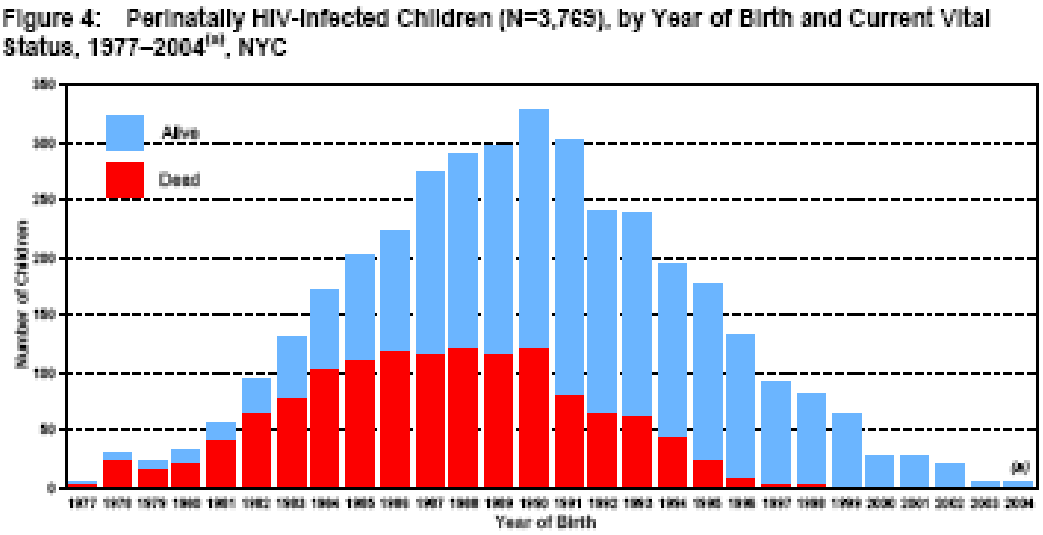
The use of HAART has lengthened the time between HIV infection and the development of AIDS by many years for a significant portion of people living with HIV, including children. With the use of HAART, the death rate of children with AIDS markedly declined and the length of time before symptoms developed increased. The New York City Department of Health and Mental Hygiene has tracked the city's pediatric HIV epidemic as part of the Pediatric Spectrum of Disease (PSD) project funded by the Centers for Disease Control.[216] In 2001, PSD reported that the average age of a child with HIV in New York City had climbed from three years old between 1989 and 1990 to six years old between 1995 and 1998. It also reported a significant increase in the proportion of HIV-positive children who were surviving and AIDS-free at age two. PSD attributed the decreased death rate to the greater number of HIV-positive infants and children who received treatment to prevent PCP pneumonia and to an increase in the number of children receiving antiretroviral treatment. They noted that by 1998, close to 60 percent of HIV-positive children were being treated with three or more anti-retroviral medications. Figure 4.4, from the New York City Department of Health and Mental Hygiene, shows that in the mid-1990s the number of children born with HIV began to decline, and the number of children born with HIV who are still alive began to increase.[217]

[215] Not all drugs that were tested in clinical trials were approved for pediatric use. Children metabolize medications differently than adults and for some medications; satisfactory levels of the drug were not achieved during the clinical trials. This is discussed further in Chapter 8.

[216] E. Abrams, J. Weedon, J. Bertolli, K. Bornschlegel, J. Cervia, and H. Mendez, "Aging Cohort of Perinatally human immunodeficiency virus-infected children in New York City," *Pediatric Infectious Disease Journal* 20, no. 5 (May 2001): 511-17.

[217] NYC DOHMH, "Pediatric HIV/AIDS in New York City, 1977-2006," http://www.nyc.gov/html/doh/downloads/pdf/dires/epi-surveillance-pedhivaids77-06.pdf (accessed July 28, 2008).

Figure 4.4



There are many antiretroviral drugs now approved by the FDA available to treat HIV/AIDS, usually as part of a HAART treatment. Studies have shown that these treatments extend survival times by years. HIV/AIDS is a chronic disease that shortens life expectancy, not a diagnosis to be followed by death in a few months or years. All of the medications, however, might have unpleasant effects and are toxic in some people. People with HIV/AIDS require frequent monitoring to ensure that the drug or drugs they are taking remain effective and to identify toxicity. The most recent guidelines for treating children with HIV/AIDS can be found in Working Group on Antiretroviral Therapy and Medical management of HIV-Infected Children, Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection.[218]

Conclusion

This chapter has given a general overview of the epidemiology and clinical course of HIV infection in children. The ability to make a diagnosis in very young infants, the decrease in the number of infants born with HIV, the use of interventions to decrease HIV-related complications, and the availability of highly active antiretroviral treatment have all had a profound impact on the course of pediatric HIV. The chapter that follows will describe how HIV affected the lives of the children in the Vera review.

[218] Working Group on Antiretroviral Therapy and Medical management of HIV-Infected Children, *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* (February 28, 2008) http://AIDSinfo.nih.gov, accessed January 9, 2009.

Chapter 5: The Child Welfare and Medical Experiences of Children Who Participated in Clinical Trials While in Foster Care

Chapter Summary

Three characteristics of the child welfare experiences stand out because they depart from typical experiences of children in foster care. First, most of the children discussed in this review came into foster care before they were one year old, often directly from the hospital where they were born. Second, child welfare files indicate that the children's family circumstances were exceptionally challenging, leading to a high number of adoptions compared to most New York City foster children, who are reunified with their parents. The third characteristic is the unusually poor health of these children's parents. Child welfare files show that more than one third died while their child or children were in foster care—the vast majority from complications from AIDS. In some cases, extended family members were also HIV infected and died from AIDS.

Most of the children described in this chapter suffered from medical complications early in life. Developmental delays, opportunistic infections associated with HIV/AIDS, and other maladies were the norm, not the exception. Also, these children died far more often than children who were not HIV infected. One-sixth died while in foster care, almost all from complications associated with AIDS. The children's medical needs shaped both their experiences in foster care and the responses of the child welfare system.

Introduction

This chapter provides a detailed overview of the general child welfare and medical experiences of the children who participated in clinical trials for HIV/AIDS while in foster care. It describes their foster care experience, from removal to discharge, their health challenges, and the medical care they received outside of clinical trials. It also discusses the circumstances in which some children died while in foster care and how end-of-life issues were handled. The experiences of these children *while they were enrolled in clinical trials* are described in Chapter 9.

How Vera Gathered This Information

From the 796 cases referred by Children's Services, Vera reviewers found 532 children who participated in 88 HIV/AIDS clinical trials between 1986 and 2005. These trials were of many different types and included both new medication and observational research studies. Chapter 8 describes the trials and the number of children enrolled in each. This chapter presents child welfare and medical information on 493 of these children (93 percent).[219]

[219] Vera staff reviewed available documents for all 796 cases. However, the data collection instrument was modified after November 2007 to make the review process more efficient (for modification details, see Chapter 2). Children whose files were reviewed after this date are not included in this chapter. As a consequence of this review modification, Vera reviewers collected child welfare information on 493 of the 532 and medical information on all 532. However, child welfare information needed to determine who was authorized to give consent for trial enrollment, such as the date parental rights were terminated, was collected on all children. None of the 36 cases

The information in this chapter comes primarily from the review of case management and case planning files, and files from Children's Services' Pediatric AIDS Unit. Vera staff also used data from the Child Care Review Service (CCRS) database.[220] These sources do not have all information for all children.[221] Vera staff did not have a uniform and complete set of information for all children.

When collecting information from the files, Vera reviewers relied whenever possible on records generated outside of the child welfare agency—such as hospital records, laboratory reports, court records, letters from medical and substance abuse treatment providers, etc.—over case worker notes that summarized medical or child welfare information. Reviewers also gave more weight to information from case planning files than information from case management files because the authors of case planning files had more direct contact with children and caregivers than Children's Services case managers. Case planning files were also more likely to contain copies of medical documents, such as records of clinic visits, hospital discharge summaries, and correspondence from physicians. Finally, Vera reviewers were instructed by senior staff to give more weight to accounts written at the time of an event than to accounts written months or years later.

Vera reviewers collected detailed information about child removals. This information, which mostly came from case management files, included the allegations made against the parents and parental circumstances at the time of removal. As noted in earlier chapters, Vera reviewers wrote structured narratives to describe the medical, child welfare, and clinical trials experiences of the children in this study. Narratives allow for the description of the unique circumstances of each child and describe events or information not included in the data collection instrument. Excerpts from those narratives are used in this chapter to illustrate and give more meaning to the data presented in the figures and text.

Describing the child welfare experiences of hundreds of children presents many challenges. Although many themes run through this report, each child, family, and community is unique.

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omitted from this analysis involve children in phase I clinical trials or children who had participated in medication trials and passed away while in foster care. The analysis in Chapter 9 is based on the entire group of 532 children who enrolled in HIV/AIDS clinical trials.

[220] The quality of the data in the CCRS is a common concern among advocates, providers, and researchers. In ten years of working with this data, Institute staff have identified areas of strength and weakness in this data. In some cases, for example, the CCRS did not record a stay in foster care. According to Children's Services staff, this might occur because after 200 entries for a child are put into various tables in the CCRS, additional entries result in the deletion of older entries. In general, Vera staff found that the CCRS data matched paper file data on dates of birth and movements into and out of care and between placements—information that was loosely tied to payments to foster care agencies during this period. CCRS data on legal activities during this period, conversely, is known to be incomplete—our analysis showed that the CCRS recorded far fewer terminations of parental rights than actually occurred. Often, racial, ethnic and religious data for children are missing for the period Vera staff examined.

[221] Statisticians often use techniques that make assumptions about, or "impute" missing data. For example, the U.S. Bureau of the Census has produced data that imputes populations for census tracts by estimating the number of people that census takers likely missed in their count. Vera staff chose not to use these techniques because of the small number of children in the review and because missing files were concentrated in a few contract foster care agencies that may not have been representative of other agencies. Vera staff also wanted to ensure that the report contained only documented information.

The goal of this chapter is to describe the children in Vera's review—their family circumstances, their communities, their health status, and their experiences with the medical and child welfare systems.

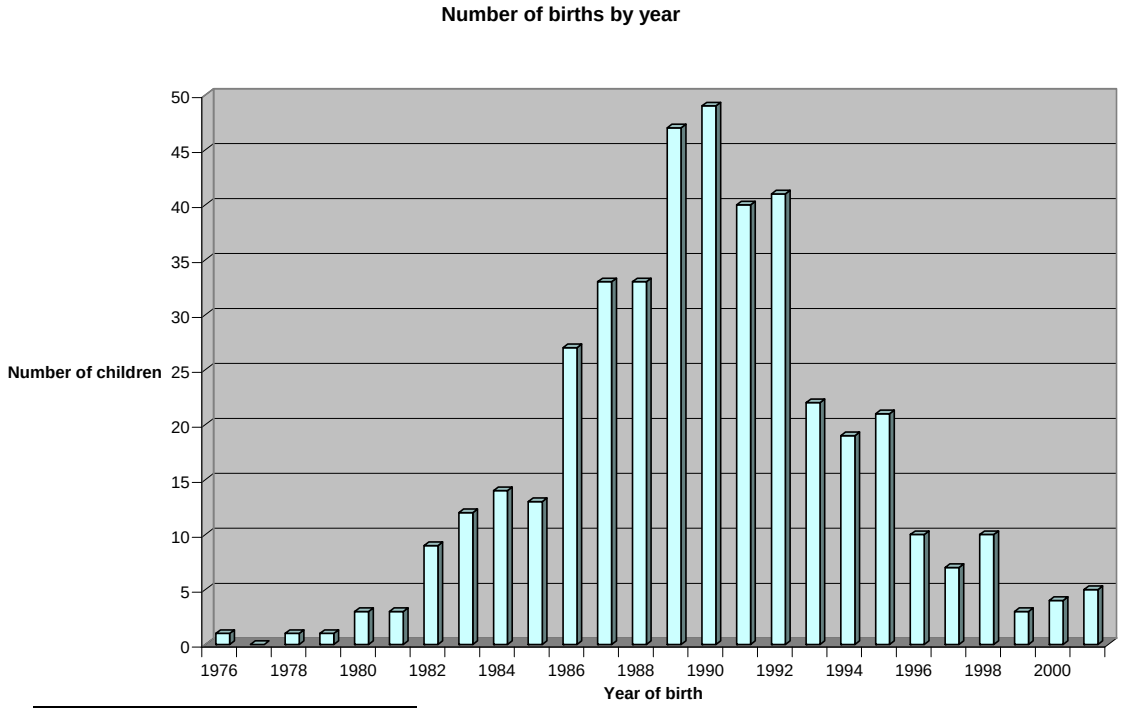
The unit of analysis in this chapter is each child who participated in a clinical trial.[222] Although some children shared the same family (the 493 children came from 457 different families), Vera staff chose to use the child as the unit of analysis because even in the same family, children were removed and discharged at different times and under different circumstances, were placed with different agencies and in different foster homes, and faced different health challenges.

To analyze this data, Vera staff ran frequencies, cross tabulations, and other statistics on the whole sample and on various subgroups, in an effort to identify patterns and anomalies. Narrative excerpts were then selected to illustrate those findings.

Demographics and Family Structure

The New York City foster children who participated in clinical trials were born between 1976 and 2001. Yet, as Figure 5.1 illustrates, 80 percent were born in the decade between 1986 and 1995, and more than half (51 percent) were born in just five years, between 1988 and 1992.

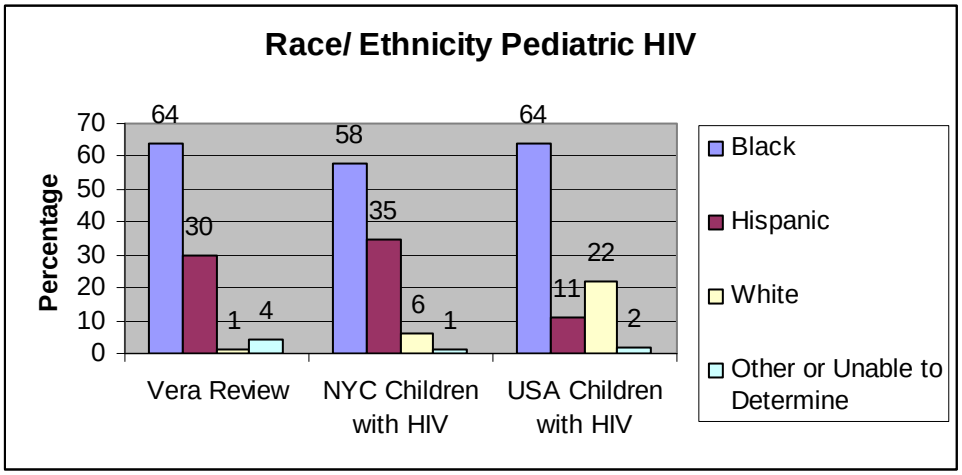
Figure 5.1: Year of Birth for Children Who Participated in HIV/AIDS Clinical Trials



[222] This differs from the chapters that deal with the clinical trials. In those chapters the unit of analysis is each *enrollment* in a clinical trial. Many children were enrolled in more than one trial, some children were enrolled in the same trial twice (for example, if the child moved to a new medical facility), and each enrollment is treated as a separate event in subsequent chapters.

The racial and ethnic composition of children in the Vera review was similar to that of children with HIV in New York City but differed somewhat from children with HIV nationally. Nationally there was a higher percentage of white children and a lower percentage of Hispanic children with HIV than in New York City (see Figure 5.2).[223] In the Vera review sixty-four percent of the children were non-Hispanic blacks, 30 percent were Hispanic of varying races, and fewer than 2 percent were non-Hispanic whites. For 4 percent of the children, Vera reviewers could not determine the race or ethnicity of the child.[224] In comparison, U.S. census figures indicate that the population of children 18 years old and under in New York City in 1990 was approximately 30 percent black, 30 percent white, 30 percent Hispanic, and 10 percent Asian and other.[225]

Figure 5.2: Race and Ethnicity of Pediatric HIV and Clinical Trial Populations*



* Percentages of U.S. children with HIV do not total 100 due to rounding. The racial/ethnic categories for the children reviewed by Vera and for U.S. children with HIV are non-Hispanic black, Hispanic, and Non-Hispanic White. For New York City children with HIV the categories are black, Hispanic, and white.

Most of the children were born in the United States—although reviewers found that at least 13 percent of custodial parents were born in Puerto Rico or another part of the Caribbean basin.[226] Parents of 86 percent of the children spoke English as the primary language, eight

[223] The data on race/ethnicity of children in NYC comes from Pediatric HIV/AIDS in New York City 1977-2006, HIV Epidemiology and Field Services Program, New York City Department of Health and Mental Hygiene, December 2007, retrieved from http://www.nyc.gov/html/doh/html/dires/hivepi.shtml. National information comes M. Lindegren, T. Hammett, and M. Butlerys, "The Epidemiology of Pediatric HIV Disease in Zeichner and Read," *Textbook of Pediatric HIV Care* (New York: Cambridge University Press, 2005): 85.
[224] Many of the child welfare paper files use the categories black, white, Hispanic, and Asian to describe children and family characteristics. These categories blend race and ethnicity. Most social scientists today distinguish between race and ethnicity and ask people to describe their identity—an option Vera staff preferred but did not have available. This data comes from the information about race/ethnicity found in the child welfare files for each child.
[225] Changes in the demographics of New York City's children are described in Chapter 3.
[226] The term "children" in this chapter refers to the 493 children where Vera staff had child welfare and medical data, as described in footnote 1.

percent of parents spoke Spanish as their primary language, one percent spoke another language, and for five percent of children reviewers could not determine the primary language in the home. Just over 60 percent of the children were the youngest members in their families. Half of the children came from families with four or more children, and 15 percent came from families with six or more children.

Based on information available in the files, the parents of nine percent of the children were or had been married. Reviewers found paternity established on a birth certificate for about a quarter of the children. They were unable to determine the relationship between the father and the mother at the time of removal for one-third of the children because the father was either unknown or not mentioned in the available files. Narratives note that many of the children had half-brothers and half-sisters.

Many of the families had prior contact with the child welfare system. One-third of the children came from families that had one or more children in foster care at the time of the first removal of the child who participated in clinical trials. Almost half the children (45 percent) came from families where one or more children had been in foster care at some time. Three of every five of the study group children had at least one sibling in foster care or living with someone besides the custodial parent at the time of removal.[227]

Pathways into Foster Care

There are many pathways into foster care.[228] The most common pathway starts with a child welfare investigation prompted by a report of abuse or neglect to the State Central Registry. Anyone can make a report, but certain professionals known as mandated reporters, such as teachers, doctors, nurses, and social workers, are legally required to report whenever they encounter suspected child abuse or neglect. After a report is made, a child protection worker conducts an investigation. If the child protective worker determines that a child is unsafe, the worker may monitor the family, provide support services, or request that the child be removed from the family and placed in foster care.

Child protective workers must have removals and others actions approved by a family court judge. This process involves the child welfare agency filing an abuse/neglect petition that requests the family court to approve the placement of a child in foster care.[229] Parents have the right to attend the court hearing and contest the investigation's findings. Family court judges make decisions about the case, including decisions to place children in foster care for a set time—usually a year during the period studied. Judges frequently approved extensions of placement when the original placement orders expired.

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[227] The statistics in this paragraph exclude families with only one child (5.5 percent) and make other adjustments based on the availability of information located by reviewers.

[228] For a description of the different ways children may enter foster care, see Chapter 6 of Timothy Ross, *Child Welfare: The Challenge of Collaboration* (Washington, DC: Urban Institute Press, 2009).

[229] In New York State, these are called Article 10 petitions, a reference to the social service law that governs abuse and neglect cases. As discussed in Chapter 3, the quality of these assessments and court oversight is a contested issue.

Voluntary placement agreements represent a second pathway into foster care.[230] In some situations, parents approach a child welfare agency and ask that their child be placed in foster care because they can no longer take care of the child themselves. In others, parents sign voluntarily placement agreements after the start of a child protective investigation.[231]

Most of the children (88 percent) entered foster care between 1987 and 1997 and most (87 percent) entered foster care only once. Eleven percent were discharged from foster care and later entered care again. Fifteen children (2.5 percent) entered foster care three times.

Most of the children entered foster care early in life. A little more than 50 percent entered care by age one month, two-thirds entered by age six months, and 74 percent entered before their first birthday. Fifty-three percent entered foster care directly from a hospital at birth.[232] Many of these children were boarder babies, described in Chapters 3 and 4 of this report. Of the children who entered foster from the hospital after birth, 98 percent entered placement by age six months.[233]

Fifty-seven children (12 percent) entered foster care initially through voluntary placements, with 50 voluntary placements taking place in removals from the community, not from the hospital at birth. All of the remaining initial entries into foster care occurred because of allegations of child maltreatment.

As Figure 5.3 shows, most of the children in the Vera review (88 percent) entered foster care between 1987 and 1997. This period corresponds to the increase in the foster care census described in Chapter 3.

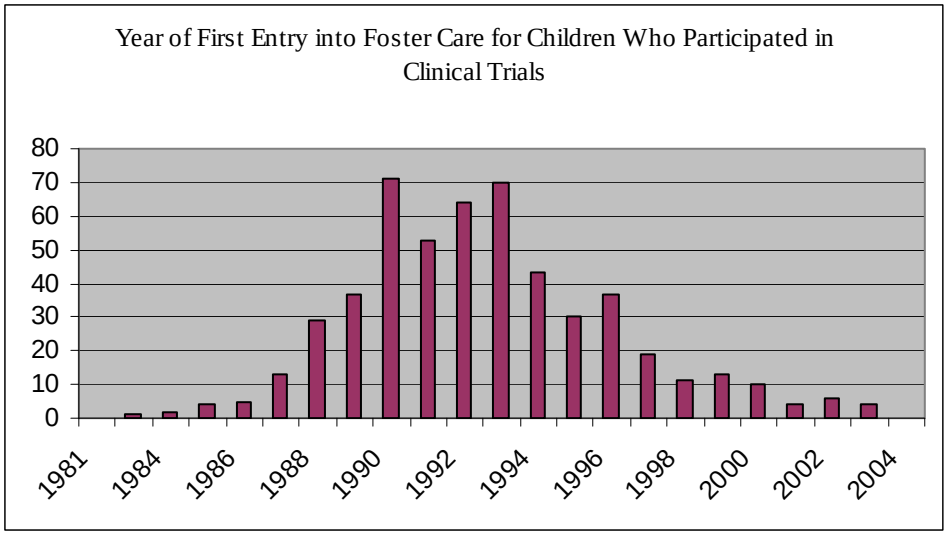
[230] See New York State Social Service Law §358-a.

[231] Some contend that child protective workers pressure parents into signing voluntary placements, arguing that few parents make a truly voluntary decision. Vera reviewers did not find overt evidence of this occurring, but the issue is contentious and has been litigated in some circumstances. For a critical discussion of voluntary placements, see Dorothy Roberts, *Shattered Bonds* (New York: Civitas Books, 2002): 82-7.

[232] Vera reviewers could not determine if a child entered foster care directly from the hospital at birth in 3 percent of the cases.

[233] It was not always possible to determine the exact date of entry into foster care for children who entered care directly from the hospital. In these cases, Vera staff used the date of entry into placement as the date of entry into foster care. It is likely that court proceedings removed the child at an earlier date but that the child remained in the hospital for a longer period for medical reasons or because no placement could be found.

Figure 5.3: Year of Entry into Foster Care



Role of HIV/AIDS in Entry into Foster Care. Every family's situation is unique, yet the files describe many children and their families with combinations of a common set of challenges: unemployment, poverty, drug use and addiction, unstable housing, homelessness, domestic violence, and medical and mental illness. Frequently, families faced two or more of these problems. Although parental HIV infection alone was not reason for removal of a child, the severity of the parents' illness and its impact on their ability to care for a child who also had complex medical problems was often noted in the case files.[234]

Almost all of the child welfare files note the impact of HIV/AIDS on the health and well-being of children and family members. Vera reviewers found documentation in the child welfare files noting that the mothers of more than 90 percent of the children (451 of the 493) were HIV positive. Medical reviewers found only five children for whom mother-to-child transmission was not the route of HIV infection. Thirty-seven of the remaining 42 children were born with HIV antibodies and their mothers were therefore all presumed to be HIV positive, though Children's Services—and in some cases the mothers themselves—may not have known their HIV status.[235]

Vera staff did not collect specific data on how the mothers of children in the Vera review contracted HIV. However, narratives written by Vera reviewers discuss multiple risk factors that are associated with HIV, such as drug use, a drug-injecting partner, multiple sexual partners and blood transfusion. Many mothers had more than one risk factor. Though the files contained less information on fathers, Vera reviewers found notes documenting that the fathers of at least 108 of the children (22 percent) were also HIV positive. The following narrative excerpts describe parental risk factors for HIV infection.

[234] This discussion should not leave the impression that most parents with HIV/AIDS became involved in the child welfare system. Many people agreed to care for the children of a parent who was ill or deceased from HIV/AIDS without contact with the child welfare system. Vera reviewers only examined the files of children that spent time in foster care.

[235] Three children were infected through blood transfusions and two children were infected through sexual contact.

> *According to the history in the case planning records, the mother became infected with HIV after a transfusion. The father is an injection drug user, but says he is negative. The mother has six children and the youngest two are HIV positive.* [236]
>
> *The mother was born in 1966. She had a long history of marijuana, cocaine, and heroin use, and regularly tested positive for cocaine throughout her child's placement in foster care. Case files describe frequent periods of prostitution, when she would disappear for days at a time without informing the baby's father of her whereabouts.*

The stage of parental illness varied. Some were unaware of their status before their child was diagnosed. Others were described as ill with AIDS. The files indicate that at the time of the first removal, mothers of at least 11 children and fathers of 12 children had passed away. By the time the children were discharged from foster care, mothers of at least 165 children and fathers of 67 children had died, primarily of HIV/AIDS.[237]

HIV had implications for other members of the children's families. Of the 493 children described in this chapter, at least 28 percent (138 of the children) had one or more siblings who were HIV positive. As the narrative excerpt below describes, grandparents were often caring for their grandchildren whose parents or other family members had succumbed to AIDS or were unable to care for their children for other reasons.

> *Before the initial removal of the child, the maternal grandmother, the maternal step-grandfather, the child's uncle, and one of the child's siblings died of AIDS-related illnesses. Shortly after the second removal of the child, the child's mother and father died of AIDS (both within a month after the second removal). Surviving family members included the maternal grandfather who resided out of state, a paternal aunt, and the maternal step grandfather's previous wife who still kept in contact with the family.*

Children Entering Foster Care at Birth (Hospital Removals). Child welfare files indicate that 261 of the 493 children (52 percent) entered foster care directly from a hospital at birth. Almost all of these cases were reported to the State Central Registry by the hospital.[238] Almost half (48 percent) of the 261 children had one or more siblings in foster care at the time of removal, and 76

[236] Throughout this report, most identifying details have been removed from narrative excerpts to protect the confidentiality of the children and families in these cases. The names of children, family members, and foster parents are never mentioned in this report. Most other identifying details, such as specific dates, names of hospitals, doctors, social workers, case planners and others have been removed unless there is a specific reason to include them.

[237] Files indicated that the mothers of 112 children died of HIV/AIDS related causes as did the fathers of 21of the children. Thirty parents died of causes unrelated to HIV, including several homicides noted in the narratives. The lack of information on parents—particularly fathers—in many cases suggests that the actual number of parental deaths is higher than the number documented.

[238] In four cases, a social service agency or the police called in a report and in seven cases the child was voluntarily placed. In 21 of these cases, Vera reviewers found notes indicating that the investigation occurred in part because child welfare authorities knew that other children of the mother were in foster care.

percent had siblings living either in foster care or with a relative—not with a parent—at the time of removal. More than four in five of these removals (83 percent) took place between 1987 and 1996.

The child welfare files cited maternal drug use as the most common reason for the child protective investigations that led to newborns being discharged from the hospital into foster care. A report or mention of a positive drug test was found for 196 (75 percent) of the 261 children (see Figure 5.4).[239]

Figure 5.4: Children with reported positive urine toxicology tests

	Reported urine toxicology status			
Urine results	**All children**		**Removed from hospital at birth**	
	No.	**Percent**	**No.**	**Percent**
At least one drug found in urine	**247**	**50.1**	**196**	**75.1**
No documentation of drugs in urine	246	49.9	65	24.9
Total	**493**	100.0	**261**	100.0

Cocaine was the drug most frequently found in newborn urine tests. The types of drugs reported as being present in the babies' urine are reported in Figure 5.5. For 71 of the 196 children (27 percent) with case notes referring to a positive urine toxicology, laboratory test results were found in the child welfare files indicating a positive urine test.

Figure 5.5: Reported Positive Newborn Urine Toxicology

	Reported urine toxicology status on 247 children with at least one substance found in their urine*			
Drug	**All children**		**Removed from hospital at birth**	
	No.*	**Percent***	**No.**	**Percent**
Cocaine	230	46.7	187	71.6
Heroin	13	2.6	12	4.6
Methadone	29	5.9	19	7.3
Other substance	27	5.5	20	7.7

* Does not total 100 percent or 247 children because some children were reported to have more than one drug in their urine..

Case notes saying that the mother had admitted drug use to a member of the hospital staff were found for 173 (66 percent) of the 261 children removed from the hospital at birth. In 48 cases (18 percent), child welfare or hospital staff suspected maternal drug use during pregnancy but the mother did not admit to drug use and the notes did not report a positive drug test.[240] In many

[239] Medical reviewers recorded discussions of a positive urine test-in medical records and in child welfare notes

[240] Hospitals documented maternal drug use as a basis for a report to child welfare authorities in several ways. Sometimes it was determined by a positive blood or urine test for drugs in the mother, sometimes by a positive urine

cases with positive drug tests, the files described siblings who were also born with positive drug tests.

Before 1992 a positive child drug test for cocaine or other illegal drugs was sufficient evidence for filing a neglect petition in family court.[241] A lack of drug treatment programs for pregnant women narrowed the options for the families and child protective workers: a 1990 survey of 78 New York City drug treatment programs found that 54 percent refused to treat pregnant women, 67 percent refused to treat pregnant women on Medicaid, and 87 percent had no services for pregnant women on Medicaid who were addicted to crack or powder cocaine.[242]

Many of the child welfare files indicated that newborns remained in the hospital for medical or social reasons after their mothers were discharged, and either the mother or the father did not visit the child in the hospital. Reviewers used strict criteria to make this assessment: the caseworker notes needed to indicate that a parent did not visit a child even once (for mothers, this referred to the period after the mother was discharged from the hospital). In many cases, a family member visited the infant for some period of time and then stopped.

Figure 5.6 lists the family circumstances that were documented in the child welfare files when the removal occurred. The category "Additional circumstances at removal at birth" includes reports that no provisions had been made for the child, that the parent had no income, and/or that the file notes described a parental history of substance abuse or child maltreatment. The numbers in Figure 5.6 are minimums: some child welfare files were missing, lost, or incomplete, and child protective workers might not have known or recorded this information in every case.

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test in the baby, and sometimes because the mother admitted to a member of the hospital staff that she had used drugs during pregnancy. With cocaine use, a positive maternal urine or blood test indicates cocaine use within 48 hours of the test. A positive urine test for cocaine in a baby indicates that the mother used cocaine within three to five days of delivery. Because the pattern of crack cocaine is generally a period of heavy use ("binging"), followed by a period of abstinence ("crashing"), a mother who is a heavy user can give birth to a baby with a negative urine test. Jane Ellis, et al., "In Utero Exposure to Cocaine: A Review," *Southern Medical Journal* 86, no. 7 (1993): 725-31from: http://www.drugpolicy.org/library/ellis.cfm (accessed October 18, 2008); and T. Adirim, "National Survey of State Maternal and Newborn Drug Testing and Reporting Policies," *Public Health Reports* 106, no. 3 (May-June 1991): 292-96.

[241] As discussed in Chapter 3, the state issued a statement in 1992, saying that positive child drug tests alone were not sufficient to warrant removal. SCR reports from hospitals, even those where a positive drug test is mentioned, did not lead to immediate removal in every case that Vera staff studied for this report. Of the 247 children with positive urine drug tests at birth, 51 were *not* removed directly from the hospital at the time of birth.

[242] See Kathleen B. DeBettencourt, "The Wisdom of Solomon: Cutting the Cord that Harms—Children and Crack Exposure," *Children Today* (July-August 1990).

Figure 5.6: Circumstances at Birth for Hospital Removals

Circumstance	Documented	Percentage of children
Maternal and/or Paternal mental illness	10	3.8
Maternal homelessness	29	11.1
Mother did not visit child in hospital	38	14.6
Father did not visit child in hospital	53	20.3
Additional circumstances at removal at birth	42	16.1

The date of hospital discharge was available for 210 of the 261 children who were discharged from the hospital into foster care at birth. Hospital stays for these children ranged from three to 773 days, with an average of 47 days. The prolonged hospitalizations resulted from a combination of medical and social circumstances, including the difficulty of finding foster parents who were willing to care for an HIV-positive child. This was particularly true for children in the earlier period of this review. The narrative excerpt below describes a common situation for HIV-exposed foster children born in the later 1980s:

> *Two weeks after the neglect petition was filed, the child protective worker substantiated the allegations and the child was remanded to stay in the hospital under the care of the Commissioner. The child was on Social Service Hold for approximately four months.*[243] *During this time, 11 agencies were contacted to locate a placement for the child, without success. Some agencies replied that they had no placements available while others said that the agency was unable to care for a child with HIV/AIDS.*

Often a newborn's medical condition caused a prolonged hospital stay. Many children removed directly from the hospital at birth were born prematurely and had complicated deliveries and medical problems during their first weeks and months of life. As shown in Figure 5.7, 77percent of all children in the Vera review and 94 percent of the children who were removed at birth had at least one medical complication during delivery or immediately after birth.

Figure 5.7: Newborns with Complications at Birth

Newborn complications	All children		Children removed from hospital	
	No.	Percent	No.	Percent
At least one complication	379	76.9	246	94.3
No complications found	114	23.1	15	5.7
Total	**493**	100.0	**261**	100.0

Source: Vera file review

[243] "Social Services Hold" refers to a situation where a child is medically ready to be discharged from the hospital, but the discharge does not occur because there is no placement for the child or because the necessary services for discharge have not yet been set up.

Many babies suffered drug withdrawal symptoms which required medical treatment. Nearly 20 percent of the children were born with congenital syphilis, requiring 10 days in the hospital for treatment with antibiotics. The specific types of newborn complications are listed in Figure 5.8. Many newborns had more than one complication.

Figure 5.8: Newborn Complications in Children in the Vera Review*

Condition	All children (N=493)		Children removed from hospital at birth (N=261)	
	No.	Percent***	No.	Percent****
Preterm birth (<_37 weeks gestation)**	159	32.3	114	43.7
Low birth weight (<_2,500 grams)**	147	29.8	108	41.4
Very low birth weight (< 1,500 grams)	46	9.3	31	11.9
Respiratory Distress	96	19.5	75	28.7
Signs and symptoms of opiate withdrawal	75	15.2	51	19.5
Irritability or Tremors	85	17.2	64	24.5
Fetal Alcohol Syndrome	8	1.6	5	1.9
Jaundice or Hyperbilirubinemia	69	14.0	46	17.6
Congenital Syphilis	98	19.9	77	29.5
Sepsis	39	7.9	30	11.5
Other conditions	182	36.9	133	51.0

Source: Vera file review

* This table reports complications among those children for whom the information was available in the child welfare files. The actual numbers may be higher, as this information was not always recorded in the casework files.

** Medical reviewers also accepted notes in medical summaries or other documents that a baby was premature or had low birth weight.

*** This is the percentage of the 493 children described in this chapter. Percentages total more than 100 because children could have more than one condition.

**** Percentage of the 261 children removed from the hospital at birth.

Child Removals After Initial Discharge from the Hospital. Forty-four percent or 216 of the 493 children described in this chapter were removed from their parents or legal guardians after their initial discharge from the hospital. Of these 216, Vera reviewers found that 50 entered through voluntary placement agreements. Of the 166 remaining children, reviewers recorded allegations of child maltreatment for 140 children and could not determine the reason for entry for the other 26 children.[244]

As Figure 5.9 shows, Vera reviewers found 261 reports made to the State Central Registry at the time of removal that included these 216 children.[245] Medical professionals were the most frequent source of reports that precipitated the removal of these children. Physicians and health care facilities accounted for 102 (39 percent) of these reports. The child welfare files contain several reasons why medical professionals made reports. These include parents not seeking medical care in a consistent manner, delays in seeking medical care for sick children, frequently

[244] This usually occurred because a file was unavailable, because notes on the period when the child was removed were not in a file that was available, or because the file notes did not contain enough information to determine the reason for removal.

[245] The number of reports exceeds the number of children because some children were the subject of multiple reports.

missed medical appointments, missing immunizations, and children with failure to thrive. In some cases, older siblings were removed as a result of an investigation that started with a hospital report indicating that a baby was born with drug exposure.

Social service agencies were the second most frequent reporters.[246] Many of these reporters came into contact with the families because of prior child welfare cases.

Figure 5.9: Source of Reports, Removals from the Community*

Source of report	Number	Percent
Medical facility or physician report	84	32.2
Social Service agency report	36	13.8
Relative or neighbor report	34	13.0
Unable to determine	30	11.5
Other	26	10.0
Hospital report at birth[247]	18	6.9
Police report	14	5.4
Other siblings in placement	7	2.7
School report	6	2.3
Anonymous report	6	2.3
Total Reports (for 216 children)	**261**	100.1**

Source: Vera file review
* These are conservative numbers: the files may not have documented all issues in a removal, some files contained limited information on removals, and some files were unavailable.
** Percentages do not total 100 due to rounding.

Voluntary placements accounted for 50 of the 216 first entries (23 percent) of children removed from the community. Voluntary placements often did not involve formal reports to the State Central Registry, as families or social service providers called the child welfare agency to discuss the possibility of voluntary placements when family members were having difficulty caring for sick children. Half of the voluntarily placed children had a mother experiencing a serious medical illness at the time of removal. In several other cases, the father or relatives signed voluntary placement agreements following the mother's illness, death, or disappearance. The narrative excerpt below is an example of one such case.

> *The father stated that he wants to sign a voluntary agreement because he is overwhelmed by the child's health problems and his own medical needs. The father had felt that he could care for the child with the help of his sister. This arrangement had worked for some time, but notes state that his sister could no longer assist him. The 90 day Uniform Case Report (UCR) says that the father has been ill but able to continue to work full time. The UCR says that the medical recommendation is for the child to be placed at*

[246] Vera staff defined social service agency reporters broadly to include visiting nursing services, home health aids-workers provided to help parents care for children, drug treatment programs, homeless shelters, and other providers of preventive and social services.
[247] In some cases, and investigation started with a report to the SCR at the child's birth, but the removal did not take place until after the child's discharge home.

Incarnation Children's Center. The mother's whereabouts at this time were unknown. A signed and dated Voluntary Placement Agreement from the father is in the files.

Vera reviewer narratives describe several other instances of voluntary placements into Incarnation Children's Center (ICC).[248] In some cases, the placements were for respite care for the parent. In other cases, the child was placed because the parent was ill or about to be hospitalized. Because ICC was a foster care facility, children had to be placed in foster care before they could be admitted. Some of the children were admitted to ICC on a short term basis; others seemed to have had longer stays than their families had anticipated at the time of placement. The following narrative excerpts describe different cases in which a child was voluntarily placed in ICC.

The mother signed a voluntary placement for both the child and his sibling when she was admitted to the hospital for surgery. The child was admitted to ICC on an emergency basis. The child's sister was placed in temporary foster care. Both children were in care for approximately 10 days before being discharged to their mother.

The maternal grandmother voluntarily placed the child at ICC as she herself has had a stroke and is unable to adequately care for the several grandchildren in her care. The other grandchildren, who do not have HIV, were placed with other relatives, while this child entered ICC. However, it became clear that the grandmother did not intend to lose custody of this child, as there were many unhappy discussions between the social worker and family members as they tried to plan for her future after she left ICC.

Several voluntary placements came about through participation in the Early Permanency Planning Program (EPPP), a program started to help parents with AIDS plan for the placement of their children in the event of their death.[249] In some families several people had HIV/AIDS, which diminished their capacity to care for children. Efforts to keep families together were further hampered by the overlap between HIV/AIDS and drug use, especially injection drug use.[250]

Similarly, child protective investigation records frequently described struggles with unemployment, drug use, parental illness, poor housing conditions, homelessness, and housing

[248] As noted in Chapter 1, ICC was a specialized congregate care facility for HIV-exposed and -infected foster children under the age of six years that operated under the auspices of the foster care agency Catholic Home Bureau until 2001. ICC provided services to HIV-infected children whose medical fragility might otherwise require hospitalization.

[249] By 1993, the Pediatric AIDS Unit—description of PAU—reported that EPPP had worked with 57 families with 157 children. At least seven of the children who participated in clinical trials entered foster care through the EPPP. Vera staff reviewed the files of at least seven other children who did not participate in trials who entered foster care through the EPPP. Four foster care agencies piloted the EPPP: Coalition for Hispanic Family Services, Harlem Dowling-Westside Center, Leake and Watts Services, Inc., and St. Vincent's Services.

[250] The connection between drug use and HIV/AIDS is discussed in Chapter 4. Few services existed for families with HIV/AIDS and substance abuse issues during the period studied. An exception is Highbridge Woodycrest, a facility opened in 1991 to provide substance abuse treatment and medical care to families with HIV/AIDS. See http://www.highbridgewoodycrest.org/main.html (accessed September 29, 2008).

instability among families whose children entered foster care after the initial discharge from the hospital. Figure 5.10 shows the parental circumstances in the 166 cases that involved removals from the community because of abuse/neglect charges.[251] Maternal drug use was by far the most common condition, cited in nearly 59 percent of these cases.[252] The lower numbers for fathers reflect the files' lack of information about fathers generally. In 74 percent of the cases, reviewers could not determine whether or not the father lived in the home at the time of the first removal.

Figure 5.10: Documented Circumstances at Time of Involuntary Removal from the Community

Removal issue	Number	Percentage
Maternal drug use	91	54.8
Paternal drug use	28	16.9
Maternal mental illness	15	9.0
Paternal mental illness	3	1.8
Maternal medical illness	23	13.9
Paternal medical illness	10	6.0
Maternal homelessness	23	13.9
Paternal homelessness	4	2.4
Mother incarcerated	3	1.8
Father incarcerated	10	6.0
Death of legal guardian at time of removal	6	3.6

n=166
Source: Vera's file review

Figure 5.11 presents the allegations described in the child welfare files. As with child welfare cases generally, neglect was the most common allegation. Vera reviewers noted neglect allegations for 119 children (77 percent).

Figure 5.11: Allegations for Children Entering Foster Care from the Community

Allegation	Number of allegations
Physical abuse	14
Sexual abuse	4
Neglect	119
Medical neglect	65
Education neglect	8
Total allegations for 140 children	210

Note: Allegations did not match the number of children because some cases involved more than one allegation.

[251] There are important legal differences between voluntary placements and involuntary removals: in cases with voluntary agreements, child welfare lawyers need court approval of the agreement but do not have to bring allegations of abuse or neglect to the court for consideration. This analysis separates children placed through voluntary agreements from those removed because of abuse/neglect petitions (known as Article 10 cases in New York).
[252] Children whose mothers died prior to removal were not counted in this statistic.

Narratives of these cases often described inadequate guardianship, usually related to drug addiction, as the basis for the investigation. A common set of characteristics were seen in many of these narratives: a single mother, unemployed, often sick, living in substandard housing, and using cocaine. Many of the parents had siblings or other family members struggling with similar challenges. Removals frequently took place when the parent left a child or children in the care of a neighbor or family member and did not return until days later, or when neighbors reported that children had been left alone.

> *When [the girl] was almost six years old a staff member from a social service agency made a report to the State Central Registry stating that "child has been found home alone on several occasions. She wanders around barefoot outside alone. There is a lot of broken glass and garbage. Yesterday there was no food in the home." When the mother was interviewed she stated she was in a methadone maintenance program. The father is physically violent with the mother. The child was not placed at this time. Two months later a caseworker, visiting the home, found the child alone, hungry, and naked. She was removed from her mother's home and placed with maternal grandmother.*

Medical neglect allegations were noted in 65 cases (42 percent). In all but 13 of those cases, the child protective case also included allegations of general neglect. In some cases, the files described medical neglect occurring because of problems with substance use.

> *When the boy was five months old, his mother relapsed on cocaine. The baby was seen by a visiting nurse who finds the house dirty and with no food. The baby appeared to have problems breathing and the nurse advised the mother to take him to the hospital, but she did not. The next day the nurse called the State Central Registry and child protective workers took the baby to the hospital. The baby is described as small for his age, has oral candidiasis, has poor head control and is underweight.*

In other cases, the files described medical neglect in the context of a troubled adult relationship.

> *The mother brought her nine-month-old child to the hospital because of a severe rash. Medical notes indicate the child had fever, scabies, severe eczema, and dermatitis, as well as a severe diaper rash. He had not been immunized or received any medical care since his birth. In response to questions about the child's poor health, the mother said that she had not been able to bring him to the hospital because of her abusive husband. The mother told the hospital social worker that another child was still at home. She said that the father physically and sexually abuses her. The notes say the mother had bruises on her arms and legs and describe her as listless and slow. She was six months pregnant at the time.*[253]

[253] During the period studied, child welfare workers, with the approval of family court judges, removed children from the care of battered women for "failure to protect" children in some cases. In response to a class action lawsuit, *Nicholson v. Williams* 344 F.3d 154 (2nd Cir., 2003), a federal judge declared this practice unconstitutional.

Some medical neglect cases involved a caregiver—either a parent, foster parent, or kinship foster parent—who was unwilling or unable to give a child prescribed medicine, including antiretroviral drugs prescribed by a doctor to treat HIV. Some of these cases involved other allegations as well as medical neglect. Others were related primarily to disagreements about the merit of antiretroviral medication. Vera reviewers found examples of children who were removed from a foster home because the foster parent had stopped giving the children antiretroviral medications.

> *During the investigation, the child's caregiver—the child's great aunt—said that she took the children to a homeopath and a nutritionist instead of a medical doctor because she disagreed with the doctor prescribing AZT and other antiretrovirals. She said that she had evidence that these drugs caused death. She described herself as a holistic health educator and believed holistic remedies were a "good practice for all parents instead of constant medication from a bottle." She said that AZT and other antiretrovirals caused AIDS and giving them to children "amounted to genocide." Hospital staff informed the caseworker that the great aunt and the child's doctor had "vast differences in philosophy" in terms of the child's medical care, a statement with which the great aunt agreed.*
>
> *Case planning notes stated that "Presently the maternal aunt/foster mother still refuses to give medication to [the child]. She said AZT is too toxic for the child and will have more damaging effects on him in the long run, she wants child to try a new drug, interferon…."[254] An allegation of medical neglect was made against the maternal aunt. The case was indicated for lack of medical care, but the child was not removed. Five months later, during a home visit, the case worker found 17 bottles of AZT and two bottles of Bactrim that appeared to be unopened. The case was reported to the Office of Confidential Investigations (OCI), which did their own investigation and found the allegations to be true.[255] OCI then approved the removal of the child and his sibling based on medical neglect and lack of supervision.*

In cases where birth parents or foster parents refused to administer FDA approved medications for pediatric HIV/AIDS prescribed by a doctor, New York State policy compelled child welfare staff to make reports of medical neglect to the State Central Register. As one state report noted in discussing grounds for reporting medical neglect for children with HIV, "If a medical professional has prescribed the treatment or care, the caretaker's failure to provide the prescribed care is sufficient to allege a lack of medical care."[256] The same report made specific

[254] Experimental use of interferon outside of clinical trials is discussed in Chapter 8.
[255] The Office of Confidential Investigations was charged with investigating allegations of abuse and neglect by foster parents.
[256] New York Interagency Task Force on HIV/AIDS, *New York Interagency Task Force On HIV/AIDS Service Program And Policy Inventory* (2002): p. 65, available at http://www.health.state.ny.us/diseases/aids/regulations/taskforce/policies.pdf. In addition, a list of frequently asked questions for mandated reporters concerning confidentiality also makes reference to situations like the ones described above: "For example, where a child is HIV positive and medical neglect is alleged based upon the family's

mention of a parent's refusing to consent to the administration of AZT within 48 hours of birth: "If a health care professional suspects that a child's likelihood of being infected with HIV will be decreased by the use of the drug AZT, and the mother is not giving her consent, a report will be registered for medical neglect."[257] As mandated reporters, child welfare and foster care agency staff risked the loss of their jobs—and some staff risked the loss of their professional licenses—if they did not make a report.[258]

Relationship Between Child Removal and Clinical Trials. Refusing to consent to a child's participation in a clinical trial, however, is not grounds for medical neglect. Under state and federal regulations, participating in a clinical trial is voluntary and requires that researchers obtain informed consent. For children to participate, these regulations and child welfare agency policy required researchers to obtain informed consent from the child's parent or guardian.[259] Vera reviewers were instructed to record notes on any child protective investigation that included any mention of a clinical trial during a child's removal.

Reviewers found no children who were removed from families because of a parent's refusal to enroll a child in a clinical trial. There was one case in which a report to the State Central Registry included an allegation that the parents had failed to give prescribed medicine (which was identified by the clinical trial name).[260] The file indicates, however, that the case involved several other allegations of medical neglect, including several missed medical appointments and a missed appointment for an operation. The State Central Registry had received four reports regarding the family in the preceding 18 months for allegations of inadequate guardianship and educational neglect. The child welfare documents indicate that the doctor who filed the report "would still like to have children in placement…Worker told him that we ought to give the family a chance." The children were not removed from the parents at that time. Two months later, another report of medical neglect was made that did not involve clinical trial medications,

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failure to obtain appropriate medical treatment for the child, the child's medical records would be relevant to the report, and would be required to be released." See http://www.ocfs.state.ny.us/main/prevention/faqs_mandatedreporter.asp#hiv (accessed January 19, 2009).

[257] *New York Interagency Task Force on HIV/AIDS*, p. 65.

[258] New York State's definition of medical neglect is similar to some other states. Vera staff found controversies surrounding refusals to administer prescribed antiretroviral medications in other jurisdictions, and debates about parental rights with respect to determining medical care for their children are longstanding. See for example Gretchen M. Roberts, J. Gary Wheeler, Nancy C. Tucker, Chris Hackler, Karen Young, Holly D. Maples, and Toni Darville, "Nonadherence With Pediatric Human Immunodeficiency Virus Therapy as Medical Neglect," *Pediatrics* 114 (2004): e346-e353; David Crowe et al., "Coercive Treatment of HIV-Positive Children Is Not Justified," *Pediatrics* 116, no. 6 (December 2005): 1605-06 (doi:10.1542/peds.2005-0018); and Bourne R. Loving, "Noncompliance: Determining Medical Neglect by Parents of HIV-positive Children," *Journal of Clinical Ethics* 11 (2000): 121–25.

[259] Chapter 6 describes federal regulations pertaining to the participation of children in research and Chapter 7 describes the policies of Children's Services and its predecessors for the participation of foster children in clinical trials.

[260] Failing to administer clinical trial medicine might not be considered grounds for medical neglect, as parents can withdraw their child from a clinical trial.

this time by the family's visiting nurse, and the children were removed. They were returned to their parents' care a year later, and the following year Children's Services closed their case.

In another case, child welfare files reflect concern that the parents of a child in a clinical trial were not adhering to a medication regimen that had begun while the child was in placement at Incarnation Children's Center (ICC). The child had recently been trial discharged back to his parents and had missed a number of medical appointments since the discharge. Doctors at ICC discontinued the child from the trial due to non-adherence after receiving documentation that the child was receiving medical care at another facility closer to the mother's home.

Foster Care Experiences

The preceding sections described the medical and social circumstances in which children entered foster care. This section describes the lives and experiences of children while in foster care and how they were discharged from foster care. It also describes the challenges of finding placements for children with HIV and the challenges faced by caregivers of children with HIV.

On average, the children in the Vera review spent about four years (50 months) in foster care during their first stay. About 13 percent of the children were discharged from foster care and then re-entered care at a later date (see Figure 5.12). Children with shorter first stays were much more likely to re-enter care: more than half of the 51 children who spent less than a year in care during their first stay re-entered care at a later date.

Figure 5.12: Stays in Foster Care

Stays in foster care	Children	Percent
1	414	84.0
2	64	13.0
3	15	3.0
Total	**493**	**100**

Source: Vera file review

Challenges of Finding Placements. Many of the people interviewed for this report described challenges faced by Children's Services and the foster care agencies in finding appropriate placements for children with HIV/AIDS and children who were HIV-exposed (antibody positive and status not yet defined).[261] The child welfare files reviewed by Vera staff mirrored these difficulties. In 1985, New York State approved a "special exceptional" reimbursement rate for caregivers fostering HIV-infected or -exposed children. The enhanced reimbursement rate helped pay for the extra costs associated with caring for an HIV-positive child, such as traveling to and from medical appointments, additional laundry and cleaning supplies, and time receiving training about how to provide specialized care. Because the frequent illnesses of many of the children made holding a job or caring for additional foster children difficult for many caregivers, the

[261] As discussed in Chapter 4, until the mid-1990s, a definitive diagnosis of HIV infection could not be made in infants who were born to HIV-positive mothers until they were 18 months old.

special exceptional rate also helped to recruit foster parents and kin who might not otherwise be able to afford to care for a medically fragile child.[262]

Foster care agencies faced additional challenges in finding placements for HIV-positive and -exposed children. These included overcoming the fear and stigma associated with HIV (particularly in the years when the general public knew little about the virus and transmission), handling confidentiality concerns, finding caregivers who could handle medically fragile children, and placing infants whose HIV status could not yet be defined. Megan McLaughlin, a policy consultant and former director of the Federation of Protestant Welfare Agencies, recalled contending with these challenges.

> *It's our job to take these kids out of the hospitals, but where are we going to put them? Many foster families have other children in them. So are you threatening the health and well-being of other children to place kids there? It sounds now like a way out, but honestly these were some of the issues...[This is the] information all of the folks were trying to get. Nobody had it.*

Confidentiality Issues. Confidentiality concerns created particular challenges when seeking a kinship placement with a family member who was unaware that a mother had HIV. When a parent specifically requested that family members not be informed of the child's status, those family members were no longer considered potential foster parents for the child.[263] Some foster parents assumed care for HIV-positive children without being aware of their HIV status. Usually, this occurred when Children's Services and/or the foster care agency were also unaware of the child's HIV status. In almost every instance where Children's Services was aware of a child's HIV status before placement, the files noted that this information was communicated to foster parents before the child came to their home.[264]

Special Medical and Behavioral Challenges. Foster parents needed special training to take care of children with HIV/AIDS, many of whom had other medical and developmental issues as well (see Figure 5.13). The severity of developmental delays in the children ranged from mild delays

[262] Vera reviewers confirmed that foster parents taking care of the children received the special exceptional rate, though narratives noted occasional problems in making payments in a timely fashion. For a description of the costs of becoming a foster parent for a child with HIV in the late 1980s and early 1990s, see Cristina Palacio and Chris Weedy, "Treatment Issues Regarding Children in Foster Care" in *Pediatric AIDS: The Challenge of HIV Infection in Infants, Children and Adolescents* (Baltimore: Williams and Wilkins, 1991): 569-76.

[263] In one outlying case, this disclosure resulted in the initiation of legal action. The narrative states: "The child's mother told the caseworker at the foster care agency that she was suing the hospital for telling her sister the child's HIV status. The hospital had called the aunt who was listed as a resource after the mother abandoned the child in the hospital."

[264] There were a handful of exceptions, however. In one case, a caseworker informed a foster parent of the child's status a few days after placement. At the foster parent's request, the agency transferred the child to another home. In two cases, foster parents were not informed for a more significant length of time. In both cases, the notes indicate that Children's Services knew the child had tested positive, but the foster care agency had not received this information.

to severely disabled, wheelchair-bound children with cerebral palsy and profound retardation. Thirty children were disabled by cerebral palsy or spastic quadriplegia and required wheelchairs or other special arrangements for transportation as well as extensive therapy. Seventy-five percent had some degree of developmental delay.

Figure 5.13: Medical and Mental Health Problems of Children*

Condition	Children	Percent of children
Failure to thrive	210	42.6
Developmental delay	370	75.1
Asthma or other respiratory problem	165	33.5
Behavioral or psychiatric problem	106	17.9
Cardiovascular problems	43	8.7
Neurological problems	92	18.7
Ear, nose, and throat problems	42	8.5
Eye problems	64	13.0

* Number of children=493. Some children had more than one condition; therefore percentages exceed 100.

The cases presented below illustrate some of the challenges faced by foster parents and foster care agencies in caring for children with multiple medical and behavioral problems.

> *The foster mother reported that he had violent temper tantrums, and had begun to kick and bite the other children in the household…His language remained limited. Although he understood simple commands and could say some words, he communicated mostly using expressive sounds and gestures, and when he was not understood, he became frustrated and was likely to cry, hit, or bite.*

The children in the Vera review were medically complex and most faced social challenges as well. Because of their complex prenatal and newborn circumstances, and without access to medical records, Vera staff found it difficult to determine which problems were related to HIV disease and which problems were in addition to HIV. Vera reviewers noted that 210 children (42.6 percent) suffered from failure to thrive. Failure to thrive means that a baby is not gaining weight, growing in length, or making expected developmental progress. It was seen frequently in HIV-infected children before the use antiretroviral treatment. Failure to thrive is also associated with other medical conditions, including heredity, intrauterine exposure to medications, drugs, and alcohol.[265] Eighty-two children (18 percent) had either a gastric tube or a nasogastric tube placed for a period of time, a procedure sometimes used for children with failure to thrive and children who need more nutrition than they can take in by mouth. Forty children (8 percent) had a permanently placed intravenous catheter that allowed them to receive intravenous fluids and medications directly into the vein. (see Figure 5.14)

[265] E. Abrams and L. Robinson, "Routine Pediatric Care," in *Textbook of Pediatric HIV Care* (New York: Cambridge University Press, 2005).

Figure 5.14 Frequency of Feeding Tubes and Intravenous Catheters

Device	Number of children	Percent of children
Feeding tube for nutritional support	42	8.5
Feeding tube for medication administration	6	1.2
Feeding tube for nutritional support and medication	40	8.1
Central intravenous catheter	40	8.1

Asthma and other chronic respiratory diseases were common. Distinguishing the symptoms of HIV-related lung disease from asthma is difficult. However, 187 children (37.9 percent) were treated with one or more medications for asthma or other respiratory symptoms.

Vera reviewers found documentation of behavioral and/or psychiatric problems in 106 children (21.5 percent). There were 23 children who were admitted to the hospital for psychiatric or behavioral problems. Some children had more than one admission, bringing the total number of psychiatric hospitalizations among children in the Vera review to 56. Fifty-eight children were treated with medications for behavioral or psychiatric problems. Of those children on psychotropic medications, 38 were treated with medications for Attention Deficit Hyperactivity Disorder (ADHD).

Ninety children were noted to have neurological problems and 30 children were treated with medication for neurological problems, most of them for seizures. Forty children were treated with medication for cardiac problems, including irregular heart rhythm and hypertension.

Children in the Vera review were frequently sick from HIV-related complications and often required frequent hospitalizations. Many of the sickest children received care at two congregate care facilities—Incarnation Children's Center and Herbert G. Birch Services. Vera reviewers recorded 1,812 hospitalizations and admissions to long term care, hospice, or other inpatient facilities (excluding Incarnation Children's Center) while in foster care for the 493 children, an average of 3.7 hospital admissions per child. Seventy-nine percent of the children (388) were hospitalized at least once. One child was hospitalized 41 times. The most frequent reasons for hospitalization include pneumonia, fever, HIV-related complications (not-specified), psychiatric and behavioral problems, and failure to thrive.

Children and their caregivers faced other challenges as well. Because the children were often ill, there were frequent doctor's visits, many were prescribed a range of medications, and children with developmental delays frequently received home- or center-based therapy. Although some children in the Vera review were relatively asymptomatic, others had full blown AIDS, and for many children the illness worsened over time.

> *The child had 15 hospitalizations. She had six episodes of pneumonia, two episodes of gastroenteritis, and four episodes of respiratory distress, one of which required admission to the pediatric intensive care unit and intubation. Her other diagnoses included varicella, lymphocytic interstitial pneumonitis (LIP), herpes stomatitis,*

> *candidiasis, recurrent otitis media, hepatosplenomegally, and generalized lymphadenopathy.*[266]
>
> *He is described as often sick and the foster mother feels that he is deteriorating physically and mentally. She reports that he is becoming very frail; he bruises almost every time he falls or bumps into something. He's declining in school. He can no longer write his name or put on his clothes.*

HIV-specialized Placement Programs. Regular foster boarding homes were often not equipped to handle the complex day-to-day tasks of taking care of a child with HIV infection. Caring for children with the medical problems described above required training and support in medication administration, maintaining a safe environment for the immunocompromised child and for the rest of the family, dealing with the behavioral problems frequent in foster children with HIV, maintaining confidentiality, and caring for a dying child.[267]

The foster care agency Leake & Watts Services, Inc. opened the first specialized placement program for HIV-positive children in 1985. By the end of the 1980s, seven foster care agencies operated HIV-specialized placement programs. The additional programs were the Positive Caring Services program at St. Vincent's Services, Catholic Home Bureau's Incarnation Children's Center, Little Flower, SCO Family of Services, New York Foundling, and St. Joseph's.[268] Because New York City's child welfare agency mandated that whenever possible, an HIV-positive child be placed with an agency that offered a specialized HIV program, more than 60 percent of the files that Vera staff reviewed came from these seven agencies.

The programs provided enhanced support to caregivers with a focus on HIV/AIDS, although each offered a different mix of services. These services included home nursing visits and, in some cases, clinics where HIV-positive children could receive routine medical care. The programs also focused on recruiting foster parents willing to take in HIV-positive children and incorporating the specialized training and procedures needed to address medical and developmental issues. In addition, the programs were staffed by social workers, nurses, therapists, and other professionals with specialized training and experience in HIV/AIDS care.

In the late 1980s, city officials at the Human Resources Administration (HRA) decided to establish a unit to provide training to foster parents of HIV-infected children, coordinate HIV

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[266] All of these conditions are associated with HIV infection. Varicella is chicken pox and can cause severe illness in children with HIV. Children with HIV often have difficulty breathing due to inflammation in their lungs known as Lymphocytic Interstitial Pneumonitis (LIP). Herpes stomatitis are sores in the mouth caused by the Herpes virus. These can be quite severe in children with HIV and may cause difficulty in eating and drinking. Frequent middle ear infections (otitis media) occur in many children, but can be more frequent in children with HIV. Children with HIV often have enlarged lymph nodes (generalized lymphadenopathy) and enlarged liver and spleen (hepatosplenomegally).

[267] This description comes from files reviewed by Vera staff, interviews with key respondents, and a program guide from one of the agencies that provided specialized HIV/AIDS placements.

[268] Like many foster care agencies from that era, St. Joseph's no longer provides foster care services. The other six agencies with specialized HIV placements are still open. During the period studied, SCO Family of Services was known as St. Christopher-Ottilie.

testing, and later, to monitor enrollments in clinical trials. In August 1988, the agency created the Pediatric AIDS Unit (PAU) as part of HRA's Special Services for Children (SSC). Because so many HIV-positive children entered care from medical facilities, the PAU began as a subunit of the Hospital Baby Project, an SSC program designated to address the boarder baby crisis. The Medical and Health Research Association (MHRA), a nonprofit research foundation with close ties to city and state government, provided funding and technical support to the unit.[269] The PAU continued to address these issues throughout the various restructurings of the child welfare system and still exists today. Its three main functions during the period Vera staff examined—coordinating the HIV testing of children in foster care, tracking the placement of children with HIV (including the training of foster parents caring for children with HIV), and implementing policy for enrolling and monitoring foster children in HIV/AIDS clinical trials—remain the same.[270] The latter responsibility continues, but to the knowledge of Vera staff, no child in foster care has been enrolled in an HIV/AIDS clinical trial since June 2005.[271]

The children were placed with 51 different agencies. Fifty-six percent of the children were first placed with one of the seven foster care agencies that offered specialized HIV/AIDS foster care and 63 percent spent time at one of these agencies at some point in their stay in foster care. Children were also placed with one of the other 44 foster care agencies that did not have specialized HIV/AIDS programs. Fifteen percent of the children spent time in direct foster care provided by the city's child welfare agency—not a contract foster care agency—and most of these placements were in kinship homes.

Varieties and Frequencies of Placement. Though most of the 493 children were initially placed in family settings, 16 percent were initially placed at Incarnation Children's Center (ICC), which specialized in providing foster care to boarder babies. Many of the placements at ICC were short: if a child's health stabilized, the child welfare agency sought to place the child in a kinship or foster boarding home. Sixty-five percent of children in the Vera review were initially placed in a foster boarding home and 16 percent first entered a kinship placement.[272] Twenty-three percent of the children spent some time at ICC.[273]

The children experienced an average of 3.1 placements while in foster care. Because children were sometimes transferred back to a previous placement, however, the average number of

[269] According to its web site, www.healthsolutions.org, the mission of MHRA (now known as Public Health Solutions) is "to facilitate the creation and administration of research projects and provide greater flexibility to seek new funding resources for research that would inform the work of the New York City Department of Health and Mental Hygiene (DOHMH) and other New York City organizations." The Commissioner of DOHMH, the City Medical Examiner and the CEO of the Health and Hospitals Corporation are ex-officio members.
[270] See PAU quarterly reports, 1992-2005.
[271] Vera staff are not aware of enrollments in clinical trials unrelated to HIV/AIDS, but have not examined that issue.
[272] The remaining three percent were initially placed in other congregate care settings.
[273] These statistics come from the CCRS and refer to children spending time living at ICC. ICC also provided some outpatient medical services to HIV-infected and -exposed foster children. The facility provided services to children regardless of whether they participated in clinical trials.

unique placements was lower—2.5 placements per child.[274] Eighty-one percent of the children, experienced three or fewer unique placements. For children in care during the 1980s and 1990s, having three or fewer placements was considered stable. One in six children experienced four to six placements during their stay in foster care. Three percent experienced more than six unique placements.

While some children were placed with only one or two foster families, and were adopted by their foster parents, other children were in much less stable arrangements. The first narrative excerpt below describes a child who was in three different foster homes before the age of two; the second describes a child who was adopted by his first foster mother.

> *This baby boy was born 12 weeks prematurely in the late nineteen eighties, and remained in the hospital for close to two months before being discharged to a foster boarding home. A PAU tracking form indicates that he first tested positive for HIV at 11 months of age. Around the time he was tested, he was removed from the house of his first foster mother because he had fallen and broken his arm. After an investigation, allegations against the foster mother were deemed unfounded; however, she requested that he be moved, saying that she experienced too much pressure as a foster parent.*
>
> *Although he was in good health except for swollen glands, his second set of foster parents requested he be moved from their house because of the risk of exposure; had he not been HIV positive the foster parents were hoping to adopt him. He moved to a different foster home at the age of two. His new foster mother had experience caring for HIV-infected children and had another HIV-positive foster child in her home. According to his new foster mother, he "weighed 17 pounds and was extremely thin." His skin was scaly and he would often scratch himself to the point of skin irritation.*
>
> *When he was two and a half years old, his mother told a case worker at the agency she "could not plan for the child." The permanency planning goal was changed to adoption and his mother voluntarily surrendered her parental rights. The following year his foster mother decided she did not want to adopt him and agency workers looked for another foster family, with no success. Six months later, the foster mother changed her mind, and adopted him just prior to his fifth birthday.*

> *Throughout his time in foster care, this child remained with the same foster family, where he was placed at three months of age. According to case notes, the child's HIV status did not become known until he was two years old. An agency progress note from 1990 states that "FM [foster mother] is denying the illness, but that [nurse] talks to FM constantly regarding HIV and AIDS. Nurse said family is very supportive—FM's two children are very involved and there is always someone in the hospital with FC [foster child]." Although the foster mother initially did have issues with dealing with the child's illness, she took an active role in planning for his medical care. Doctors and agency workers talked with the foster mother before enrolling him in any clinical trials.*

[274] These numbers are from the CCRS. In two of the 494 cases, CCRS had no movements for the children and they were excluded from this analysis. These numbers slightly underestimate the number of placements, as Vera reviewers reported that CCRS did not capture every placement transfer. Child welfare policy calls for minimizing the number of placements that a child experiences, as transfers are often traumatic.

> *In 1991, parental rights were terminated on the grounds of abandonment and he was adopted six months later. A UCR before the adoption states that "regardless of FC's marginal health condition, [FM] and her grown children remain enthusiastic about adopting [FC]. [FC] has become an essential part of the family and the grown children are involved in supervising, helping develop his socialization skills and to monitor his health care under [FM's] management."*

Changes in placement were usually due to many of the social and medical complexities inherent in caring for an HIV-positive foster child. Many changes in placement were made to keep children with their siblings or members of their extended family, or to comply with parents' wishes for who should care for their child. In other cases, changes occurred in the foster family (e.g., foster parent sickness or death, or a return to work) that made foster parents doubt their ability to take care of the child.

Vera reviewers found few details of placement changes that occurred because of abuse or neglect within the foster home, though some changes in placements appeared to occur due to child maltreatment while in foster care. In some instances, investigations by the Office of Confidential Investigations (OCI) were mentioned but the results were not described. In other situations, a child was placed in a new foster home shortly after the mention of a safety incident in the case notes, but there are no references to an OCI investigation or other explanation for the move. Given the paucity of information on these circumstances, other than to say that these instances appeared infrequently, Vera staff could not produce reliable numbers on how often child maltreatment occurred in foster care.

Reviewers noted that although few of the children in the Vera review remained in foster care past age 10, adolescence was often a difficult time for those that did. Some adolescents experienced frequent changes in placement and placement into congregate care facilities. Some refused to take antiretroviral medications and also engaged in risky sexual behavior.[275]

> *By the time she was an adolescent, the child's mother, father, and sister had died. The caseworker notes comment that she had not finished grieving the loss of her sister when her father, with whom she was very close, passed away…When her grandmother—who had been her former kinship foster mother—died, problems in her foster home escalated to the point that the foster parents asked for her to be transferred. She was hospitalized at a psychiatric institution where she was diagnosed with depression, and she continued to not comply with prescriptions for HIV medications. Upon discharge from the hospital, she was placed in a different foster home. At age 16 and still in foster care, she refused to take medication or go to school.*

[275] These behavior problems in adolescents with perinatally acquired HIV infection have been described in medical and other publications. Commentary on this can be found in S. Nicholas, and E. Abrams, "Boarder Babies with AIDS in Harlem: Lessons in Applied Public Health," *American Journal of Public Health* 92, no. 2 (Feb 2002): 163-65.

Cases like these represent a small number of children in the Vera review. Most children had relatively few placements. A significant number either returned to their families or were adopted after one or two unique placements.

Permanency Planning Goals. When a child enters foster care, case workers establish a Permanency Planning Goal (PPG), a plan for his or her discharge. Examples of PPGs include "return to parent," "return to guardian," "adoption," and "independent living." The PPG affects how case workers plan for a child. For example, a PPG that changes from "return to parent" to "adoption" indicates that case workers no longer believe that a child can be returned home safely and will look for a pre-adoptive placement if the child's current caregiver will not consider adoption. Changes in PPGs can occur for many reasons, including a parent's death or chronic illness, refusal to comply with a service plan—especially a drug treatment plan, or consistently missing meetings with case workers. Vera reviewers attempted to collect information on PPG changes. As files did not consistently document reasons for PPG changes, however, these efforts were often unsuccessful. Data on PPG changes has therefore not been included in this report.

Parents, Caseworkers, and Foster Parents. Reviewers recorded a spectrum of relationships that developed between parents, caseworkers, and foster parents. In many cases, caseworkers and parents met with initial mutual distrust. These relationships seemed to shift over time, often mediated by the skills and stability of the caseworker and other child welfare staff, parents' health and drug involvement, and the health of the child.

Many narratives described parents struggling with addiction. Some parents entered drug treatment programs before and after the removal of their children. Others were referred for treatment but did not attend. In many cases, Vera reviewers noted patterns of abstinence and relapse as well as periods of health and illness that correlated with the frequency of visits with children in foster care and contact with the foster care agency. During healthy, drug-free periods, many parents maintained regular contact with the agency and had visits with their children. In some cases, parents took steps to prepare for their children's return, such as finding housing and taking parenting classes.

> *Around the child's second birthday, many things began to change. After having received only positive reports of her progress in treatment and the optimism of her counselor that she would soon live a drug-free life and be able to care for her son, the mother got in a fight with two other residents at her drug treatment program and was offered an ultimatum: either she accepted a more restrictive program or she would have to leave. She left, losing contact with the agency for about three months. When she contacted the agency again, her visits with her child became sporadic. The mother's parental rights were terminated; by that time she had been out of contact with the agency for more than six months.*

Consistent with studies of the relationships between parents and child welfare case workers, the casework notes also described the relationship between parents and foster care agencies as infused with both subtle and overt conflicts.[276] Below are two examples.

> *The caseworker noted that, although the mother had "attempted to impress upon worker her desire to have her children returned, she was resistant to some of the worker's suggestions." She resisted supervised agency visits as opposed to visiting her children in her mother's home. She was also opposed to engaging in discussions about treatment for drug abuse or mental health issues.*

The notes described some situations where the parents doubted caseworkers' commitment to helping families reunite:

> *[A]Uniform Case Review in 1992 says that the "Natural parents have been seen frequently at agency, along with older siblings as they frequently visit the children here and continuously request their return home." The document goes on to say that there is "very strong family bonding among the siblings, as well as between parents and children. The mother is the more reliable parent and appears to be in charge. She has frail health but will fight for her children and her rights. She becomes very emotional and distraught at the prospect of the two younger children remaining in foster care. She feels that the New York 'system' is trying to destroy her family."*

In other situations, the notes suggested that parents and caseworkers formed relationships in which caseworkers provided practical support to parents planning for their children, emotional support in dealing with the issues in their lives, and referrals for medical care and other services. With few exceptions, the file information indicated that parents who visited consistently and completed court-mandated services received caseworkers' support for the return of children to their custody. The families in the Vera review, however, are distinguished from other accounts of families with children in foster care by the deteriorating health of the parents and children. Often, particularly in the early years of HIV when few treatment options existed for adults or children, parents' attempts to reunite their families were hampered by their own deteriorating health or by their child's complex medical needs.

> *The parents tried for years to get their daughter back. They were successful at securing good housing and passing clean urine tests, but the child remained in foster care. Social workers had concerns about the parents' serious illnesses, and doubted the parents' capacity to care for the child. The child stayed at ICC for 11 months before she was healthy enough to be placed with a foster parent. During this period she was hospitalized several times for failure to thrive and pulmonary infections. Both parents were HIV positive and had tuberculosis. The mother missed many visits due to repeated hospitalizations. She died when the child was three years old.*

[276] For a discussion of common conflicts between case workers and parents, see Dorothy Roberts, *Shattered Bonds: The Color of Child Welfare* (New York: Basic Books, 2002).

Many files showed caseworkers who were unable to engage parents in efforts to plan for their child. Other's showed parents engaged in planning for their child temporarily, for a few weeks or months after placement. Case notes often cited relapse into drug use, incarceration, or worsening illness as reasons why planning stopped. In some cases, the notes indicated that parents had extended hospitalizations for months at a time; others did not want their children to see them looking ill. Some parents stated explicitly that they would not visit the child because they knew they could not care for the child's needs and seeing the child would only be a reminder of loss. Often, the circumstances of parents' lives presented multiple obstacles to being able to plan or care for their children. The following example documents a home visit to a mother described as not keeping appointments to see her child.

> *The mother states that she wants to plan for her kids but it is impossible, as her boyfriend beats her whenever she tries to leave the house. She still has no public assistance budget. She lost her public assistance because she missed her "face to face" while she was in the hospital. Caseworker and supervisor tell her that [subway] tokens and lunch will be provided if she attends her next meeting at the agency.*

A child's illness often led to improvements in relationships among parents, caseworkers, and foster parents. The files document a pattern in which tense relationships became communicative and supportive when children's health began to decline. Particularly near the end of the child's life, adults often came together to make important decisions about the child's care and to be with the child at this difficult time.

> *The foster parents and biological parents met with doctors and shared concerns regarding the child's treatment, especially near the end of the child's life…The parents regularly met with child's doctors and discussed treatment options …The child died in the foster home with the foster parents, birth parents, and the agency staff at his bedside.*

Pathways Out of Foster Care

Almost all of the children in the Vera review have been discharged from foster care. Figure 5.15 shows the different ways they left foster care (showing first, second, third, and final discharges). The majority of children left care through adoptions. A smaller percentage left foster care because they died or were returned to a parent or other family member. Together, these reasons account for 94 percent of all discharges.

Figure 5.15: Discharges from Foster Care

Discharge reason	Discharge				
	1st	2nd	3rd	Final discharge	Percentage of final discharge
Adoption†	297	23	3	321	65.1
Death‡	73	4	1	78	15.8
Return to birth parent	69	15	1	42	8.5
Release to relative	25	2	1	15	3.0
Other*	12	3	0	7	1.4
Still in care/discharge reason missing**	17	12	1	30	6.1
Total discharges* **	**493**	**59**	**7**	**493**	**99.9**** **

Source: Child Care Review Service, December 30, 2006

† Though subsidized and unsubsidized adoptions are recorded separately in administrative record, this table combines the two categories because all but three of the 323 adoptions were subsidized adoptions.

‡ Eighty children died in the Vera review died while in foster care. Seventy-eight of these children were in the group of 493 described in this chapter. The additional two children are described later in other sections of this report.

* Other category includes discharges to own responsibility, release to a resource person, end of court ordered services, and running away from foster care.

** Children in this category are either still in care or the entry indicating that they were discharged from foster care was not entered into the Child Care Review Service database. In two instances, the CCRS did not have any entries for children in foster care.

*** Out of the 493 children, 434 children were only discharged once (2nd and 3rd discharge reason are not applicable). Fifty two children were discharged twice (3rd removal not applicable) and only seven children were discharged three times.

**** Percentages do not total 100 due to rounding.

The majority of discharged children (60 percent) left foster care through adoption after a single stay in foster care. Ninety-four children (19 percent) left care to live with their birth parent or a relative after their first stay in foster care. Fifty-one of those 94 children re-entered foster care at a later date. Of those 51 children, 16 (31 percent) were discharged to a parent or relative after their second stay in care.[277]

Seventy-eight children (15.8 percent) of the 493 children described in this chapter died while in foster care. Two additional children out of the entire sample of 532 children also died—both had been enrolled in an observational research studies only trial. Twenty-five children died while they were enrolled in clinical trials of medications for treating HIV/AIDS. The Vera review did not identify any child who died as a direct result of participation in clinical trials. The circumstances of these 25 deaths are discussed in detail in Chapter 9, which discusses children's experiences in clinical trials. Deaths of children and end of life issues are discussed later in this chapter.

Before a child in foster care can be adopted, a court must rule that the child is "legally free" for adoption. For a child to be legally free for adoption means that the birth parent's parental rights have been severed—this is also known as a Termination of Parental Rights (TPR). Parents

[277] The information in this paragraph comes from the CCRS. This data is current through 2006. Fewer than 25 children were still in foster care while Vera staff conducted this review.

may lose their rights when the foster care agency petitions the family court to terminate parental rights—often after periods without contact between parents and the foster care agency.[278] Parents have the right to contest these terminations and the judge decides the issue. Also, parents may surrender their rights. Parents may surrender their rights for many reasons: to facilitate an adoption in a way that may allow them some contact with the child after adoption, to avoid a court hearing they feel they will lose, or to end contact with the child welfare system. Reviewer narratives indicate that in many cases, ill-health of the parents played a role in their decision to surrender their parental rights. In some cases, children became legally free for adoption because both parents died.

In cases in which parental rights were severed, the city's child welfare agency became the child's legal guardian.[279] Child welfare procedures for terminating parental rights resulted in a status called joint guardianship, in which a contract foster care agency assumed increased decision-making powers, including the right to proceed with an adoption and the right to approve medical care. As discussed in Chapter 7, this policy allowed contract foster care agencies to approve clinical trial enrollments in some cases.

Figure 5.16 shows the different ways that children in the study population were freed for adoption.

Figure 5.16: Mechanism for Freeing Child for Adoption[280]

	Mother	**Father**
Mechanism	**Number**	**Number**
Termination of parental rights (TPR)	188	162
Voluntary surrender	58	21
Death of parent	84	38
Unable to determine	45	69
Missing	1	89
Total	376	379

Source: Vera file review

[278] In cases in which the biological parents' whereabouts were unknown, the contract foster care agencies seeking termination were required to conduct a "diligent search" to locate and inform them of the hearing. Parents whose rights are at issue are entitled to be notified of the hearing, if possible, and to an opportunity to tell the judge why termination should not occur. Vera staff found evidence of these searches in many cases. Many advocates for parents, however, contend that the searches often overlook opportunities to contact parents, especially fathers.

[279] The law concerning ending parental rights is complex and has changed over time. New York State Social Service Law §§384-b; 358-a(3)(b) explains the current law. The federal Adoption and Safe Families Act of 1997 mandated termination of parental rights if a child spent 15 or any 22 month period in foster care with some exceptions. Prior to ASFA, there were no time limits for TPRs.

[280] The number of TPRs in this table does not equal the number of TPRs in the table on mechanism for adoption because for some children only one parent's rights were terminated and in some cases the child was not adopted. Some children became legally free through more than one mechanism. For example, some agencies petitioned the family court to terminate parental rights (TPR) even though a parent was deceased. In some cases, the agency petitioned the family court for a TPR on more than one father where paternity was not firmly established.

Vera reviewers found termination of parental rights hearings to be the most frequent mechanism for freeing children for adoption, although death and voluntary surrenders were also common. Vera reviewers could not determine the method by which a father's rights were terminated for 158 children, either because of a missing file or more often because the available files did not provide enough information. For 72 (15 percent) of the 493 children, the father's name is never mentioned in the files and the notes say that the father is unknown.

Figure 5.17 shows that child welfare officials terminated the parental rights of 188 mothers and 168 fathers. It also shows that the mothers of 80 children and the fathers of 81 children could not be located at the time of the TPR. Vera reviewers found documentation of a diligent search for the mothers of 57 children and the fathers of 52 children. Search documentation often included copies of letters to numerous institutions, such as the armed forces, corrections agencies, and psychiatric facilities. Vera reviewers noted, however, that in some cases searches were conducted in which the parent's name was misspelled, which may have made the search ineffective.

Figure 5.17: Circumstances at TPR
(Some parents had more than one circumstance)

Circumstance	Mother	Father
Total terminations of parent rights (TPR)	188	168
Unable to locate parent for TPR	80	81
Unable to locate, documentation of diligent search	57	52
Parent incarcerated at TPR	6	10
Parent mentally ill at time of TPR	8	1
Parent refuses to plan at time of TPR	38	27
Not in contact with agency at TPR	123	126
Not in contact with child at TPR	135	132
Parent medically ill at time of TPR	12	6

Source: Vera file review

Voluntary Surrender of Parental Rights and HIV/AIDS. Parental rights often ended due to death or a voluntary surrender by a dying parent. The following case illustrates the context in which voluntary surrenders of parental rights often occurred.

> *The children's mother, who is described as being very ill and emaciated, told the foster care agency director that she wanted to see her children, but did not want her children to see her in her present condition. The mother died of AIDS in the following year. Five months after the mother's death, the father voluntarily surrendered his parental rights. He stated that he was only willing to surrender his rights if the children were adopted by his mother, with whom they were placed. The court informed the father that conditional surrenders are not allowed, but that his mother says she wants to adopt the children and there are no plans to re-place the children. Several months later, the paternal*

grandmother adopted the two living children. The younger of the two died several months after the adoption, of AIDS-related kidney failure.

Establishing a date when parental rights were terminated is critical in determining who had the authority to give consent for the child's enrollment in a clinical trial. In some cases—primarily those with one or more types of files missing—Vera reviewers could determine neither the mechanism used to free the child nor the date the child was freed, and therefore could not determine if policy for consent to clinical trial enrollment had been followed. Child welfare files frequently list different dates for when a TPR was filed, when a judge approved the TPR, the judge's order for the TPR, and the legally freed date. Although in most cases these dates were similar, they occasionally differed enough to raise concerns about which date ended a parent's right to participate in medical decision making.

As discussed in detail in Chapter 7, before a TPR occurs, policy and regulations provide for a parental role in medical decision making, including decisions regarding enrollment in clinical trials. For 70 percent of children in the Vera review for whom a TPR occurred, however, files indicated that the parents were not in contact with the contract foster care agency at the time of the TPR. Without contact, meetings between a parent and agency staff, clinical research staff, or child welfare staff to discuss a clinical trial were difficult to arrange.

Circumstances at Adoption. Many of the adoptions described in this chapter were kinship adoptions that involved the voluntary surrender of parental rights by parents who, because of their child's medical problems and medical problems of their own, wanted their children adopted within the family.

At the age of two, the child was moved to a new foster boarding home because his foster mother had become ill and needed hospitalization. The new foster mother was also interested in adopting the child. The following year, the mother's parental rights were terminated and the agency began to explore the possibility that a maternal aunt who lived in another state could be a permanent resource for the child. A year later, agency notes document that the aunt traveled to New York to visit the child on a biweekly basis. The aunt states that she wants to adopt to maintain family ties and because she reared the sibling of this child. The child also would occasionally visit the aunt at her home. Later in the year, the child was placed with the aunt as a kinship pre-adoptive placement. The adoption was finalized in the following year.

Because many children with HIV—particularly those who were medically fragile or severely disabled—were difficult to place, they were often placed with foster parents who may not otherwise have been considered as adoptive resources. Some foster parents were older and/or of a different race or ethnic group than the child they cared for. Others initially resisted adopting a child who they believed would die, but changed their minds. Others decided to adopt out of attachment to the child and concern for the child's health, even though this had not been their original intent.

> *When the child was almost three years old, the agency requested permission from Children's Services for HIV testing because of failure to thrive and generalized lymphadenopathy. When [the child] tested positive, the agency had to transfer the child and her sibling to another foster home because the first foster mother had not listed her home as being available to HIV-positive children. After an initial emergency placement, the child and her sibling were placed in the foster boarding home that would eventually become their adoptive home. There seems to have been many attempts at locating suitable adoptive parents for the two children, but unfortunately all these leads fell through for various reasons: inappropriate match for family, inability to handle sibling's behavior, and the child's HIV status among them. The last foster parents stepped forward, even though initially they did not want to adopt children. The reason for the change in intent was that they had grown attached to him and worried that the child might become ill due to all the stress and interactions associated with the search for an adoptive family.*

Many of the narratives describe a strong bond between the children and their foster parents. There were many examples of terminally ill children who died at home with their foster parents, and of foster parents who worked closely with the child's biological family to provide care and comfort to the child at the end of his or her life. Vera reviewers found several cases where the foster parents pressed for adoption of their terminally ill foster child to meet the child's wishes, sometimes succeeding only a few days before the child died.

> *Around the time that her adoption was supposed to be finalized, her health had deteriorated, requiring her hospitalization. The court would not finalize the adoption without her physical presence in court, even after her doctor wrote a letter pleading with the court on her behalf… The child was discharged from the hospital and her adoption by her foster mother was finalized in court a week later. A death certificate in the file for this child indicates that she died a month later.*

Health Status and Medical Care of Children in Vera's Review

This chapter has described how children came into foster care, their foster care experiences, and how they left foster care. The remainder of the chapter describes the medical issues and the health status of the children by discussing HIV Diagnosis and Testing, Medical Care of Children in the Vera Review, and Death of Children and End of Life Issues.

HIV Diagnosis and Testing. For every HIV test result found in a child's file, Vera medical reviewers noted the type of test (antibody, PCR, viral culture), the date of the test, and the source of the information (laboratory report, physician or nurse's note, child welfare case worker note, or PAU recording form). Dates when the child was first noted to have an AIDS-defining diagnosis were recorded as well. This information was then used to determine the date that the

child met the 1994 surveillance definition for HIV infection or for seroreversion.[281] As Figure 5.18 shows, Vera medical reviewers were able to document that 418 children in the review met the surveillance definition for HIV-infection and 54 children seroreverted. There was insufficient information in the files to confirm the diagnosis in 21 children.[282]

Figure 5.18: HIV Status of Children in Vera's Review

HIV status	Number	Percentage
HIV infected	418	84.8
HIV exposed/Seroreverted	54	10.9
Unable to determine	21	4.3
Total	**493**	**100.0**

The age at which the child was diagnosed as HIV positive was calculated using the child's birth date, and the date of the HIV test or AIDS-defining diagnosis on which the definition of HIV infection was met. Vera reviewers also recorded the reason for HIV testing. Children were tested because they were symptomatic, they had siblings known to be HIV positive, or their mother was known to be HIV positive or at high risk for HIV.

> *Children's Services became involved with the family again when the child was hospitalized for pneumonia in 1987. The mother told the doctor that she had used intravenous drugs and alcohol during the pregnancy and that she was still using drugs, had active tuberculosis and was not taking her medication. A medical discharge summary states that "[the child] was found to have failure to thrive, generalized lymphadenopathy, a grade 1/6 [heart] murmur, an irregular heart rate and signs of pneumonia…HIV antibody was positive by ELISA and a confirmation test (Western Blot)."* [283]

Earlier testing and diagnosis became widespread in the mid-1990s due to more accurate testing techniques and more rigorous testing requirements. In 1993 Children's Services implemented a policy requiring that children entering foster care be screened within 30 days of entering care to determine if there was a need for HIV testing. In 1997 New York State implemented mandatory

[281] Centers for Disease Control, "1994 Revised Classification System for Human Immunodeficiency Virus Infection in Children Less than 13 Years of Age," *Morbidity and Mortality Weekly Report* 43, no. RR-12 (September 30, 1994). This is discussed in greater detail in Chapter 4.

[282] Vera medical reviewers did not count a child as HIV positive unless he or she met the CDC criteria (see Appendix 7). In many cases for which there was insufficient information to meet all criteria, the reviewers found other evidence that convinced them that the child was HIV positive. For example, a child for whom only one PCR test result was found and no antibody tests were found, whose mother was known to be HIV positive, and who had an enlarged liver and spleen, is very likely to be HIV positive. Nevertheless, the child does not meet the CDC criteria and so would be counted as unable to determine.

[283] Tuberculosis is a disease frequently experienced by people with HIV/AIDS. See Chapter 4 for an explanation of HIV testing methods.

screening of all newborns.[284] As Figure 5.19 shows, most of the children were found to have been tested because their mothers were known to be HIV positive or at high risk for HIV. As reflected in Figure 5.19 and in the narrative above, many children were tested for more than one reason.

Figure 5.19: Reasons for HIV Testing of Children*

Reason for HIV testing	Children	Percentage of children
Mother HIV infected	172	34.9
Mother high risk for HIV	115	23.3
Child symptomatic for HIV	162	32.9
Child with positive toxicology or withdrawal symptoms	92	18.7
Sibling HIV infected	37	7.5
Foster care placement screen	45	9.1
Cannot determine from records	129	26.2
Other	32	6.5

* Number of children=493. More than one reason listed for some children.

Impact of HIV Testing and Diagnosis. As discussed earlier in this chapter, Children's Services was aware of the HIV status of most children at the time they were placed, and agency policy was to make foster parents aware of the diagnosis and provide them with training and increased support. Foster parents were aware that HIV infection in babies who were HIV antibody positive at birth could not be determined definitively until the child was 18 months.[285] There were, however, cases in which the child was diagnosed after being placed. This news was often devastating to the foster parents. Some continued to care for the child after the diagnosis and went on to adopt the child, as noted in previous narratives and in the following case.

> *Even though the foster mother cared a great deal for the child, she did not know the child's HIV status at the time of placement. She reported that, had she known, she never would have accepted the placement. She felt that she was placed at risk. Even so, the foster mother was interested in adopting. When the foster mother passed away from cancer a few years later, the agency considered removing the child and transferring her to a new home. The foster father and his biological daughter decided that the child was a part of the family and they could not stand to have her removed.*

[284] See Bulletin, dated September 13, 1993, from Robert L. Little to All Staff, Child Welfare Administration, Executive Directors, Voluntary Child Care Agencies, Pediatric AIDS Unit Liaisons, Voluntary Child Care Agencies, re: Bulletin: HIV Testing of Children in Foster Care No 93-2; D. Abramson, "Appendix L: Passing the Test: New York's Newborn HIV Testing Policy, 1987-1997," in M. Toto, D. Almario, and C. McCormick, *Reducing the Odds: Preventing Perinatal Transmission of HIV in the United States,* http://books.nap.edu/openbook.php?record_id=6307&page=313 (accessed January 7, 2009).

[285] This changed in the mid-1990s with the advent of direct viral testing. This is discussed in detail in Chapter 4.

Some requested that children be removed from their homes after the diagnosis; this occurred in kinship and non-kinship foster homes and for the children resulted in separation from caregivers and siblings.

> *Both parents were incarcerated and the baby's sisters were placed with relatives. Case file notes say "relatives are unwilling to care for [the child]." Notes further state that sibling separation was indicated since, "child coming into foster care because he was born positive to HIV: his relatives are not interested because child is HIV positive."*

Medical Care of Children in Vera's Review. As will be discussed in Chapter 7, child welfare policy required that all children who were HIV positive or HIV exposed receive care at a health facility that specialized in HIV care. Physicians who were engaged during this period described to Vera interviewers the challenges and rewards that doctors, nurses, social workers, and other hospital staff encountered in caring for children afflicted with this new and poorly understood illness. In addition to treatment, research, ethical, and public health difficulties, there were also many emotional challenges. The children were often extremely ill and spent long periods of time in the hospital. Caring for a child with HIV, especially a foster child, involved ongoing and complex relationships with biological parents and extended family, foster parents, and staff from social service agencies and the city's child welfare agency. Particularly in the early years of pediatric HIV there was relatively little to offer in the way of treatment. Dr. Hermann Mendez, a pediatrician at Kings County Medical Center, recalled the impact of combination therapy, which became available in the mid-1990s.

> *I [have a] vivid memory of participating in a conference with a mother about her dying child, her choosing the dress …to use to bury her, because she was seven years old, she weighed only 19 pounds. [She was] completely wasted. We were going to bury her in her first communion dress. And that kid's still alive today, because as soon as we knew in 1996 that there was HAART [Highly-active antiretroviral treatment] therapy—and that it was working for the adult patients…we extended the benefit to the kids. And we told the mother, "Listen, this [has] never been used. The kid may grow a horn on the side, we don't know, but we have nothing to lose."*[286]

Many of the pediatricians who cared for the children in the Vera review were also clinical trials researchers. Vera medical reviewers noted that most children received care from the same physician while they were enrolled in a clinical trial and while they received treatment with antiretroviral medications and prophylaxis against opportunistic infections outside of a clinical trial.

Vera medical reviewers noted the names of each antiretroviral medication that a child was taking outside of a clinical trial. This information was found in parts of medical records

[286] This quote refers to the use "off label" use of protease inhibitors in children, during the period when they had been approved for adult use but not yet approved for use in children.

contained in child welfare files and in nursing and progress notes made by agency staff. As described in Chapter 2, the amount of information available for each child varied greatly. Therefore the information that follows represents a minimum rather than a comprehensive report on treatment outside clinical trials.

The Vera review found that 299 children (60.6 percent) received treatment with antiretroviral therapy during periods when they were not enrolled in clinical trials.[287] All of the children (100 percent) who received antiretroviral treatment outside of a clinical trial were treated with AZT and/or another medication in the NRTI class.[288] Fifty-two children (17.3 percent) received NNRTIs, 106 (35.4 percent) received protease inhibitors, and one child was treated with the newest type of antiretroviral medication—a fusion inhibitor.

Eight-one of the 493 children described in this chapter were enrolled in observational studies only. Thirty-two of those children (39.5 percent) were HIV positive. Twenty-five of the 32 HIV-positive children in observational trials were treated with antiretroviral medications outside of a clinical trial.[289]

Children in the Vera review received treatment to prevent bacterial infections and to prevent Pneumocystis carinii pneumonia (PCP), a frequent cause of death among children with HIV. Three hundred and fifty five children (72 percent) received prophylaxis with trimethoprim-sulfamethoxazole (also known as Bactrim or Septra), Dapsone, or Pentamidine to prevent PCP.[290] Monthly infusions of intravenous immunoglobulin (IVIG) were given to 98 children (19.9 percent) to provide protection against bacterial infection. Sixty-one children were treated with medication to either treat or prevent tuberculosis or infection with mycobacterium intracellularae avium (MAI), an organism that affects people in the very late stages of AIDS.

Some of the advocates concerned about the participation of foster children in clinical trials have raised questions about the use of nasogastric and gastric tubes.[291] Vera reviewers found that 88 children had nasogastric tubes or gastric tubes. The tubes were used for both nutritional

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[287] This information was not available for all children. The numbers presented here represent a minimum number of children who received antiretroviral treatment outside a clinical trial. Some child welfare files had detailed medications lists while others did not. Children who were in observational research studies and seroreverted would not have been treated with antiretrovirals. Some children were adopted while still enrolled in a clinical trial and Vera reviewers would not be able to determine what treatment they received after the clinical trial ended.

[288] A full discussion of the types of medications used to treat pediatric HIV/AIDS can be found in Chapter 4. Additional information on the treatment of children with pediatric HIV/AIDS can be found in [288] S. Zeichner and J. Read, *Textbook of Pediatric HIV Care* (New York: Cambridge University Press, 2005); and Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection*, February 28, 2008, from http://AIDSinfo.nih.gov (accessed January 9, 2009).

[289] Since children were enrolled in observational trials at birth, it was expected that approximately two-thirds of them would not be HIV-infected. The decision to start antiretroviral treatment in an HIV-positive child depends on the child's clinical status and immune system.

[290] Dapsone and Pentamidine are used for prevention of PCP in people with HIV who are allergic to trimethoprim-sulfamethoxazole.

[291] Both nasogastric and gastric tubes are used to feed or give medication to adults and children who are unable to consume adequate amounts of liquid or food. Nasogastric tubes are inserted through the nose and passed down the esophagus into the stomach. Gastric tubes (G-tubes) are used for longer periods of time and are inserted surgically through the abdominal wall into the stomach.

support and medication. Figure 5.14 describes the number and percentages of tube placements. Edward Handelsman, a pediatrician and clinical trials researcher, discussed the use of feeding tubes during an interview with Vera staff. Handelsman noted that the use of feeding tubes is often part of the medical care of sick children with HIV.

> *And although it's not a pleasant thing, you know, the reality is that we do have lots of kids, whether they're foster kids or non-foster kids, whether they've got HIV or diabetes or whatever, [and they] get things against their personal will. A three-year-old isn't able to say "I don't want that vaccination…"*

Many of the children with feeding tubes were medically fragile children who were living at ICC. These children had more advanced disease, as less medically fragile children were unlikely to be admitted to ICC. Mimi Pasqual, a former child care worker, described some of the difficulties that feeding tubes presented for the children and child care staff at ICC, noting that the children disliked the tubes, and that avoiding having a tube placed was sometimes used to encourage the children to take their medication.

The use of feeding tubes and intravenous catheters are not without risks and complications. The Vera review found that there were 12 hospital admissions to treat complications arising from gastric tubes and 13 hospital admissions to treat complications from the presence of a catheter.

Death of Children and End of Life Issues. Eighty children of the 532 children in the Vera review died while in foster care. Out of respect for all children, this section will discuss all 80 deaths, rather than the 78 deaths that occurred among the 493 children. As illustrated in Figures 5.20 and 5.21, the majority of deaths (85 percent) occurred between 1990 and 1995, prior to the use of combinations of different classes of antiretroviral drugs including protease inhibitors to treat HIV infection.[292] In addition to a decrease in the number of deaths after 1995, the median age of death increased by two years.

Figure 5.20: Deaths of Children by Year

	532 children		**493 children**	
	Number of children	**Percentage of children**	**Number of children**	**Percentage of children**
Number of deaths	80	15.0	78	15.8
Number of deaths before 1996	68	85.0*	66	84.6*
Number of deaths after 1996	12	15.0	12	14.2

* Percentage of children who died, not percentage of all children.

[292] See Chapter 4 for a description of protease inhibitors and other antiretroviral medications used to treat HIV/AIDS.

Figure 5.21 Average Age of Death for Children in the Vera Review

	532 children	**493 children**
Mean age of death (in years)	4.9	5.0
Range (in years)	0.39-17.1	0.36-17.1
Mean age of death before 1996	4.7	4.8
Mean age of death after 1996	6.3	6.3

At the request of Vera staff, Children's Services requested data from the New York City Department of Health and Mental Hygiene's HIV/AIDS Reporting System (HARS) to determine how many children in the Vera review are alive today.[293] This data is presented in Figure 5.22. Of the 799 children whose files Children's Services asked Vera staff to review, 531 matched with children known to be HIV positive in New York City.[294] The mortality rate among children in the Vera review (29.4 percent have died according to the DOHMH information) is lower than that of all children with HIV in New York City born during the same period (35.2 percent of whom have died).[295] Though not conclusive, this comparison is an indication that children did not appear to have been at increased risk for death by participating in HIV/AIDS clinical trials while in foster care.[296] As demonstrated in the two graphs in Figure 5.22, the distribution of the children reviewed by Vera (graph on the left) is similar to the distribution of all children in New York City with HIV. Births of children in both groups increased steadily until 1990 and then began to decline. Children born in the mid-1990s were almost all still alive as of 2004 in contrast to children born in the earlier years of HIV

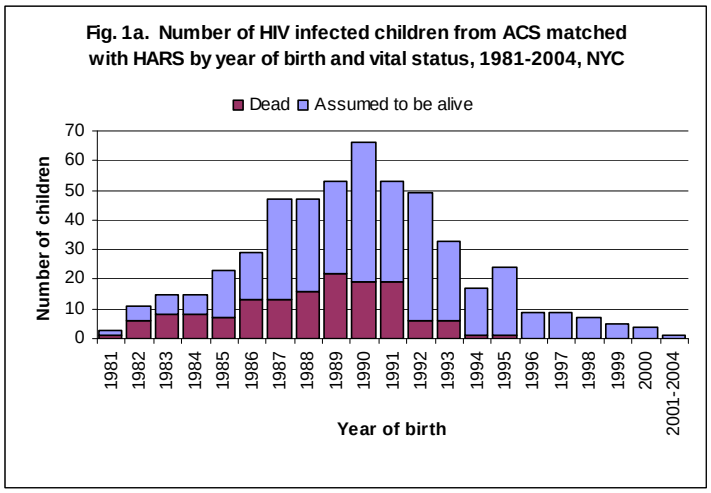
[293] The New York City Department of Health and Mental Hygiene (DOHMH) collects data on the numbers of people in New York City with HIV infection and with AIDS. This surveillance data allows the city to track the epidemic and plan for preventive and treatment services. The DOHMH data includes deaths of children born with HIV in New York City who moved out of state and subsequently died.

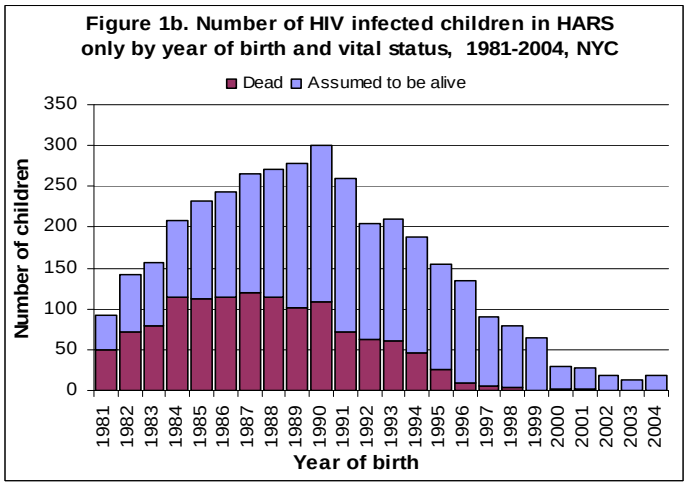
[294] Because many of the children whose files Vera reviewed seroreverted and thus were not HIV infected, it is expected that not all of the 796 names on the Vera review list would be found in the New York City surveillance data.

[295] Data provided by New York City Department of Health and Mental Hygiene.

[296] Some might argue that this data supports the position that children in foster care *benefited* from clinical trial participation. While that conclusion *might* be true, Vera staff cannot draw that conclusion on this data alone due to methodological weaknesses in the comparison. Citing confidentiality laws, DOHMH provided aggregate numbers, not individual data. Vera staff could not determine if all of the 531 children identified by DOHMH as HIV positive were the same children that participated in the clinical trials that Vera reviewers identified. The health status at the time of entry into foster care and into clinical trials of the DOHMH group cannot be determined, and the samples were not precisely matched by birth year.

Figure 5.22





The causes of death among children in the Vera review include AIDS encephalopathy, bacterial pneumonia, PCP pneumonia, wasting syndrome, MAI infection, lymphoma, kidney failure, and liver failure.[297] Many of the children who died were extremely ill in their last year of life, with frequent and prolonged hospitalizations, and with severe limitations on their ability to carry out normal activities.

> *After the first removal, the child was admitted to the hospital for six months in 1989. He was re-admitted one month later and remained hospitalized for another five months. His diagnoses were pulmonary tuberculosis, chronic diarrhea, failure to thrive, developmental delay, transfusion-dependent anemia, chronic fevers, bleeding anal fissure, thrombocytopenia, and sepsis. He underwent several medical procedures including bronchoscopy, placement of a catheter, anal dilation, and excision of fissure. Approximately a year and a half later, he was taken by ambulance to the hospital because he was experiencing respiratory distress. He died the following day.*

Caring for terminally ill children presented medical, ethical, legal, and emotional challenges for medical and child welfare professionals and for foster and biological families.[298] There were many complicated decisions to be made, often in short time periods. These decisions included when to stop treatment, when and how to put a do not resuscitate (DNR) order into effect and give only palliative care, and when to discharge a child from the hospital if the child or a caregiver felt strongly that a terminally ill child should die at home.

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[297] MAI is Mycobacterium Avium Intracellularae, a bacterium similar to tuberculosis. It is an opportunistic infection that occurs in people with end stage AIDS.

[298] For a discussion of the experiences of doctors who treated primarily adult patients with HIV/AIDS, see Ronald Bayer and Gerald M. Oppenheimer, *AIDS Doctors: Voices from the Epidemic: An Oral History* (New York: Oxford University Press, 2000). For a discussion of issues faced by children and families, see Nancy Boyd-Franklin, Gloria L. Steiner, and Mary G. Boland, eds., *Children, Families, and HIV/AIDS: Psychosocial and Therapeutic Issues*. (New York: The Guilford Press, 1995).

Vera reviewers saw many examples of severely ill children for whom DNR orders were considered or obtained. For some children it was because caregivers and doctors felt that there was no further benefit to treatment and that resuscitation would only increase the child's suffering.

> *When she was almost 12 years old a physician writes Children's Services describing her condition. The physician stated that she had "AIDS encephalopathy, is in pain, and is being fed with a nasogastric tube. She is blind and is unaware of her surroundings. Her condition is irreversible with a poor prognosis. Resuscitation would impose an extraordinary burden on the patient in light of her medical condition and the expected outcome. After consulting with the foster care agency, the foster family and our medical staff, we are requesting permission to institute a DNR order."*

For other children, seeking a DNR order and the decision to provide only palliative care was done to honor the wishes of a terminally ill child to die at home, among family members.

> *She had frequent hospital admissions for fever and for transfusions and two episodes of Pneumocystis carinii pneumonia (PCP). The first episode of PCP was complicated by severe Stevens-Johnson Syndrome due to an allergy to Bactrim.*[299] *In 1991 she was admitted to the hospital with pancytopenia. Her condition deteriorated despite multiple transfusions and courses of broad spectrum antibiotics. A bone marrow aspirate finally grew out MAI [Mycobacterium avium intracellularae]. The physicians wanted to aggressively treat the MAI; the foster care agency staff felt that the child was terminally ill and that the child's stated wish to die at home should be respected. Consent for palliative care only and for hospital discharge was obtained from the father who was incarcerated. The child died at home attended by the foster mother, members of her biological family, and the agency nursing staff.*
>
> *The hospital discharged the child home because "child was asking to see siblings all the time, and nothing was being done for him medically in the hospital." He was on AZT, then on ddI and Bactrim. He was diagnosed as having "wasting syndrome." The child died four days later, at the age of four.*

Vera reviewers found documentation of the involvement of parents and other family members in end-of-life decisions and that parental consent was sought before a DNR order could be instituted. Where parents or family members were not in agreement with a DNR, their wishes were respected. There were many instances in which a foster care agency staff member made sure that a parent knew that their child was dying, arranged for the parent to be able to visit with the child, and arranged for the parent to be present at a funeral. Foster care agency staff provided grief counseling to parents and foster parents.

[299] Stevens-Johnson Syndrome is a severe allergic reaction to medications, and may be initiated by many medications including the antibiotic trimethoprim-sulfamethoxazole (Bactrim or Septra). Two children in the Vera review experienced Stevens Johnson Syndrome. Neither case occurred during a clinical trial.

Conclusion

This chapter described the lives of New York City children who participated in clinical trials while in foster care. It described complex relationships among parents and families, foster families, foster care agencies, child welfare staff, and medical providers. The children whose lives (and deaths) are described in this chapter were born exposed to or infected with HIV, into families that suffered from poverty, unemployment, unstable housing, substance abuse, and illness. Their experiences were also shaped by the stigma and fear attached to being HIV positive during much of this period.

The child welfare system faced many challenges in responding to the needs of these children and their families. Special foster care programs were established, foster parents were recruited and trained, the Pediatric AIDS Unit was established to track HIV testing and treatment of foster children, and relationships were developed between child welfare providers and medical providers. In this context, some physicians recommended participation in clinical trials. The following chapter discusses the federal regulations that apply to the enrollment of children in clinical trials.

Chapter 6: The Federal Research Regulations

Chapter Summary

Federal regulations contain specific measures to protect people who participate in research studies. The regulations provide additional protections for children and "wards of the state" by limiting the types of research in which they can participate and by requiring that an independent advocate be assigned to monitor a foster child's participation in some types of trials. Concerns about protections for children in research increased in the early part of this decade after federal laws were enacted that encouraged increased clinical trials participation by children and a Congressional report found that knowledge of the regulations was inconsistent.

Several factors specific to pediatric HIV/AIDS clinical trials made implementing these regulations challenging. These included researchers' and officials' inexperience with these specific regulations, the nature of pediatric HIV/AIDS, and a history of low levels of trust between researchers and communities with high rates of pediatric HIV/AIDS.

An investigation of Columbia University Medical Center by the Office for Human Research Protections (OHRP), a federal agency responsible for enforcing federal research regulations, found that Columbia's Institutional Review Board failed to approve some pediatric HIV/AIDS clinical trials under specific categories as mandated by the federal regulations. OHRP also found that the IRB did not obtain sufficient information regarding the selection of foster children as participants in some HIV/AIDS clinical trials as federal regulations required. The investigation did not substantiate other allegations made to OHRP. Investigations by OHRP of similar complaints at 19 other medical centers in New York City and across the country came to similar conclusions. At each of these sites, OHRP approved corrective action plans aimed at preventing future violations.

Introduction

This chapter describes the federal regulations that apply to foster children who participate in research.[300] It begins with a discussion about the treatment of research subjects, in the United States and internationally, which exposed the need for regulation. Next, it discusses challenges faced in applying these regulations to foster children in New York City who were considered for participation in pediatric HIV/AIDS clinical trials. The chapter concludes with a case study based on the federal Office for Human Research Protections' investigation between 2004 and 2006 of HIV/AIDS clinical trials conducted by Columbia University Medical Center.

[300] These regulations, which can be found online at http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm, and in Appendix 8 are quite technical. As our aim is to describe them in accessible language, most of the references to regulation text appear here in footnotes.

Background: Why Government Regulates Research

Prior to World War II, few standards, regulations, or codes had been developed to address research involving human subjects.[301] The Nuremberg Code, written in response to revelations of Nazi experiments, represented the first international standard for research ethics involving human participants.[302] Rules and ethical guidelines in the United States developed slowly—despite concerns raised by some doctors and government officials. The Tuskegee syphilis study of the early 1970s received the most public attention, but several other controversial studies also helped to raise the profile of the issue (see Appendix 1 for a brief history of medical research with vulnerable populations).[303]

In 1974 the passage of the National Research Act (Public Law 93-348) led to the creation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The commission, which was charged with identifying basic ethical principles to guide research involving people, issued a number of reports over several years, including reports on research involving fetuses, prisoners, and children.[304] In 1981 the Food and Drug Administration (FDA) and the Department of Health, Education, and Welfare, (HEW, now the Department of Health and Human Services) released regulations governing people's participation in research. These regulations, commonly referred to as "45 CFR 46 Subpart A" (CFR stands for Code of Federal Regulations), provided basic protections for research participants and harmonized most of the differences in protections between the FDA and HEW. Subpart A, however, did not include special protections for *children* involved in research. In 1983, six years after the commission published a report titled *Research Involving Children*, the U.S. Department of

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[301] This section relies primarily on Marilyn Field and Richard Berman, eds. *Ethical Conduct of Clinical Research Involving Children* (Washington, DC: The National Academies Press: 2004): pages 44-57, which provides a discussion of the development of research ethics related to adults and children.

[302] Regulations and rules often refer to people involved in research as "human subjects" or "research participants." For a discussion of the development of the Nuremberg Code, see George, J. Annas and Michael A. Grodin, eds., *The Nazi Doctors and the Nuremberg Code: Human Rights in Human Experimentation* (New York: Oxford University Press, 1992).

[303] Many cite a 1966 article by Dr. Henry K. Beecher, which documented 22 examples of research that endangered "the health and life of their subjects without informing them of the risk" as heightening the awareness of research ethics issues. See Henry K. Beecher, "Ethics and Clinical Research," *New England Journal of Medicine* 274 (1966): 1354-1360. In the Tuskegee study, doctors in the U.S. Public Health Service withheld treatment from a group of African American men enrolled in a study of syphilis for decades after the discovery of a cure for the disease. See James Jones, *Bad Blood: The Tuskegee Syphilis Experiment* (New York: Free Press, 1993); Susan M. Reverby, ed., *Tuskegee's Truths: Rethinking the Tuskegee Syphilis Study*. Chapel Hill: University of North Carolina Press, 2000. Other research in the 1950s and 1960s that created public concern includes a study that involved intentionally infecting children who were developmentally delayed with hepatitis at the Willowbrook Institution in New York State, dozens of studies involving inmates at Holmesberg prison near Philadelphia, and the testing of the birth control pill on Puerto Rican women. See Saul Krugman, "The Willowbrook Hepatitis Studies Revisited: Ethical Aspects," *Reviews of Infectious Diseases* 8 no. 1 (January/February 1986): 157-162; see also Allen Hornblume,, *Acres of Skin: Human Experiments at Holmesburg Prison* (New York: Routledge Press, 1999).

[304] *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, issued in 1979, is the most often cited of the National Commission's work. The federal Department of Health, Education, and Welfare (predecessor to the Department of Health and Human Services) adopted much of the report for its policy on research ethics. See http://www.hhs.gov/ohrp/human subjects/guidance/belmont.htm, last accessed August 20, 2007.

Health and Human Services (DHHS) issued regulations regarding the participation of children in research.[305] Specifically, 45 CFR Subpart D of the DHHS regulations that pertain to people participating in research apply to children.[306] These regulations remained unchanged throughout the period this report examined and applied to all of the clinical trials discussed in this report.[307] The FDA, however, did not issue regulations pertaining to children until 2001.

Regulations for Enrolling Foster Children in Clinical Trials

Research is likely to involve an element of risk for participants. Ethical standards therefore require that potential participants be well informed of these risks before they consent to participate. As they may be developmentally incapable of understanding complex medical issues and dependent upon adults—usually parents—for making legal decisions, children require special attention in this regard. Concerns about the capacity of parents and local and state government to make decisions for foster children make them an especially vulnerable subgroup of children. The following sections describe regulations and procedures that have been developed to protect human subjects, and especially children and those in foster care.

Institutional Review Boards and Approving Research. The federal regulations require most research involving human participants to be reviewed and approved by an institutional review board (IRB).[308] An IRB typically comprises at least five people of diverse backgrounds and expertise who ensure that the research procedures (often called "protocols") comply with the federal regulations.[309] The IRB may approve a research protocol, ask for changes in the way proposed research will be conducted, or disapprove a research protocol.[310]

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[305] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *Report and Recommendations: Research Involving Children* (Washington, DC: US Government Printing Office, 1977).
[306] Formally, the regulations are Code of Federal Regulations, Title 45-Public Welfare, Department of Human Services, Part 46, Protection of Human Subjects, Subpart D. See Appendix 8.
[307] The regulations define research as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge." See 45 CFR 46.102(d). A person participating in research—whom the regulations refer to as a human subject—is "a living individual about whom an investigator (whether professional or student) conducting research obtains (1) Data through intervention or interaction with the individual, or (2) Identifiable private information." See 45 CFR 46.102 (f). These broad definitions mean that all the clinical trials we reviewed are considered research, and each foster child who participated in one of these trials did so as a research subject. These regulations apply to research funded by the Department of Health and Human Services, which includes the National Institutes of Health and the Centers for Disease Control (see 45 CFR 46.101), and to research directly supervised by the federal government as well. Today, the Food and Drug Administration (FDA) also regulates the participation of children in clinical trials, but the FDA regulations did not apply to children during the time the clinical trials this report examines took place. The FDA regulations are at 21 CFR 50 and are similar to 45 CFR 46. See United States Food and Drug Administration, *Comparison of FDA and HHS Human Subjects Protection Regulations*, last accessed on August 29, 2007 at http://www.fda.gov/oc/gcp/comparison.html.
[308] The regulations require that research be reviewed by an IRB. The regulations say nothing about the IRB being certified. Though that IRB does not have to be at the institution that conducts the research, the institutions that conducted the clinical trials that are the subject of this report each had their own IRB(s).
[309] 45 CFR 46.101(a) 2 requires IRB review. 45 CFR 46.107 contains rules for IRB membership.
[310] See 45 CFR 46.109(a).

An IRB must make a series of determinations to approve a research project, including research that involves foster children.[311] In general, it must find that the possible participants are well informed about the study procedures and the expected risks and anticipated benefits. It must find that the risks to potential participants are minimal and reasonable compared to the anticipated benefits. It must find that researchers recruit people fairly—for example, that the research does not inappropriately target a particular group, especially when the research includes children, prisoners, or other vulnerable populations. Sometimes an IRB will decide that a study requires a data and safety monitoring plan to ensure that it remains safe for participants.[312] Many of the trials discussed in this report included data safety monitoring boards that tracked adverse events experienced by participants.[313]

The IRB must also find that researchers will seek and document informed consent from the people who participate in the research or permission from a legally authorized representative or guardian in research involving children.[314] Without a proper informed consent process, researchers are prohibited from enrolling a person in a research study that requires IRB approval.[315] The information that must be disclosed as part of the consent process is spelled out in the regulations. A partial list of the information that must be discussed with potential participants (or their parents or guardian in the case of research involving children) includes:[316]

- why and how the research will be conducted;
- the risks, benefits, and discomforts of the research;
- alternatives to research participation;
- how confidential information will be protected;
- compensation for participation, if any; and
- who participants can contact about their rights and any problems people encounter as research subjects.

Consent documents—to be signed by the participant or his or her authorized representative—must contain a statement that "participation is voluntary, refusal to participate will involve no

[311] See 45 CFR 46.111(a).
[312] See section 6 in 45 CFR 46.111(a).
[313] Chapter 8 discusses the role of data safety monitoring boards in some of the clinical trials examined in this report.
[314] See 45 CFR 46.111(a) sections 4 and 5. In some cases, researchers may ask the IRB for a waiver of informed consent. To our knowledge, researchers did not seek waivers of informed consent in any of the clinical trials examined in this report. 45 CFR 46.116 (c) and (d) describe situations in which the IRB may waive informed consent. In general, a waiver of consent is allowed only when the study creates minimal risk and the waiver will not alter the welfare of the participants. In studies conducted as part of an FDA approval process, FDA regulations do not allow for waivers of informed consent.
[315] See 45 CFR 46.116(a): "Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative."
[316] The elements of consent are listed at 45 CFR 46.116 (a) 1-8. Additional elements of consent, such as the conditions when a researcher may end someone's participation in a study, additional costs, consequences of withdrawal, and the number of people in the study are listed in 45 CFR 46.116 (b) 1-6.

penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled."[317]

In essence, the regulations attempt to ensure that *before* a study begins, researchers and another group—the IRB— have satisfactorily addressed the ethical issues of involving people in research. As one bioethicist opined before the regulations were instituted, "If a study is unethical to start with, it does not become ethical because it produces useful results."[318]

Special Protections for Children. The federal rules contain additional regulations that apply to research involving children, including foster children.[319] All studies require a parent or guardian to provide permission (the corollary of informed consent for children) for a child to participate.[320] The regulations define a guardian as "an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care."[321] This definition differs from the common understanding of "legal guardian," a term that usually refers to a court-appointed guardian, "a person or an agency to whom the court gives authority to take responsibility for the care of a child."[322] In some circumstances, including some situations in

[317] The quoted material is from 45 CFR 46.116 (a) 8.

[318] Henry K. Beecher, "Research and the Individual," as quoted in Field and Berman," *Ethical Conduct of Clinical Research Involving Children* (Washington, DC: The National Academies Press, 2004).

[319] Subpart D (45 CFR 46.402(a)) defines children as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted." Children in New York, with some limited exceptions that do not apply to the foster children who were enrolled in clinical trials, cannot consent to treatments or procedures until they are 18 years old. Virtually all of the children in New York City foster care who participated in HIV/AIDS clinical trials between 1988 and 2001 were under 18 years old, meaning that the regulations in Subpart D applied to those studies. The regulations contain two other subparts that apply to groups that face obstacles in asserting their rights as research subjects. 45 CFR 46 Subpart B contains regulations related to pregnant women, human fetuses and newborns, and Subpart C contains regulations related to prisoners. FDA regulations also include the same rules at 21 CFR 50 Subpart D. To comply with the Children's Health Act of 2000, the FDA adopted Subpart D, excluding 46.408(c) as an interim rule on April 24, 2001. See *Biotechnology Law Report* 20 no. 5 (October 1, 2001): 714-716.

[320] 45 CFR 46.408 notes that the waivers of informed consent discussed in 45 CFR 46.116 apply to parental permissions in research with children. To our knowledge, researchers did not ask for waivers of parental permission in the clinical trials examined in this report. In addition to obtaining the appropriate consent/permission from a parent or guardian, the researchers must seek the child's assent, or agreement, if the child is capable of providing it. The IRB must make sure that appropriate procedures are in place for soliciting assent. In virtually all of the enrollments examined in this report, researchers did not obtain assent because the children who participated in the trials were too young to understand or suffered from developmental delays or educational deficits (see Chapter 10).

[321] The definition for assent refers to 45 CFR 46.402(e).

[322] The definition of guardianship is for "guardianship of a person" and can be found at http://www.nycourts.gov/courts/nyc/family/faqs_guardianship.shtml. New York State statutes give several types of courts—surrogate court, supreme court, county court, and family court—the authority to appoint several types of guardians; the situation which creates the need for a court-appointed guardian determines which court has authority. In New York, Section 1013(a) of the Family Court Act gives the family court jurisdiction over proceedings alleging abuse or neglect. For cases involving abuse or neglect (and any other cases in family court), Sections 661-664 of the Family Court Act grant family court judges the authority to appoint guardians. See also Surrogate's Court Procedure Act Article 17. Child welfare policy documents defined guardian as "a person who has been given letters of guardianship for a child by a court of law." See New York City Child Welfare Administration Procedure No. 94 "Medical Consents for Children in Foster Care," March 15, 1994, p. 2.

New York during the time this report examines, the commissioner of social services had the right to consent to general medical care on behalf of a child in foster care though the child was in the "care and custody" not the "care and guardianship" of the commissioner.[323]

The regulations require the IRB to categorize a study involving children into one of four types described in Figure 6.1. The first category, studies that involve no more than minimal risk, are commonly referred to as "404 studies" (each of the four categories is typically referred to by the last three digits in the citation, which in this case is 45 CFR 46.404).[324] Minimal risk is often understood as the risk incurred during the course of a routine medical check-up and includes blood draws, telling researchers about psychosocial histories, and other routine testing.[325] Some studies involve more than minimal risk. For studies that involve greater than minimal risk but that also offer the prospect of direct benefit to children ("405 studies"), an IRB must determine that the anticipated benefits outweigh the risks and that these risks and benefits are at least as favorable to participants as alternative approaches to treating a condition.

To approve studies that involve more than minimal risk with no prospect of direct benefit ("406 studies"), the IRB must find that the research represents "only a minor increment over minimal risk," that the research involves procedures similar to those the child regularly experiences, and that the study will produce important knowledge about the participant's condition. Studies that do not fall into any of these three categories are "407 studies" that undergo a special process that requires the additional approval of the Secretary of Health and Human Services. Prior to 2001, very few studies sought approval through this process.[326] To Vera researchers' knowledge, none of the trials discussed in this report were approved as 407 studies. Both 406 and 407 studies require researchers to obtain permission from both parents "unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child."[327] In most of the families described in the child welfare files that Vera staff reviewed, only one parent, usually the mother, had care and custody of the child prior to the child's entry into foster care.

Regulations for Children in Foster Care. The regulations in 45 CFR 46.409 apply to "wards of the state." Children in foster care are one category of these wards.[328] The regulations in their entirety are:

[323] The legal basis for the commissioner to consent is discussed in Chapter 7.
[324] See 45 CFR 46.404.
[325] The regulatory definition is "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." See 45 CFR 46.102(h)(i).
[326] See Allen Fleischman and Lauren Collogan, "Research with Children" in *The Oxford Textbook of Clinical Research Ethics*, edited by Ezekiel Emanuel, Christine Grady, Robert Crouch, Reidar Lie, Franklin Miller, and David Wendler (New York: Oxford University Press, 2008): p. 453.
[327] The quote is from 45 CFR 46.408(c).
[328] Wards of the state include other groups as well, such as children living in psychiatric facilities and homes for the developmentally delayed and youth in juvenile placement or incarcerated in corrections facilities.

> §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.

The special protections for foster children—including appointment of independent advocates—apply only to 406 and 407 studies (and not to 404 or 405 studies).

The regulation for wards of the state adds two additional protections for foster children in 406 and 407 studies. First, the regulation places limits on the types of studies in which foster children may participate. Research specifically about foster children is allowed, but as far as Vera researchers know, none of the clinical trials examined in this report focused exclusively on foster children; each study was open to children regardless of their foster care status. The regulation prohibits studies conducted in places where the majority of children in the study are in foster care, unless the research is exclusively about foster children. Concern about compliance with this regulation helped lead to the OHRP investigation of Columbia University Medical Center, which is described later in this chapter.

The second additional protection afforded by the regulations is that when an IRB approves a 406 or 407 study that may involve children in foster care, the IRB must appoint someone who is independent of the study, the researchers, and the "guardian organization" to look out for the child's best interests. For foster children, the guardian organization refers to the child welfare agency and contract foster care agencies. This appointed person, usually called an independent advocate, must act in the best interest of the child while they are in the research study.

The regulations also state that parental permission for enrolling a child in a clinical trial can be waived for "neglected and abused children"—a description that applies to some children in foster care.[329] Only the IRB can approve this waiver, however—not child welfare officials—and it may do so only to protect the child-subjects. For example, the IRB might consider it

[329] See 45 CFR 46.408(c).

unreasonable to require researchers to get permission from a parent convicted of assaulting their child. In such a situation, the IRB may substitute another mechanism for obtaining permission.

Fig. 6.1: Subpart D Categories for Research Involving Children

Subpart D Risk Category	HHS will conduct or fund research in which the IRB finds that:
45 CFR 46.404: Research not involving greater than minimal risk.	Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in §46.408.
45 CFR 46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects	More than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that: (a) The risk is justified by the anticipated benefit to the subjects; (b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and (c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in §46.408.
45 CFR 46.406 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	More than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that: (a) The risk represents a minor increase over minimal risk; (b) 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; (c) 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; and (d) Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in §46.408.
45 CFR 46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children	The research does not meet the requirements for approval in 46.404, 46.405, or 46.406. Other conditions apply to this category, but they are omitted here because to our knowledge, none of the clinical trials examined in this report were approved under this category. Research in this category must be approved by the Secretary of DHHS.

Note: The language in this table is directly from the regulations themselves.

The Challenges of Applying the Federal Regulations to Pediatric HIV/AIDS Clinical Trials

The federal regulations provide a map for researchers, IRBs, and child welfare officials who are considering a study that involves children in foster care. Implementing the regulations after they were instituted in 1983, however, did not happen seamlessly. A 2001 report on a review of 45 CFR 46 Subpart D by the Secretary of Health and Human Services noted, for example, that "problems and concerns related to research involving children generally have resulted from a failure to implement the existing regulations appropriately and consistently, not from

fundamental deficiencies of the regulations."[330] In 2002, federal legislation required further examination of issues related to the participation of children by the Institute of Medicine, in part because of laws that expanded clinical research involving children.[331]

Several factors specific to pediatric HIV/AIDS clinical trials made implementing these regulations even more challenging. These included researchers' and officials' inexperience with these specific regulations, the fact that many large trials took place at multiple sites, the multifaceted expression of pediatric HIV/AIDS, and low levels of trust between researchers and communities with high rates of pediatric HIV/AIDS. Some of the reasons why regulations were challenging to follow in some situations are discussed below. These challenges, however, did not remove the obligation that researchers, institutions, and others had to follow those regulations.

When the National Institutes of Health first wrote New York City child welfare officials to ask whether foster children could participate in pediatric HIV/AIDS clinical trials in 1988, the regulations for children (45 CFR 46 Subpart D) had been in place for five years and the regulations for research generally, for seven years. Consequently, neither the IRBs nor the federal officials charged with enforcing the regulations had significant experience with them.[332] Little research or academic writing on the participation of children in research existed at that time, and Vera staff found no articles on the participation of foster children in research that referenced Subpart D dated prior to 1988.

Because the disease and the regulations were new, standard conventions had yet to be established or clarified. For example, as noted earlier in this chapter, the regulations require IRBs to assess studies for "minimal risk," "a minor increment over minimal risk," and "the prospect of direct benefit." Not only did strict definitions for these terms not exist in 1988, but their meaning is still a subject of debate.[333] Similarly, during the 1980s and early 1990s, IRBs had to make determinations about risk without full knowledge of pediatric HIV/AIDS disease. Also, the lack of treatment options made it difficult to draw sharp distinctions between research and treatment, leaving many caregivers, researchers, IRBs, and child welfare officials seeing clinical trials as both.[334]

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[330] Department of Health and Human Services, *Protections for Children in Research: A Report to Congress in Accord with Section 1003 of P.L. 106-310, Children's Health Act of 2000* (May 2001): p. 3.

[331] See Field and Berman, *Ethical Conduct of Clinical Research Involving Children*, p. 2, which cites the Best Pharmaceuticals for Children Act of 2002 (Public Law 107-109). The Institute of Medicine is part of the National Academies of Sciences.

[332] See *Protections for Children in Research*, p. 14: "In OHRP's experience…noncompliance has resulted from inadequate training and education of IRB members and investigators about the provisions of the regulations, and not fundamental deficiencies of the regulations themselves."

[333] See *Protections for Children in Research*, p. 4. Eighteen years after the implementation of Subpart D, this report found that "[b]ased upon the diverse comments received regarding the interpretation of *minimal risk*, and the critical importance of this interpretation to the overall effectiveness of applying the regulation, it would be premature to adopt an absolute standard without further discussion that fully engages all of the relevant parties, including both federal and private organizations, and the public, before definitive guidance on this point is issued."

[334] Bioethicists sometimes refer to a patient's belief that a clinical trial offers the best treatment as "the therapeutic misconception," especially in trials with placebo arms (only two of the trials involving new medications or the use of vaccines reviewed in this report involved a "no treatment" placebo arm). Some observers argue for a sharp distinction between treatment and research, while others see an overlap between the two as inevitable. The

Additional challenges arose out of the nature of pediatric HIV itself. As discussed in Chapter 4, some untreated HIV-positive babies developed AIDS and died in infancy, while others showed few symptoms for years before developing AIDS, and still others were not infected and seroreverted within the first 18 months. IRBs therefore needed to assess risks and benefits for children who would have any of these different disease trajectories. Also, because many large clinical trials took place at multiple hospitals and clinics, the same trials were reviewed by different IRBs. This meant that, depending on how the different IRBs judged the risks and benefits, different sites within the same study could operate under different sections of the regulations. Theoretically, an IRB at one hospital might have approved a research project as a 406 study that requires the appointment of an independent advocate for foster children, for example, while another might classify the study as a 404 or 405 study, which would not require an advocate.

It should be noted, as well, that the regulations do not spell out the role and activities of the independent advocate mandated for children in foster care participating in 406 studies. The advocate is expected to "act in the best interests of the child," but there are no set of specified activities for the advocate to undertake, such as visits with the researchers, meetings with the child's pediatrician, reviewing medical records, speaking with caregivers, or reporting to IRBs—though the IRBs could have stipulated the roles of the advocates.[335] The silence of the regulations on the activities of the advocate role reduced the chances that independent advocates would provide effective protection for foster children in HIV/AIDS clinical trials.

Issues related to race and ethnicity complicated matters too. As discussed in Chapters 3 and 4, New York City children with HIV/AIDS, including those in foster care, came disproportionately from African American and Latino families. Issues of trust and cultural competency made the informed consent process that much more challenging to implement.[336]

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introduction to a 2008 article in the *Journal of the American Medical Association* (JAMA) shows the persistence of this latter view in reference to pediatric HIV: "Children comprise a large subgroup of patients with human immunodeficiency virus (HIV) infection, and their treatment must be defined by pediatric clinical trials." See Raymond Barfield and Javier Kane, "Balancing Disclosure of Diagnosis and Assent for Research in Children with HIV," *JAMA* 300 no. 5 (August 6, 2008). Bioethicists have studied the "therapeutic misconception" for the decades but have not reached consensus on its definition, in part because "the extreme heterogeneity of clinical trial design makes generalizations about realistic expectation of direct benefit very difficult." See Larry R. Churchill et al., "Clinical Trials and Medical Care: Defining the Therapeutic Misconception." PLoS Medicine 4 no. 11 (November 2007): e324.

[335] *Protections for Children in Research* solicited expert opinion on issues related to Subpart D. Only six sentences in the report related directly to the participation of foster children in research (see p. 9). The report noted that one expert commented that "protections for wards could be increased if the regulations had a definition for 'advocate' which focused on the role of such an individual in protecting the child."

[336] For the role of trust in decisions by African Americans to participate in AIDS clinical trials, see Sohini Sengupta, Ronald P. Strauss, Robert DeVellis, Sandra Crouse Quinn, Brenda DeVellis, William B. Ware, "Factors Affecting African-American Participation in AIDS Research," *Journal of Acquired Immune Deficiency Syndromes* 24 no. 3 (July 1, 2000):275-284. As groups, African Americans and Latinos enroll in clinical trials at a lower rate than whites in the United States (see, for example, Vivek H. Murthy, Harlan M. Krumholz, and Cary P. Gross, "Participation in Cancer Clinical Trials: Race-, Sex-, and Age-Based Disparities," *JAMA* 291 (2004):2720-2726. The gap in clinical trials enrollments may be explained in part by different levels of trust of doctors among these groups (see V. Shavers, "Racial Differences in Factors that Influence the Willingness to Participate in Medical Research Studies,"

For many reasons, including the history of medical research involving African Americans and Latinos, these groups have less trust than whites that their physicians will fully disclose the risks of research and are more likely than whites to believe that physicians will expose them to unnecessary risk.[337] During the era studied in this report, people's experience of financially stressed medical facilities in communities with high rates of pediatric HIV likely increased alienation from medical institutions in general.

OHRP's Investigation of Columbia University Medical Center. The investigation of Columbia University Medical Center (CUMC) by the Office for Human Research Protections (OHRP) that took place between 2004 and 2006 illustrates some of the challenges of implementing the regulations for pediatric HIV/AIDS clinical trials. OHRP, a division of the U.S. Department of Health and Human Services, aims to protect "the rights, welfare, and well-being of subjects involved in research conducted or supported by the Department of Health and Human Services (HHS) and helps ensure that such research is carried out in accordance with the regulations described at 45 CFR part 46."[338] The agency monitors compliance at nearly 10,000 universities, hospitals, and other research institutions in the United States and abroad that have formal agreements ("assurances") that they will comply with the regulations.[339] In monitoring compliance, OHRP responds to complaints of violations of the regulations. The account below draws on documents obtained through a Freedom of Information Act request to OHRP concerning an investigation in response to allegations of violations at CUMC.

In March 2004, OHRP received a letter from the Alliance for Human Research Protection (AHRP), a nonprofit advocacy group, alleging that Incarnation Children's Center (ICC), a residential facility that once provided medical services to HIV-positive children in foster care under the auspices of Catholic Home Bureau (a contract foster care agency), violated 45 CFR 46.[340] ICC was affiliated with the Department of Pediatrics of Columbia University and provided

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Annals of Epidemiology 12, no. 4:248–256.). For a discussion of cultural competency in health care, see Jordan J. Cohen, Barbara A. Gabriel, and Charles Terrell, "The Case For Diversity In The Health Care Workforce," *Health Affairs* 21 no. 5 (September/October 2002):90-102.

[337] See Giselle Corbie-Smith, Stephen B. Thomas, Diane Marie M. St. George, "Distrust, Race, and Research," *Archive of Internal Medicine* 162 (2002):2458-2463. The abstract for this article states that the research found that African American respondents were more likely than white respondents not to trust that their physicians would fully explain research participation (41.7 percent vs 23.4 percent, $P<.01$) and to state that they believed their physicians exposed them to unnecessary risks (45.5 percent vs 34.8 percent, $P<.01$). African American respondents had a significantly higher average distrust index score than white respondents (3.1 vs 1.8, $P<.01$). After controlling for other sociodemographic variables in a logistic regression model, race remained strongly associated with a higher distrust score. Discredited allegations that the U.S. government created AIDS to kill African Americans may have exacerbated concerns about trust in some situations—see Christopher Andrew and Vasili Mitrokhin, *The Sword and the Shield: The Mitrokhin Archive and the Secret History of the KGB* (New York: Basic Books, 2000): p. 243-245; Cathy Cohen, *The Boundaries of Blackness: AIDS and the Breakdown of Black Politics* (Chicago: University of Chicago Press, 1999).

[338] See the agency's web site, http://www.hhs.gov/ohrp/about/ohrpfactsheet.htm, last accessed August 8, 2008.

[339] Ibid.

[340] Letter, March 10, 2004, from Vera Hassner Sharav, president, Alliance for Human Research Protection, to Michael Carome, OHRP, and David Horowitz, FDA, re: Trials involved: Phase 1 Drug trials used foster children in violation of 45 CFR 46.409 and 21 CFR 50.56.

medical care to children at the facility as well as to HIV-positive foster children in the community through an outpatient clinic.[341] ICC served as a sub-site of the Columbia University Medical Center Pediatric AIDS Clinical Trials Unit (see Chapter 8 for more information about the PACTUs). Clinical trials conducted at ICC were approved by the CUMC IRB. A pediatrician on the faculty of CUMC, Stephen Nicholas, served as ICC's medical director and then executive director until 2001, when the facility changed its status to a skilled nursing facility unaffiliated with any foster care agency.[342] This meant that, after a CUMC IRB approved a clinical trial, ICC was certified to enroll children in that trial provided the children qualified for it.

The AHRP letter alleged that the federal regulations prohibited wards of the state (which includes foster children) from participating in research that involves more than minimal risk. It also contended that every foster child enrolled in research is entitled to an advocate as mentioned in 45 CFR 46.409. The letter asserted that ICC clinical trials participants "were children diagnosed with HIV infection—in some cases infants who were merely 'presumed' to be HIV infected," and it suggested that some children participated in the trials unnecessarily. The letter also alleged that the New York State Department of Health misrepresented the trials to the public and that Children's Services' policy violated 45 CFR 46 by allowing foster children to participate without proper consent. The letter made specific mention of eight clinical trials, all of which involved testing "safety and toxicity as well as maximum dose tolerance." [343]

OHRP opened its investigation in May 2004 and requested information from CUMC about the eight clinical trials mentioned in the AHRP letter.[344] CUMC responded, writing that "CUMC is proud to have contributed to the PACTG [Pediatric AIDS Clinical Trials Group] research referenced in your inquiry."[345] The reply highlighted improvements that had been made in CUMC's human research protections efforts in the previous two years, including mandatory training for researchers, IRB members, and staff. The letter noted that the National Institutes of Health had initiated the studies, which were carried out at institutions around the country, and that the research at CUMC "has helped transform pediatric HIV-infection from a terminal

[341] Columbia's response to OHRP, the Vera Institute's review of records and interviews confirm that ICC operated a group home and an outpatient clinic. See letter, July 28, 2005, to Karena Copper, OHRP, from Steven Shea, senior associate dean for clinical affairs, CUMC, and Laura Forese, vice president/chief medical officer, New York Presbyterian Hospital. Columbia Presbyterian and New York Hospital merged in 1998 (see http://www.nyp.org/news/hospital/hospital-merger.html, last accessed October 28, 2008).

[342] That same year, Nicholas left ICC to become Chief of Pediatrics at Harlem Hospital.

[343] The letter listed the following clinical trials, each funded by the National Institutes of Health and conducted as part of the Pediatric AIDS Clinical Trial Group discussed in Chapter 4: PACTG 299, PACTG 377, PACTG 218, PACTG 253, PACTG 402, PACTG 265, PACTG 345, and PACTG 292. The AHRP letter characterized all eight trials as Phase I trials. Five of the trials, 265, 292, 345, 377, and 402, were Phase I/II trials. Phase I/II trials determine dosing by testing safety and tolerance in a small group of participants and then safety and effectiveness in a larger group of participants.

[344] Letter, June 1, 2005, from Bernard Schwetz, director, OHRP, to Bill de Blasio, chair, Committee on General Welfare, the Council of the City of New York.

[345] Letter, August 19, 2004, from Harvey Colten, vice president & senior associate dean for the faculties of health sciences & medicine, CUMC, and Steven Corwin, senior vice president/chief medical officer, NYPH, to Kristina Borror, director, Division of Compliance Oversight, OHRP.

condition to a chronic condition, and provided children with successful treatment opportunities they otherwise would not have received."[346]

CUMC's review of their records found that 17 children had enrolled in four (PACTG 218, 265, 345, and 377) of the eight studies mentioned in the AHRP letter and that no children had enrolled in the remaining four trials through CUMC or ICC. Nine of the 17 children were in foster care at the time of their enrollment. Each of the nine foster children had been enrolled in one of three trials.[347]

CUMC asserted that all four of the clinical trials in which children it cared for had been enrolled were 404 or 405 studies and thus did not require independent advocates.[348] The initial response from CUMC made explicit reference to HRA/Children's Service's policy regarding the participation of foster children in clinical trials. The response also noted that the enrollments took place through ICC's outpatient clinic—not the ICC group residence: "Our records reflect that none of the subjects in ACTG 218, 265, 345 and 377 were residents of the ICC group home during the time when they were enrolled in these studies."[349] This assertion is important because the regulations appear to prohibit conducting trials at an institution where the majority of subjects are in foster care.[350]

On May 23, 2005, OHRP issued the first of two official findings in its investigation.[351] This first determination letter stated that CUMC's IRB had failed "to obtain sufficient information" about the selection, the consent and permission processes, and additional safeguards required for foster children participating in the trials.[352] In short, OHRP found that the CUMC IRB did not adequately consider the special circumstances of foster children when it reviewed the studies. OHRP did not, however, cite CUMC for enrolling children without an informed consent procedure—OHRP requested and received informed consent forms for each of the nine foster children who participated in the three trials at CUMC.[353] The internal documents and

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[346] Ibid.

[347] CUMC reported that children in foster care were enrolled in PACTG 377, 218, and 345. CUMC reported that no children in foster care enrolled in PACTG 265 at its institution.

[348] Letter, 8/19/2004 from Harvey Colten (CUMC) and Steven Corwin (NYPH) to Kristina Borror (OHRP).

[349] ICC, CUMC, and Columbia Presbyterian hospital are all located in Manhattan's Washington Heights neighborhood within a roughly 20 square block area of one another. The quote is from a letter, July 28, 2005, from Steven Shea, senior associate dean for clinical affairs, CUMC, and Laura Forese, vice president/chief medical officer, NYPH, to Karena Cooper, compliance oversight coordinator, OHRP.

[350] The regulations prohibit 406 studies at institutions that house only wards of the state that are not related to their status as wards. It is not clear how 45 CFR 46.409(b) applies to multi-site studies or to ICC. The residential part of ICC housed only children in foster care. However, the trials OHRP examined also recruited subjects at many other sites—places that served all children. ICC also provided treatment and enrolled children in clinical trials through its outpatient clinic. Some of the children seen at the clinic might be in foster care but not living at ICC, others were not in foster care or living at ICC. To further complicate matters, some children who lived at ICC may have received medical care at nearby Columbia Presbyterian hospital, which served all children, not just those in foster care.

[351] The first OHRP determination letter, issued on May 23, 2005, is available at http://www.hhs.gov/ohrp/detrm_letrs/YR05/may05c.pdf, last accessed September 10, 2008.

[352] Specifically, OHRP found violations of 45 CFR 46.111.

[353] At CUMC's request, OHRP approved redaction of the names on the consent forms to prevent the disclosure of the participants' names and, thus their HIV status, in the event of a Freedom of Information Act request. See Record

correspondence reviewed by Vera's staff indicate that OHRP dismissed the allegation that the studies involved children who were not infected with HIV.[354] Instead, the agency found that the IRB did not properly consider issues concerning children in foster care when it first approved the studies.

The investigation, however, continued as OHRP questioned several parts of CUMC's response to its inquiries. OHRP asked for more information about the "HRA Medical Panel," noting that there was no documentation from the panel in the IRB minutes. OHRP observed that although CUMC claimed that the each of the trials was approvable under 404 or 405, the IRB minutes did not document that the studies were actually approved as 404 or 405 studies. In its first determination letter and other communication, OHRP requested additional information from CUMC, including the current number of 406 studies being conducted (in 2005) and whether any of the current studies had enrolled children in foster care. CUMC reported that of the 441 research studies that involved children and that were approved by CUMC and Columbia University's Morningside campus IRBs between July 1, 2004, and June 30, 2005, 17 were approved under 406. None enrolled children in foster care.[355]

The investigation of Columbia generated concerns in other parts of government. The federal Office for Civil Rights contacted OHRP about possible racial or ethnic discrimination in the trials, and OHRP agreed to coordinate their efforts with that agency.[356] A National Institutes of Health official called OHRP and, according to telephone notes, said that the "leadership of PACTG was not paying enough attention to enrolling wards of the state."[357] The notes say that on July 8, 2005, the Division of AIDS (DAIDS), a part of the National Institutes of Health's National Institute Of Allergy and Infectious Diseases (NIAID), sent a letter to their network of researchers informing them that after July 24, 2005, DAIDS would require documentation of the specific category of research (404, 405, 406, or 407) under which the IRB approved any new study.[358] OHRP alerted federal officials at the NIH, the Food and Drug Administration, and the Office for Civil Rights that it was conducting "a preliminary inquiry" into foster children and clinical trials issues at more than 70 institutions across the country.[359]

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of Cooper Telephone Contacts, May 21, 2005 and May 22, 2005 obtained through Freedom of Information Act request.

[354] OHRP determination letter dated May 23, 2005: "It was alleged by the complainant that prior to confirmatory diagnostic HIV testing, infants were enrolled in the above-referenced research to treat HIV infection; …Based upon information provided in NYPH/CUMC's reports, OHRP finds that this allegation is not substantiated."

[355] Letter, September 29, 2005, from Steven Shea (CUMC) and Laura Forese (NYPH) to Karena Cooper (OHRP).

[356] Jacqueline Sherman, "Oversight: Participation of New York City Foster Children with HIV and AIDS in Clinical Trials," Briefing paper prepared for the General Welfare Committee of the New York City Council, May 5, 2005, obtained from OHRP via a Freedom of Information Act Request.

[357] Record of Karena Cooper (OHRP) telephone contacts, July 14, 2005, from Sandra Lehrman, director, Therapeutics Research Program, Division of AIDS.

[358] The notes indicate that DAIDS referred to the process of protocol registration: a site cannot start to enroll participants into a study funded by DAIDS until DAIDS registers the protocol. The funding for conducting a trial cannot flow from DAIDS to the site until *after* protocol registration, giving the agency leverage to ensure that its requirements are met.

[359] E-mail, May 10, 2005, from Karena Copper to Anthony Fauci (NIH), Ed Tramont (NIH), David Lepay (FDA), Lana Skirboll (NIH), Robinsue Frohboese (Office for Civil Rights), and Lester Crawford (FDA).

In its ongoing investigation of Columbia, OHRP considered two issues: the appropriate category for trials that were part of the investigation and the penalty Columbia should receive for violating the regulations.

OHRP examined whether any of the trials in the investigation should be classified as 406 studies (instead of the 404 and 405 studies as CUMC claimed). Because the requirement for appointing an independent advocate for foster children only applies to 406 studies, a finding that any of the studies could be approved only under 406 would mean additional violations occurred. In considering whether any trials should be classified as 406 studies, OHRP examined one trial in particular—PACTG 218, a Phase I trial of an HIV vaccine.[360] Three weeks before issuing its second determination letter, OHRP staff discussed whether 218 could be approved by an IRB as a 405 trial.[361]

OHRP also needed to decide what penalty Columbia would receive for the violations the investigation identified. OHRP enforcement has several options, from mandating corrective action plans to recommending that an individual or an institution be prohibited from receiving federal research grants.[362] For an individual researcher a ban, technically called debarment, might end his or her research career. The consequences of debarment for an institution are also severe. Many large institutions, including Columbia University, receive more than $100 million in research grants each year.[363] An institution-wide suspension would not only prohibit new grants during the debarment period, but might also have significant consequences on recruiting and retaining faculty. OHRP's most common enforcement action, however, is to request a corrective action plan that identifies how an institution will prevent a violation from recurring.

OHRP issued its second and final determination letter on February 17, 2006. That letter found no additional violations but reiterated previous findings and accepted Columbia's plan to prevent future violations. Without taking a position on the appropriate category for each study, OHRP found that "CUMC IRB documents…revealed no evidence that the CUMC IRB considered and made the required findings in 45 CFR 46.404-409."[364] The letter updated the actions that OHRP and CUMC had taken regarding the investigation and included details about corrective actions that CUMC had taken to avoid future violations. The corrective action plan included training of all university staff on the regulations for involving children in research,

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[360] Handout, "Meeting re: ACTG #218—approvable under 46.405?" May 3, 2005, obtained through Freedom of Information Act request.

[361] Vera's review found that three children participated in PACTG 218 while in foster care. See Chapter 7 for more information.

[362] For a discussion of enforcement actions, see http://www.research.va.gov/programs/pride/conferences/docs/compliance-Borror.ppt, last accessed September 10, 2008. The OHRP web site also discusses enforcement. OHRP recommends debarment to officials at Health and Human Services using the regulations at 45 CFR 76.

[363] In 1996, Columbia University received $137,815,335 in research grants from the National Institutes of Health. See National Institutes of Health, "NIH FY 1996 Extramural Awards To All Organizations Total Dollars Awarded Ranked By Organization, Printed In Rank Order," February 25, 1997, retrieved October 31, 2008 from http://report.nih.gov/award/trends/rnkall96.txt.

[364] Letter, February 17, 2006, from Karena Cooper, compliance oversight coordinator, OHRP, to Steven Shea, senior associate dean for clinical affairs, CUMC, and Laura Forese, vice president/chief medical officer, NYPH.

increasing the number of IRBs, upgrading IRB tracking systems, and instituting new forms and procedures for reviewing research.[365] OHRP reviewed three CUMC IRB applications to ensure that the promised changes in IRB procedures took place. The letter ended the investigation, although it noted that "OHRP must be notified should new information be identified which might alter this determination."

In June 2006, OHRP issued determination letters to 19 institutions across the country for violations related to the enrollment of foster children in the HIV/AIDS clinical trials originally cited in the AHRP letter.[366] The 19 institutions included the New York City medical centers Bronx-Lebanon and Bellevue Hospital Centers. [367] The SUNY Health Science Center at Stony Brook had also received a determination letter in February 2006 regarding two of the clinical trials cited.[368] Each of these letters refers to an IRB's apparent failure to categorize the research as 404, 405, 406, or 407 studies and/or to obtain sufficient information regarding the selection of foster children as participants in the trials. At each of the 19 other sites that received the June 2006 determination letters, OHRP approved corrective action plans aimed at preventing future violations.

The OHRP investigations indicate that IRBs at many institutions across the country did not properly document their activities and did not take the special circumstances of children in foster care into consideration. As is its mandate, OHRP focused its activities on compliance with federal regulations. The investigation at CUMC, however, left many other questions unanswered. OHRP did not seek to make determinations on how many children in foster care participated in clinical trials or whether the person who signed the consent form had the legal authority to do so, nor did it examine what adverse events or benefits occurred to the children, if any, due to trial participation. The investigation did not examine whether foster children made up a disproportionate number of children in HIV/AIDS clinical trials or specify the policy of New York City's child welfare agency for enrolling and monitoring foster children in clinical trials. The next chapter addresses this last topic.

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[365] Ibid.

[366] See http://www.hhs.gov/ohrp/compliance/letters/2006.html for links to each of the 19 letters, last accessed September 10, 2008.

[367] See letter, June 19, 2006, from Julia Gorey, Division of Compliance Oversight, OHRP, to Steve Anderman, senior vice president/chief operation officer, Bronx Lebanon Hospital. This was a follow-up letter approving a corrective action plan for the determinations that OHRP outlined in a letter dated February 17, 2006 from Julia Gorey to Steve Anderman, as well as citing additional concerns. Also see letter, June 19, 2006 from Kristina Borror, director, Division of Compliance Oversight, OHRP, to Lynda Curtis, senior vice president/executive director, Bellevue Hospital Center. This was a follow-up letter to the letter dated February 17, 2006 from Kristina Borror to Carlos Perez, senior vice president/executive director, Bellevue Hospital Center.

[368] Letter, February 17, /2006, from Carol Weil, Compliance Oversight Coordinator, OHRP, to Judy Matuk, director, Research Compliance, SUNY Health Science Center, Stony Brook.

Chapter 7: New York City's Policy for Enrolling and Monitoring Foster Children in HIV/AIDS Clinical Trials

Chapter Summary

Prior to 1988, New York City child welfare officials did not approve enrollments of foster children in clinical trials. In 1988, the National Institutes of Health asked New York officials at the Human Resources Administration, which at the time included the city's child welfare agency, to consider allowing foster children to participate in a specific clinical trial related to HIV/AIDS. This prompted HRA officials to review state and federal regulations and other issues associated with clinical trial participation. Following this review—which involved city, state, and national public health officials as well as medical professionals in New York City and elsewhere—child welfare officials crafted a policy that allowed individual foster children to participate in clinical trials under two conditions: the city commissioner responsible for the child welfare agency had to approve the enrollment and, where parental rights had not been terminated and parents could be located, one or both biological parents had to provide informed consent for participation. Situations where parents could not be located would be handled on a case by case basis.

In 1991, following complaints from physicians, contract agency staff, and advocates that the process of reviewing each case individually was delaying foster children's access to new treatments, child welfare officials established a new policy. The new policy called for the commissioner to approve or disapprove specific clinical trials once they had been reviewed by a panel of medical experts, child welfare agency lawyers, and child welfare staff who specialized in HIV/AIDS issues. In 1994, officials streamlined the policy further: if parental rights had been terminated and the child was in the joint guardianship of the commissioner and a contract foster care agency, contract agency staff could sign informed consent forms for enrollment in clinical trials. In 1998, the agency modified its policy to allow Phase I clinical trials under certain circumstances and with an additional case-by-case review by an independent physician.[369] *Within months, in 1999, Children's Services informally suspended its policy of approving specific clinical trials. No new written policy was issued. Instead, Children's Services allowed enrollment in individual cases after review of the trial and the children's medical history by an independent physician.*

Introduction

This chapter describes the development, evolution, and implementation of Children's Services policies for enrolling New York City foster children in clinical trials related to HIV/AIDS between 1988 and 2001. The information presented here comes primarily from a review of

[369] Clinical trials of new medications are typically conducted in three phases (see Chapter 8 for a detailed discussion of these phases). In brief, Phase I trials, which usually involve few participants, test the safety, tolerance and toxicity of a new drug or procedure. Phase II trials test the efficacy of the new drug or procedure and Phase III trials compare the new drug or procedure against the best available treatment.

several boxes of documents given to Vera by Children's Services. The boxes contained policy bulletins, memoranda, and correspondence sent within Children's Services and its predecessor agencies and between their staff and people outside the organization. External correspondents included representatives of the NYC Department of Health and the National Institutes of Health, and individual physicians, foster care agency staff, and the New York State Office of Children and Family Services. In addition, the chapter draws on quarterly reports from the Pediatric AIDS Unit (PAU) and a review of individual and family child welfare files. Where indicated, this information is supplemented by excerpts from interviews with key respondents.

Background on How the Policy Question Arose

In the mid-1980s, when child welfare officials first became aware that HIV-positive children were entering the foster care system, few realized the impact the epidemic would have. In 1985, 82 children under age 13 had been diagnosed with AIDS in New York State.[370] By 1987, New York City had 70 foster children known to be HIV infected. That number rose to 327 by January 1990, and to 587 by fall 1992.[371] Instead of a small number of severely ill and dying children who spent most of their lives in the hospital, foster care officials were confronting a growing population of HIV-positive children with special developmental and medical needs. This generated a host of policy challenges related to testing, tracking, confidentiality, placement, day care, education, and medical services.[372] These questions arose at a time when few predicted that the increase in foster care placements experienced in the mid-1980s would accelerate through the end of the decade.

The impetus for a policy regarding the participation of foster children in clinical trials did not arise until January 1988, when the National Institutes of Health asked the city's child welfare authorities to consider allowing foster children to participate in a clinical trial of intravenous immunoglobulin (IVIG) as a treatment for AIDS.[373] This request set in motion a series of memos, meetings, and discussions.

To understand how the policy developed out of these activities, it is helpful to be familiar with the structure of the agency and the units within it that played a major role. The two short

[370] New York State Department of Health Public Health Memorandum Series PH-15, September 4, 1985, "Guidelines for the Education and Day-Care of Children Infected with Human T-Lymphotropic Virus Type III/Lymphodenapathy-Associated Virus (HTLV III/LAV)", p. 1. The numbers cited in 1985 and 1987 likely underestimate the number of HIV-exposed children because HIV testing did not occur on a routine basis.
[371] Letter, February 22, 1990 from Amy Van Dorfy, executive assistant to the assistant deputy commissioner for Policy and Planning, Child Welfare Administration (CWA), New York City Human Resources Administration (HRA), to Angela Collier, U.S. General Accounting Office; letter, January 6, 1993, from Claude B. Meyers, assistant deputy commissioner, Office of Policy and Planning, CWA, HRA, to Drs. Harold E. Fox, Anne Gershon, and Jane Pitt, Women and Children Care Center, Columbia-Presbyterian Medical Center.
[372] See, for example, memo, March 31, 1993, titled "CWA HIV/AIDS Activities and Initiatives March 31, 1993" (no author), a lengthy document which discusses HIV/AIDS prevention programs for adolescents, specialized HIV foster care programs, HIV data collection issues, HIV-related foster care standards, state policy on HIV testing, clinical trials issues, and the Early Permanency Planning program (discussed in Chapter 5).
[373] Letter, December 1, 1988, from Mark S. Rapoport (MD, MPH), deputy commissioner, New York City Department of Health, to Susan A. Larabee, Special Services for Children (SSC).

sections below review the evolution of the child welfare agency's administrative structure and the government offices that were primarily responsible for formulating the policy.

Agency Structure. In 1987, the city's child welfare agency, then known as Special Services for Children (SSC), came under the umbrella of New York City's Human Resources Administration (HRA), a "superagency" created during the 1960s. In addition to SSC, HRA also oversaw a broad array of other public welfare and human services programs, such as those that provide income assistance and food stamps. SSC became the Child Welfare Administration (CWA) in 1989, but it remained under the direction of HRA. In January 1996, child welfare became the responsibility of the newly created Administration for Children's Services, a freestanding agency that reports directly to the Mayor's Office.[374]

Policymakers. Three units within HRA played the largest parts in developing clinical trials policy: the commissioner's office, the Office of Legal Affairs (OLA), which provided legal services and opinions to the child welfare agency and other divisions within HRA, and the Pediatric AIDS Unit (PAU). The PAU, which is described in greater detail in Chapter 5, had administrative responsibility for implementing clinical trials policy, including tracking participation of foster children in HIV/AIDS clinical trials.[375]

Early Steps Toward a Policy

Prior to 1988, HRA did not have a formal policy concerning the enrollment of children in foster care in clinical trials, but HRA lawyers understood that the agency did not consent to clinical trial enrollment.[376] HRA's commissioner, William J. Grinker, responded to NIH's request by asking OLA to explore its medical, ethical, and legal implications. Christina Palacio, an OLA lawyer, coordinated this effort and communicated directly with Grinker on its progress.[377]

The agency's goal was to make a "determination of HRA's legal authority to consent to trial study participation" and to develop criteria and methods to determine whether and when it might consent to such participation.[378] HRA staff consulted with a range of medical professionals and government officials. This included staff at the NIH-National Institute for Child Health and Development (NICHD), clinical trial researchers for pediatric-HIV clinical trials at several New York City medical centers, representatives from the New York City Department of Health

[374] See *Protecting the Children of New York: A Plan of Action for the Administration for Children's Services.* December 19, 1996.
[375] See PAU quarterly reports, 1992-2005.
[376] Memo, March 16, 1994 from Carol Marcus to Commissioner Marva Livingston Hammons, "Participation of Foster Children who are HIV Seropositive or who are HIV Infected in Clinical Trial Protocols." This memo summarizes policy development in the previous two years.
[377] Memo, April 4, 1989 from Cristina Palacio, executive assistant to the New York City Corporation Counsel, to William Grinker, commissioner, HRA, "HIV Clinical Trials." One person Vera staff interviewed said that Grinker addressed many policy issues in this fashion.
[378] Memo, March 16, 1994 from Carol Marcus to Commissioner Marva Livingston Hammons, "Participation of Foster Children who are HIV Seropositive or who are HIV Infected in Clinical Trial Protocols."

(NYCDOH), the Health and Hospitals Corporation (HHC), the New York State AIDS Institute (a division of the New York State Department of Health), and the National Medical Association (an association of physicians of African descent).[379] OLA staff also "conducted an exhaustive review of the ethical, medical, and legal implications of foster child participation…[that] included consideration of the past abusive use of other disenfranchised and vulnerable populations in medical research."[380]

Section 383-b of New York State's social services law addresses medical treatment for abused and neglected children. It reads as follows:

> *§383-b. Medical treatment for abused or neglected children; consent of commissioners. The local commissioner of social services or the local commissioner of health may give effective consent for medical, dental, health and hospital services for any child who has been found by the family court to be an abused child or a neglected child, or who has been taken into or kept in protective custody or removed from the place where he is residing, or who has been placed in the custody of such commissioner, pursuant to section four hundred seventeen of this chapter or section one thousand twenty-two, section one thousand twenty-four or section one thousand twenty-seven of the family court act.*[381]

OLA lawyers determined that New York State social service law gave local service district commissioners—in this case the commissioner of HRA—the authority to authorize enrollment as part of the commissioner's overall responsibility for medical treatment and health services.[382] To qualify for the commissioner's approval, however, a trial had to "constitute medical care" and not have increased knowledge as its only goal.[383]

In preparing their response to NIH, HRA staff also asked for information on the clinical trial that prompted the policy review. That trial, PACTG 045, sought to evaluate whether intravenous immunoglobulin (IVIG) administered on a monthly basis helped prevent HIV-positive children

[379] The NMA was founded in 1895 to promote "parity in medicine, elimination of health disparities, and promotion of optimal health."
[380] Memo, March 16, 1994, from Carol Marcus to Commissioner Marva Livingston Hammons, "Participation of Foster Children who are HIV Seropositive or who are HIV Infected in Clinical Trial Protocols."
[381] In a letter, September 5, 1990, from Barbara Sabol to New York State Department of Social Services's Tom McGraw, Sabol writes that "It is our position that the ultimate responsibility for medical and health care of a foster child lies with the local commissioner. After careful legal and ethical analysis, HRA determined that consenting to participation of a foster child in clinical trial studies is within the authority granted the commissioner of a local district by SSL 383-b to consent to medical and health services for a child in protective custody." CWA Procedure 94-1, Medical Consents for Children in Foster Care dated March 15, 1994, p. 16, sites New York State Social Service Law 398, State Department of Social Services' regulations (18 NYCRR 507.1), NYCRR 441.22 and other sources in addition to 383-b as the legal bases for consent for general medical care by the commissioner.
[382] Letter, September 5, 1990, from Barbara Sabol, HRA commissioner, to Tom McGraw, Local District Policy Communications Unit, New York State Department of Social Services, re: Proposed ADM titled "Foster Care; Adoption; Required Confidentiality of HIV-Related Information," p. 2.
[383] Memo, March 16, 1990, from Carol Marcus to Commissioner Marva Livingston Hammons, "Participation of foster children who are HIV Seropositive or who are HIV Infected in Clinical Trial Protocols."

from developing serious bacterial infections.[384] The study protocol mandated that children be randomly assigned to receive either a placebo or IVIG.[385] HRA officials consulted with Winston Price, a physician and member of the National Medical Association, and Mark Rapoport, also a doctor and deputy commissioner at the NYCDOH, for their opinions about the trial.[386] Both recommended that HRA approve of the foster children's participation.[387]

Following these consultations, Grinker determined that foster children could and should participate in HIV/AIDS clinical trials in certain situations, including PACTG 045. He asked OLA to develop a process for approving the enrollment of individual children. As part of this process, OLA developed a letter of agreement spelling out the conditions of foster children's participation and the obligations to which medical researchers and their institutions had to agree. NYCDOH advised HRA on the letter of agreement, as did the National Institutes of Health's National Institute for Allergy and Infectious Disease (NIH-NIAID), which sponsored PACTG 045. NYCDOH suggested a number of additions.[388] Those additions, incorporated into HRA's final version, were:

1. that both the letter of agreement and the consent form used by HRA and consenting natural parents explicitly set forth that the research will be conducted in compliance with 45 CFR 46.409.
2. that both the agreement and consent recognize that membership in the control group (and therefore participation in the study) will not preclude receiving any treatment of known efficacy or benefit for which the subject is otherwise qualified by reason of meeting the selection criteria for the other treatment;
3. that the agreement and consent state that membership in the control group will not preclude IVIG treatment where beneficial for a child whose condition worsens while participating in the study;
4. that the risk-benefit equation expressed in the consent be modified and that both the letter of agreement and the consent set forth (in the selection of subjects for participation):
    - the risk of harm to the subject by reason of his or her participation in the study must be out-weighed by a genuine possibility of substantial benefit to the subject;

[384] Letter, December 1, 1988, from Mark S. Rapoport, deputy commissioner, Department of Health, to Susan A. Larabee.
[385] AIDS Clinical Trials Group Study protocol 045, dated September 1987.
[386] Letter, December 12, 1988, from Winston S. Price, third vice president, National Medical Association, to William J. Grinker; letter, January 20, 1988, from Betsy Mayberry, administrative director for operations, SSC, HRA, to Mark Rapoport, deputy commissioner for personal health services, NYCDOH..
[387] Memo, May 23, 1990, from Christine Palacio, to HRA Commissioner Barbara Sabol,,"Participation of Foster Children with HIV-related Illness in Clinical Trial Studies."
[388] Letter, December 1, 1988, from Mark S. Rapoport, NYCDOH deputy commissioner for personal health services, to Susan A. Larabee, deputy general counsel, HRA, and Office of Legal Affairs.

- the risk associated with IVIG treatment must be no worse than that associated with any other therapy for which the subject is otherwise qualified.[389]

The final letter of agreement required the investigating physician on commissioner-approved enrollments to abide by the confidentiality regulations of the Social Services Law. It also required the institution to "designate an independent advocate to represent the interests of each foster child in the study, as required by federal regulation [45 CFR 46.409]."[390] Additionally, the letter stated that the independent advocate required by 45 CFR 46.409 will be appointed by the hospital IRB, with "serious consideration…given to the appointment of a person recommended by the National Medical Association."[391] The letter of agreement also stated that the commissioner's consent would be determined on a case by case basis for children whose parents' whereabouts were unknown. In cases where a parent had consented, the commissioner would also consent, subject to the conditions laid out in the agreement. The final version of the agreement between the clinical trial researcher and HRA also required that the investigating physician provide monthly reports to the Child Welfare Administration and the agency medical director. The process called for letters of agreement with each institution that enrolled a foster child in a clinical trial where the enrollment had been approved by the commissioner.

Internal Debate about Access and Protection. In December 1988, as SSC worked on a process for enrolling foster children in the IVIG study, Charlotte Von Clemm, an SSC staff person who attended a meeting of doctors providing care to HIV-infected children, learned that children in foster care were enrolled in clinical trials. In a subsequent memo to Palacio she wrote, "My greatest concern is that babies are being held in the hospitals and not being declared medically ready because the doctors don't want to lose them from their studies (they actually admitted it!!)."[392] On January 17, 1989, Grinker ordered his staff to "…take whatever steps are necessary to see that this does not happen in the future and if there are any known current instances of such participation, that they be terminated immediately."[393]

After making inquiries about this situation, the HRA deputy commissioner in charge of Special Services for Children, Brooke Trent, reported on February 3, 1989, that the children in question were involved in observational studies, not trials of new drugs. Trent told Grinker that she planned to require hospitals to inform SSC "of any instance where a parent has consented

[389] Ibid.
[390] Memo, May 23, 1990, from Christina Palacio, to Barbara Sabol, "Participation of Foster Children with HIV-related Illness in Clinical Studies."
[391] See sample letter of agreement in Appendix 9.
[392] Memo, December 22,1988, from Charlotte von Clemm, to Cristina Palacio, cc: Brooke Trent, "Involvement of SSC Children in Hospital Protocols"; Memo, January 11, 1989, from Susan Larabee, to Brooke Trent, "Participation of HIV+ Foster Children in Experiment Studies [sic]."
[393] Memo, January 17, 1989, from William Grinker, to Brooke Trent and Susan Larabee, cc: T. Maher, "Involvement of SSC Children in Experimental Studies."

and a child is enrolled."[394] Her staff did not know of specific children held in hospitals for observational studies. Nevertheless, she reported that "hospital, agency and SDSS [New York State Department of Social Services] staff" each had reported hearing of similar situations. The "boarder baby" phenomenon—children who were in hospitals and awaiting a foster-care placement (see Chapters 3 and 4)—had already prompted two lawsuits resulting in court orders to speed placement of infants who had no medical need to stay in a hospital. Several days later, Grinker clarified his position that "there should be no instance of [clinical trial] involvement at all except as specifically authorized by the Commissioner except where a biological parent has authorized participation."[395] Grinker's memo made clear his preference that in the future the commissioner's approval would be required even when the biological parent gave consent.

Von Clemm—who was not directly involved in developing clinical trials policy—also reported that the doctors had asked her about HRA's position on three issues about clinical trial participation for children in foster care. The doctors wanted to know 1) who should give consent, 2) what happens if the mother consents but HRA does not agree that participation is in a child's best interest, and 3) if the mother consents, but the foster home is far from the hospital, should the foster mother be obligated to continue participation or should the child be withdrawn from the trial.[396]

In an internal memo dated January 11, 1989, HRA legal staff proposed that the agency should require the commissioner to consent for all children in foster care, even in cases where a biological parent had already signed an informed consent form. The memo also states that if the whereabouts of a biological parent are known, the "Commissioner will only consent if the parent does." It recommends, finally, that if a biological parent cannot be located *or* the commissioner is the legal guardian of a child (which usually means that parental rights have been terminated or surrendered), consent should be determined on a case-by-case basis.[397]

When presented with a hypothetical situation in which a biological parent consented to allow a child into a trial that child welfare officials judged to be not in the child's best interest, HRA legal staff determined that the parent's decision (provided he or she had custody) would prevail unless it appears to be cause for neglect or abuse.[398] Since most foster children were removed from their parents on abuse/neglect petitions, OLA lawyers reasoned that any decision that

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[394] Memo, February 3, 1989, from Brooke Trent to William Grinker, "Participation of HIV+ Foster Children in Hospital Protocols."
[395] Memo, February 14, 1989, from William Grinker to Brooke Trent, cc: S. Larabee, C. Palacio, T. Maher, "HIV+ Foster Children – Your Memo of 2/3."
[396] Memo, December 22, 1988, from Charlotte von Clemm to Cristina Palacio, cc: Brooke Trent, "Involvement of SSC Children in Hospital Protocols;" Memo, January 11, 1989, from Susan Larabee, to Brooke Trent, "Participation of HIV+ Foster Children in Experiment Studies [sic]."
[397] Memo, January 11, 1989, from Susan Larabee, to Brooke Trent, "Participation of HIV+ Foster Children in Experimental Studies." The requirement that the commissioner approve all enrollments during this period is consistent with a book chapter written by Palicio. See Cristina Palicio and Chris Weedy, "Treatment Issues Regarding Children in Foster Care," in Philip Pizzo and Catherine Wilfert, eds., *Pediatric AIDS: The Challenge of HIV Infection in Infants, Children and Adolescents* (Baltimore: Williams and Wilkins, 1991), p. 569-576.
[398] Memo, December 22, 1988, from Charlotte von Clemm, to Cristina Palacio, cc: Brooke Trent, "Involvement of SSC Children in Hospital Protocols."

concerned a child's safety, including the decision to participate in a clinical trial, needed to be reviewed by CWA. Palacio, the OLA lawyer, relayed to Grinker the concerns of CWA staff that the hospitals did not know of the procedure for enrolling foster children in trials, especially the requirement that the commissioner approve enrollment even after obtaining parental consent.[399]

In an interview with Vera staff, Grinker recalled that his senior management team had "agonized over the policy."[400] Referring, in particular, to the Tuskegee syphilis study, an infamous medical study in which African American men were left untreated as part of research conducted by the public health service, he said, "We knew about Tuskegee and we did not want to set up that kind of a situation."

At the same time, Grinker had wanted to make sure that children in foster care had access to new treatments: "We had no idea what the long term effects [of being born with HIV] would be, but the speculation was that these kids were doomed to a short, terrible life. Anything that could be done should be done."[401]

In 1989, a federal Department of Health and Human Services working group and NIH's AIDS Program Advisory Committee recommended that processes be developed for enrolling foster children in HIV/AIDS clinical trials.[402] Grinker's opinion at the time was that the clinical trials policy should let at least some of the kids participate if it offered possible benefits.

Other key respondents familiar with the policy discussion recalled the tension in his decision between providing access to treatment and ensuring proper treatment of children in foster care.

> *…I can remember Grinker being somewhat swayed by [the doctors'] arguments and saying, "Well, if there's something out there that these kids could get…"—because there was nothing—"…I would want them to be in there"…. [O]ne of the doctors said, "Well, why don't you just let us decide who should be in there or not?" And Grinker said, "No, I can't abdicate my responsibility and just let the docs decide. We have to come up with something…". So that might be around the time that they started trying to come up with actual policy about how the clinical trials would be set up and which kids would be able to participate.*

The materials Children's Services shared with Vera researchers contained no evidence that HRA consulted with the New York State Department of Social Services (NYS DSS) officials about the decision to enroll children in clinical trials in 1988 and 1989.[403] The files indicated,

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[399] Memo, July 7, 1989, from Cristina Palacio, to William Grinker, cc: Solomon Malach, Martin Baron, "Trial Studies."

[400] Interview with William Grinker, March 30, 2007. Another key respondent had the same recollection.

[401] Interview with Grinker, March 30, 2007.

[402] Draft, May 7, 1992, "Points to Consider: Involving HIV Positive Children Who are Wards of the State in HIV/AIDS Research," a document prepared by the Department of Health and Human Services, Office of the Surgeon General, Public Health Service Panel on Women, Adolescents, and Children with HIV Infection and AIDS.

[403] Until the formation of the New York State Office of Children and Family Services (OCFS) during the administration of Governor George Pataki, child welfare agencies in New York State were supervised by the New York State Department of Social Services. Unlike most states, which have a "state administered" system in which state agencies operate the child welfare system, New York is one of ten states that have a "state supervised" child

however, that by the summer of 1989, HRA's commissioner and staff knew that NYS DSS was supporting a narrower policy that allowed a foster child to participate in clinical trials only with parental or legal guardian consent.[404] In addition, the state had asked Incarnation Children's Center about clinical trials involving foster children in the spring of 1990.[405] In the summer of 1990, NYS DSS circulated a draft administrative directive (ADM) that more strictly limited the participation of foster children in HIV/AIDS clinical trials.[406] Barbara Sabol, who had been appointed HRA Commissioner after the election of David Dinkins as mayor in 1989, sent a letter in September 1990 to the state saying that the proposed regulation on foster child clinical trial participation is "of most concern."[407] In part, the concern was based on an internal study by the PAU of four foster care agencies that found that 70 percent of HIV-positive children did not have an "available parent" to make informed consent decisions.[408] Sabol's letter went on to describe HRA's policy: "…we require HRA approval of a trial study protocol prior to enrollment of any foster child, even if parental consent has been obtained…. In addition to [HRA's] consent, we require that parental consent be obtained, when a parent is available. (If a parent refuses to consent, HRA will not consent to that child's enrollment.)"

Sabol urged the state to support HRA's policy, arguing:

> *It is widely believed by the medical community that many of the clinical trials offer the best available medical care for children with HIV, and that the drugs available through clinical trials may be an HIV-infected child's best hope for treatment. Surely, it is not fair to prohibit HIV-infected children in foster care from being enrolled in appropriate clinical trial studies simply because their parents are unavailable.*[409]

The state withdrew the ADM.[410] Vera's search of administrative directives, informational letters, and local commissioner memorandums to local districts from NYS DSS and its successor

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welfare system in which local districts are responsible for child welfare within the parameters of state social service law and regulations.

[404] Memo, July 24, 1989, from Cristina Palacio, to Bill Grinker, "Trial Studies."

[405] Letter, April 24, 1990, from Constance Gaynor, ICC, to Helen Dowd, New York State Department of Social Services, in response to Dowd's inquiry that discusses four clinical trials (PACTG 045, PACTG 051, PACTG 128 and Burroughs Wellcome AZT Treatment IND) and indicates that foster children at ICC are enrolled in PACTG 051 and Burroughs Wellcome AZT Treatment IND.

[406] Letter, September 5, 1990, from Barbara Sabol, to Tom McGraw, NYS DSS,re: Proposed ADM [Administrative Directive] entitled "Foster Care; Adoption; Required Confidentiality of HIV-Related Information." An administrative directive, or ADM, is a formal policy that local service districts, including New York City, are legally obligated to follow.

[407] Ibid. The letter outlined other concerns with the ADM and asked that NYS DSS separate issues of testing and clinical trials from issues of adoption and confidentiality.

[408].Ibid.

[409] Ibid.

[410] Memo, April 23, 1991, from Nancy Erickson to various CWA staff, re: Proposed ADM: "Foster care and adoption: Agency Responsibilities and Issues Concerning HIV-Infected Foster and Adoptive Children."

agency, the New York State Office of Children and Family Services, found little mention of clinical trials from 1990 to 2001 and no language that contradicted HRA policy.[411]

Summary. In the late 1980s HRA had not yet issued a formal policy concerning clinical trials participation by children in foster care.[412] The memos and letters Vera reviewed indicated that the agency had made a series of decisions and developed a process that allowed for the participation of foster children in clinical trials. That process involved the following steps:

1. Physician requests that a specific child be enrolled in a specific trial.
2. Office of Legal Affairs (OLA) and the Pediatric AIDS Unit (PAU) consult with outside experts to determine if the trial meets the standards for the participation of children in foster care.
3. OLA makes recommendation to the commissioner to approve or disapprove enrollment.
4. If the commissioner approves enrollment, OLA lawyers draft a letter of agreement.
5. The commissioner and the clinical trial researcher sign the letter of agreement. An independent advocate is appointed, if necessary as per 45 CFR 46.409.
6. Consent is obtained from a biological parent or legal guardian if one is available. If the biological parent is unavailable, then the commissioner reviews enrollments on a case-by-case basis.
7. If consent is obtained and HRA approves the trial, the child is enrolled.

Early Implementation Issues

The process of implementing the policy for enrolling and monitoring foster children in clinical trials encountered many obstacles, all of which arose within a high-pressure medical, child welfare, political, and legal environment. Four challenges stand out.

1. HRA did not have in-house expertise on clinical trials generally or HIV specifically and did not employ a staff physician. Instead, the agency relied on outside medical experts and consultants.
2. Implementing the process required significant staff time, especially from the legal department.
3. HRA had to communicate the process and enforce it among a network of contract agencies over which it exercised limited control and a network of hospitals over which it had no formal control.

[411] See http://www.ocfs.state.ny.us/main/policies/search/searchright.asp, a searchable database of policy directives. Searching on relevant search terms (e.g. "clinical trial" and "research") did not identify policy directives that contradicted HRA or Children's Services' policy.
[412] Memo, July 24, 1989, from Cristina Palacio, to Bill Grinker, re: Trial Studies.

4. The majority of HIV-positive children in care had parents who retained parental rights but were difficult to locate.

The documentation Vera reviewed suggests that these challenges provided the impetus for subsequent changes in the city's procedures. The following discussion of the initial rollout of the process illustrates some of those challenges and the strategies the agency used to try to overcome them.

Initial Policy Rollout. Grinker reviewed the first letter of agreement for PACTG 045 in March 1989. More than a year had passed since the initial letter regarding clinical trials from NIH, and during that time physicians had made three additional requests to include children in new clinical trials, two conducted by the Pediatric AIDS Clinical Trials Group (PATCG) and a third conducted by a pediatrician at a New York City hospital. The first trial, PACTG 051 (051), sought to determine the effectiveness of daily oral AZT combined with monthly infusions of IVIG when compared to oral AZT alone. Its goal was to determine which treatment reduced the frequency of serious bacterial infections in children experiencing HIV symptoms.[413] When HRA staff started to review the trial, the Food and Drug Administration (FDA) had approved AZT for use in *adults* with HIV, but AZT remained an investigative new drug (IND) for children—making it difficult to obtain outside of a clinical trial setting. PACTG 052 (052) assigned HIV-positive children to receive either AZT or a placebo every six hours for two years.[414] The third trial examined a laboratory technique for diagnosing HIV infection called polymerase chain reaction (PCR).[415]

In her first memo concerning the 051 and 052 trials to Grinker, Palacio, the lawyer from OLA, highlighted several issues with the studies.[416] She noted that tests of AZT with a small number of HIV-positive children who were not in foster care had showed clinical improvements

[413] National Institute of Allergy and Infectious Diseases, ACTG 051, A Double-Blind, Placebo-Controlled Trial to Evaluate Intravenous Gamma Globulin in Children with Symptomatic HIV Infection Receiving Zidovudine, Version 4.0 FINAL, September 15, 1989.

[414] A placebo is an "inactive pill, liquid, or powder that has no treatment value [and] in clinical trials, experimental treatments are often compared with placebos to assess the treatment's effectiveness." See http://clinicaltrials.gov/ct/info/glossary#placebo. Researchers often use placebos so that neither the researcher nor the patient knows if they are receiving the experimental treatment. Research in many fields has identified a "placebo effect"—participants in research may fare better than non-participants because they believe they are receiving a new treatment even when they are not. See Harry Guess, Linda Engel, Arthur Kleinman, and John Kusek, eds., *Science of the Placebo: Toward an Interdisciplinary Research Agenda* (London: BMJ Books, 2002).

[415] National Institute of Allergy and Infectious Diseases, ACTG 051, A Double-Blind, Placebo-Controlled Trial to Evaluate Intravenous Gamma Globulin in Children with Symptomatic HIV Infection Receiving Zidovudine, Version 4.0 FINAL, September 15, 1989. In many protocols, AZT is also called ZDV or Zidovudine—for simplicity, this report refers to Zidovudine as AZT. Protocol for PACTG 052: The Safety and Effectiveness of Zidovudine in the Treatment of HIV-Infected Children with Mild to Moderate Symptoms, last updated on www.clinicaltrials.gov on June 23, 2005. Protocol: Using the Diagnostic Assay (PCR) Polymerase Chain Reaction and Viral Co-cultures to Study 20-30 Foster Children Who Have Seroreverted.

[416] Memo, April 4, 1989, from Cristina Palacio, to William Grinker, "HIV Clinical Trials."

in most of the children, though the results depended in part on how the drug was administered.[417] The memo discussed AZT's potential toxicity, noting that it could reach "life threatening levels," but remarked that the adult studies found that the benefits outweighed the risks. The memo also highlighted concerns about the treatment of bacterial infections on the protocol, whether asking foster parents to administer AZT four times a day presented any problems, the risk of the three lumbar punctures in the protocol, and the need to "beef up" a consent form for older minors.[418]

To further understand the scientific merits of the clinical trial and to assess the benefits and risks to foster children, OLA staff consulted with medical professionals outside the agency. There were few pediatric HIV/AIDS experts at the time and HRA did not employ a physician with HIV expertise. Agency staff consulted with physicians at NYCDOH and the National Institutes of Health.[419] At OLA's request, two doctors at NYCDOH reviewed the 051 and 052 studies. Both doctors recommended that HRA approve foster child enrollment in the protocols, concluding, "the 'bottom line' is that the studies <u>are</u> appropriate, beneficial, and necessary for the HIV-infected children under HRA's care."[420]

OLA lawyers disagreed, however, with NYCDOH's assessment of 052.[421] After consulting with two colleagues, Palacio told Grinker that a "study involving a placebo group is inappropriate for foster children" and inconsistent with the justification for allowing foster children into studies.[422] She also questioned the NYCDOH's protocol review process. NYCDOH had consulted with the clinical trial researchers of both studies at Mt. Sinai Medical Center in making their determination, "hardly giving [HRA] an independent assessment," in Palacio's opinion. She also wrote that NYCDOH seemed "totally unaware of the special considerations involved in consenting to such studies for foster children."[423] Palacio recommended rejecting 052 and Grinker did not approve the trial.[424]

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[417] Palacio referred to Phase I clinical trials of AZT in children. AZT had already been approved in adults. New York City children in foster care did not participate in Phase I trials of AZT. For more information on clinical trial phases, see Chapter 8.

[418] A lumbar puncture (also called a spinal tap) is a common medical test that involves taking a small sample of cerebrospinal fluid (CSF) for examination. In a lumbar puncture, a needle is carefully inserted into the lower spine to collect the CSF sample. See http://kidshealth.org/parent/general/sick/lumbar_puncture.html, last accessed October 30, 2008.

[419] Letter, February 28, 1990, from Stephen W. Nicholas, to Maria Favuzzi, recommending approval of PCR studying an investigation setting; letter, August 10, 1990, from Sarmistha B. Hauger, to Cristina Palacio, recommending approval of PCR study only if certain conditions are met; letter, August 14, 1990, from Israel Lowy, to Cristina Palacio, recommending against approval of PCR study; letter, August 18, 1990, from Virginia Anderson, to Cristina Palacio, recommending approval of PCR study; letter, July 6, 1989, from Mark Rapoport, recommending approval of PACTG 051 and PACTG 052. Steven Merahn, undated notes recommending approval for PACTG 051 and PACTG 052; letter, January 22, 1990, from Jonathan Horowitz, to Maria Favuzzi, recommending approval of PCR study.

[420] Letter, July 6, 1989, from Mark Rapoport, to Christina Palacio, "Study #051 and #052, using AZT & IVIG in HIV-infected Children." Underlining in original document.

[421] OLA staff in this discussion refers to Palacio, Karen Goldstein, and Martin Baron.

[422] Memo, July 25, 1989 from Cristina Palacio to William Grinker, re: AZT Clinical Trial Studies.

[423] Ibid.

[424] According to an August 29, 1989, memo from Palacio, to Grinker, Protocol 052 closed after a study showed AZT to be effective in asymptomatic adults.

On the other hand, OLA staff felt that 051 might offer benefits to children in care not otherwise available outside of a clinical trial—provided the concerns Palacio highlighted in her initial memo were addressed.[425] To learn more, Palacio spoke with James Balsley, a physician at the National Institutes of Health. According to a memo that Palacio wrote to Grinker, Balsley said that the correction of an editorial mistake in the protocol had addressed the problem of bacterial infections, and that a new formulation of AZT had made the medication easier to administer. He also reported that AZT toxicity for children mirrored that of adults: In the safety and toxicity (Phase I) part of 051—which HRA did not consider for foster children—one child out of the 70 participants had died of neutropenia (reduced white blood cell counts), but the child suffered from neutropenia before she entered the study and researchers did not attribute the death to AZT. Moreover, the study's Data and Safety Monitoring Board had reviewed the initial batch of data on adverse events earlier that month and approved continuing the study. Palacio also wrote that NYCDOH staff felt that the lumbar punctures presented a minimal risk that was outweighed by the benefit of knowing of any effects related to HIV on the central nervous system. Finally, Palacio said that she would raise the issue of the consent's language with the individual investigators.[426] After speaking with Balsley, Palacio reported that some physicians used AZT to treat HIV-positive children outside of clinical trials, but that this happened less often in New York City due to the cost of AZT and because outside of clinical trials, AZT came only in tablet form.

In light of this information, in August 1989 OLA staff recommended that Grinker approve the participation of foster children in 051. He did so in September 1989, and OLA drafted and sent a letter of agreement to NIH for review in October. NIH took three months to review and comment on the draft, sending suggested revisions in January 1990, after Barbara Sabol had become HRA's new commissioner.[427] During the time NIH was reviewing the letter, AZT became available through a pediatric Investigational New Drug (IND) trial sponsored by the pharmaceutical company Burroughs Wellcome.[428] Citing the urgent need for treatment and the National Institute for Allergy and Infectious Disease's IRB's approval of the Burroughs Wellcome AZT Treatment IND, the FDA waived the usual requirement for local IRBs to review and approve the IND. The waiver did not affect other aspects of participation: enrolling in the IND required parent or guardian consent.[429] Grinker approved the enrollment of foster children into the Burroughs Wellcome IND shortly thereafter.[430] OLA staff reviewed the 051 protocol

[425] Memo, August 29, 1989, from Palacio, to Grinker, "AZT Clinical Trial Studies."
[426] Ibid.
[427] Letter, January 24, 1990, from George Counts, DAIDS/NIAID, to OLA's Carol Marcus.
[428] Form letter, October 26, 1989, from Terri Creagh-Kirk, Borroughs Wellcome, and James Balsley, National Institute for Allergies and Infectious Diseases to "Doctor." See also "A Treatment IND for Retrovir Brand Zidovudine (AZT) Therapy of Pediatric Patients with HIV Disease TX 304," October 6, 1989. For a discussion of INDs, see Chapter 8.
[429] The FDA required that any changes to the NIAID approved consent form must pass local IRB review.
[430] Vera staff did not find a dated letter from the commissioner approving foster child enrollment in the Burroughs Wellcome AZT Treatment IND. However, Vera staff reviewed an undated form letter from Grinker authorizing participation in the IND and references to foster children enrolling in the Burroughs Wellcome IND in other correspondence with the commissioner. For example, see memo, November 13, 1989, from Martin Baron, to

again in light of the availability of the Burroughs Wellcome AZT IND and then waited for the new commissioner to review clinical trials policy.[431] Sabol formally approved 051 for foster child enrollment in July 1990.[432]

Streamlining the Process: Approving Trials

Vera staff did not find documentation indicating that Grinker or subsequent commissioners under Mayors Dinkins or Giuliani explored eliminating the option of enrolling children in foster care in clinical trials during the period from 1988 to 1999. The files indicate that each HRA, CWA, and ACS commissioner knew about the policy, and in at least two cases the HRA commissioner received a formal memo from legal staff outlining the history of clinical trials policy and asking whether the policy should continue.[433] Until the late 1990s, policy documents concerning clinical trials policy focused, instead, on how to make decisions more efficiently and how to streamline the enrollment process if a commissioner approved foster child participation in a particular trial.

As the number of HIV-infected children in foster care and the number of pediatric clinical trials for HIV/AIDS increased, the files indicate that pressure built to reduce delays in HRA's review process. In November 1989, HRA agreed to a recommendation from the NYCDOH and the AIDS Clinical Trials Group (ACTG)—a group that included adult and pediatric researchers at the time—that the three agencies (HRA, NYCDOH, and ACTG) hold joint meetings to review issues of foster child participation in future clinical trials and to speed HRA's review process.[434] In agreeing to the meetings, HRA reiterated that it retained responsibility for clinical trials policy for children in its care: "It must be understood, however, that the decision concerning whether to consent to any future clinical trials cannot be delegated…but must be made by HRA."[435]

William Grinker, "AZT Treatment/Clinical Trials;" and letter, February 1, 1990, from Nancy Arroyo, PAU, to Saint Vincent's Services that indicates the commissioner of social services has approved enrollment of foster children in the Burroughs Wellcome AZT Treatment IND.

[431] Memo, November 13, 1989, from Martin Baron, to William Grinker, "AZT Treatment/Clinical Trials."

[432] Letter, July 6, 1990, from Barbara Sabol, to Henry Sacks; handwritten notes of Maria Favuzzi, July 25, 1990.

[433] Memo, May 23, 1990, from Cristina Palacio, to Barbara Sabol, "Participation of Foster Children with HIV-related Illness in Clinical Studies;" memo, March 16, 1994, to Marva Livingston Hammons, from Carol Marcus, "Participation of Foster Children who are HIV Seropositive or who are HIV infected in Clinical Trial Protocols;" note, March 29, 1994, from Inell Gilmore, executive assistant to administrator/commissioner, to Carol Marcus, "Participation of Foster Children who are HIV Seropositive or who are HIV Infected in Clinical Trial Protocols." We did not find a formal memo to Kathryn Croft or Nicholas Scoppetta, but each received memos regarding specific clinical trials and signed letters of agreement for clinical trial enrollments.

[434] Memo, November 13, 1989, from Martin Baron, associate general counsel, Foster Care/Office of Legal Affairs, to William J. Grinker, administrator/commissioner, HRA, cc: Karen Goldstein, Cristina Palacio, Anne Sommers, Pat Burton, Nancy Arroyo, "AZT Treatment/Clinical Trials." In addition, researchers conducting the Burroughs Wellcome AZT Treatment IND cited delays and refusals to consent by social service agencies for the unexpectedly low enrollment in the study. See T. Creagh, M. Elkins, E. Andrews, J. Balsley, B. Yankaskas, H. Tilson, "Zidovudine Therapy in Pediatric Patients: Report on the Zidovudine Pediatric Patient IND Program," *Journal of Clinical Research and Drug Development* 8 (1994): 249-257.

[435] Memo, November 13, 1989, from Martin Baron, associate general counsel, Foster Care/Office of Legal Affairs, to William J. Grinker, administrator/commissioner, HRA, cc: Karen Goldstein, Cristina Palacio, Anne Sommers, Pat Burton, Nancy Arroyo, "AZT Treatment/Clinical Trials."

Physicians and medical researchers at major hospitals and some community activists also expressed concerns about the time HRA needed to make decisions about enrollments. In general, these groups felt that HRA's delays meant a delay in treatment for sick and dying children.[436] Several physicians we interviewed described the desperation they felt during that time. As one physician recalled:

> *Now that AZT looked good [in adults], you know, the pediatricians were clamoring for access to this drug. And Burroughs Wellcome, the manufacturer of the drug, said, "Yes, we're going to do a study with pediatrics. We're only going to have seven sites, and each site will have ten patients." And we begged to be one of those sites, because we had people dying all over the place.*

A related concern was that foster children might be denied access to new treatments because the limited number of slots in a trial might be filled before HRA made its enrollment decisions. Following her appointment as HRA's commissioner in late spring 1990, Sabol received a letter from four physicians who treated children with HIV and conducted pediatric HIV/AIDS clinical trials at New York City medical institutions.[437] The letter requested that HRA reconsider its consent process. "[T]he safeguards set up to protect foster children from being exploited now have the unintended effect of limiting their access to new therapies," they wrote. The doctors asserted that delays by HRA could deny foster children access to the best and "sometimes the only treatment." They also noted that the NIH, the FDA, the Health and Hospitals Corporation, and the participating hospitals' IRBs had all approved the protocols submitted to HRA. To remedy the time lag, the four physicians suggested that CWA send a delegate to some of the local IRB review meetings. But Sabol declined the invitation, saying HRA needed to make "separate determinations" about the medical and scientific validity of individual trials.[438]

Another letter from a physician/researcher was more blunt: "By the time [045] was approved by your agency the protocol closed. The same thing happened with protocol [051]—IVGG—Albumin with AZT. The third one…is pending for the last 2-3 months. By the time it is approved the protocol will again be closed."[439] His letter to Sabol pointed out that several other states were

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[436] Judith M. Martin and Henry S. Sacks, "Do HIV-Infected Children in Foster Care Have Access to Clinical Trials of New Treatments?" *AIDS & Public Policy Journal* 5, no. 1, p. 3-8.

[437] Letter, May 31, 1990, from Henry Sacks, William Borkowsky, Anne Gershon, and Ayre Rubinstein, to Barbara Sabol, commissioner, and HRA, "Treatment for HIV-infected foster kids." The physicians practiced medicine at Mount Sinai Medical Center, Bellevue Medical Center, Columbia University Medical Center and Albert Einstein College of Medicine, respectively. Separately, Sabol received a letter, October 17, 1990, from Senih Fikrig, a pediatrician and principal investigator at Kings County Hospital Center, that said that because of prolonged decision making on the part of HRA, "these children are deprived of certain treatment protocols that might be of benefit to them." The pediatric committee of the activist group ACT-UP also raised this issue, though at a later date.

[438] Letter, July 6, 1990, from Barbara Sabol, to Henry Sacks (PhD, MD), Mt. Sinai Pediatrics ACTU, re: Response to May 31, 1990 letter on concerns re: HIV-infected foster kids.

[439] Letter, October 17, 1990, from Senih Fikrig to Barbara Sabol.

approving protocols for children in foster care, and he concluded by noting that HRA's stance was "…hardly a leadership position compatible with the medical history of this city."[440]

Communication and Oversight of the Process. In other correspondence and PAU documents, doctors and CWA staff raise issues that reflected the difficulty of communicating and overseeing a process with a large provider network. In 1989, a physician/researcher wrote to inform HRA that four foster children were enrolled in clinical trials at his institution and he only recently found out that he needed to obtain HRA's approval after obtaining consent from the biological parents.[441] An HRA attorney responded that she had verbally communicated this requirement to the doctor at a conference the previous year, and that she had done so again in subsequent conversations with the physician's lawyer, and in discussions with him of protocol 051.[442] Faced with the choice of interrupting the children's treatment or accepting what HRA's lawyer termed a "policy violation," however, HRA allowed the children to remain enrolled in the clinical trial, provided the physician provided the agency with consent forms for the four children.[443]

The documents we reviewed showed that some physician/researchers continued to be unclear about their obligation to notify HRA after a birth parent consented to allow his or her child to participate in a trial. As late as 1993, a physician apologized to the PAU director for not informing the unit when children in foster care entered trials after biological parents signed consents.[444] On at least three different occasions in the early 1990s, the PAU sent out surveys to clinical trial researchers to ensure that the unit knew of all foster children enrolled in clinical trials. Follow up with clinical trial researchers is listed as a routine activity in PAU quarterly reports from 1992 through the start of this study.[445]

The PAU confronted a similar, and persistent, challenge in communicating with the large network of foster care providers.[446] In 1990, the PAU director wrote to 12 agencies that had not responded to initial inquiries about the number and identities of HIV-positive children in their care.[447] On at least three additional occasions, the PAU provided the contract foster care agencies with a list of children in their care and asked them to update missing or inaccurate information, including information about the status of children's enrollment in clinical trials or research protocols.[448]

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[440] Ibid.
[441] Letter, October 5, 1989, from Henry Sacks, director, Clinical Trials Unit, Mount Sinai Medical Center, to William Grinker.
[442] Letter, October 16, 1989, from Cristina Palacio to Henry S. Sacks.
[443] Letter, December 19, 1989, from Henry S. Sacks, PI, Mount Sinai Medical Center, to Cristina Palacio, cc: Nancy Arroyo, Martin Baron..
[444] Letter, April 7, 1993, from Elaine Abrams to Maria Favuzzi.
[445] K134 interview.
[446] This discussion includes both contract foster care agencies and direct foster care services provided by the child welfare agency. Contract agencies provide most of the foster care in New York City.
[447] Letter, August 30, 1990, from Maria Favuzzi, to Executive Directors [of Voluntary Child Care Agencies].
[448] Ibid.; Memo, September 25, 1995, from Pat Burton, to Foster Care Agency and DFCS Liaisons to CWA's Pediatric AIDS Unit, re: Children Reported to the Pediatric AIDS Unit as HIV Positive; memo, March 11, 1997, from Regina Prince to Foster Care Agency and DFCS Liaisons to CWA's Pediatric AIDS Unit, re: Children

The PAU also spent time tracking down test results of children in care—despite a formal policy that required the contract agencies to share all test results with the PAU.[449] In the first 11 months of 1993, the PAU issued 1,673 consents for HIV testing but received only 777 test results (46 percent) from the contract agencies. Follow up activities with the "PAU liaisons" at each agency produced another 617 results, including withdrawals of request for consent in ten percent of cases and 17 percent still "to be tested."[450] Although most of the originally unreported test results were negative, the follow up showed 26 positive test results that initially had not been reported to the PAU.[451] After the follow up, test results remained unknown for 279 cases (17 percent). The PAU continued to receive fewer test results than it had authorized throughout the 1990s.[452]

Other information presented similar challenges. Tables in a June 30, 1996 report show large amounts of missing demographic information on HIV-positive children in foster care. In addition, the PAU lacked diagnostic information (indicating whether HIV-positive children showed symptoms of AIDS or not) on 73 of the 628 (11.6 percent) HIV-positive children in care.[453] Also in 1996, the PAU did not have the name of the HIV-specialized medical center for 32 percent of the HIV-positive children in care (212 of 612 children).[454] In 2005, a longtime PAU staff member wrote to her supervisor that the agency routinely did not receive discharge information on HIV-positive children leaving foster care until "months or years later"—a fact that Vera reviewers occasionally noted independently during their review of child welfare files.[455]

Creating the Medical Advisory Panel. In 1990, in response to the "numerous legal issues relating to HIV illness confronting the foster care system" and the increasingly apparent need for clarity and consistency in creating and executing clinical trials policy, a small group of staff from Office of Legal Affairs, the Commissioner's Office, and the Pediatric AIDS Unit began meeting every two weeks.[456] In May 1990, the group recommended that HRA convene a group of pediatric AIDS specialists to review clinical trials and to "provide [HRA] with timely and informed advice on medical treatment for HIV ill children."[457] The panel would be modeled after the Child Fatality Review Panel at HRA. Sabol endorsed the proposal and on June 26, 1990, the

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Reported to the Pediatric AIDS Unit as HIV Positive; memo, March 10, 1998, from Hee Sun Yu, assistant commissioner, Office of Medical Services Planning, to Congregate Care and DFP Executive Directors.

[449] Bulletin 93-1, September 13, 1993, required that "Foster care agencies must notify the PAU of the results of any HIV testing approved by the PAU," p. 21.

[450] PAU quarterly report to MHRA, dated August 4, 1994.

[451] Ibid.

[452] This assessment is based on a review of all available PAU quarterly reports from 1992 to 2007.

[453] PAU quarterly report, January 31, 1997, p. 3.

[454] PAU quarterly report, April 29, 1996, p. 4.

[455] Attachment to e-mail, February 7, 2005, from Glenda Carroll to Elizabeth Roberts and Sally Serio, re: Time-sensitive requests. An undated memo titled "Plans for PAU for the next 18 months" says, "children can be in care for months/years and no updated information is shared with us."

[456] Memo, May 29, 1990, from Anne Sommers to Barbara Sabol, re: AIDS Medical Advisory Panel.

[457] Ibid.

Medical Advisory Panel (MAP) was established to "advise HRA and CWA upon various medical/treatment issues that arise in the field of Pediatric AIDS."[458] Although descriptions of the MAP emphasized its role in reviewing clinical trials, HRA staff felt that the group might also answer other questions related to HIV/AIDS care and treatment. By establishing a standard procedure, HRA hoped to speed the review process by having a pre-approved group of specialists available to provide expert input on specific clinical trials.

HRA staff recruited MAP members in the summer of 1990 and requested that NYCDOH designate two members as well.[459] HRA envisioned three or four of the MAP members providing advice on any given trial protocol under consideration by HRA. Pediatric HIV/AIDS physicians and clinical trial researchers praised HRA's decision to create a more streamlined process and volunteered to serve on the newly formed panel.[460] By the end of 1990, HRA had recruited at least 22 physicians including doctors from the NYC Department of Health and the NYS Department of Health's AIDS Institute.[461]

Federal Steps that Sped Access to Drugs Targeting HIV. While HRA was creating the MAP, the federal government was taking steps to increase access to drugs that targeted HIV/AIDS. In June 1990, following the FDA's approval of the pediatric use of AZT the previous month, the U.S. Public Health Service circulated a proposed policy statement that addressed access to investigational drugs for HIV/AIDS. The proposal, in essence, aimed to make "investigational agents…more widely available to people with AIDS and HIV-disease who have no therapeutic alternatives and who cannot participate in the controlled clinical trials."[462] In July 1990, the New York State Department of Social Services sent an informational letter informing all local social service districts, including New York City, of a recent federal decision to allow Medicaid to pay for the use of AZT treatment for children age 13 and younger.[463]

HRA continued its effort to streamline the review process. In spring 1991, the PAU contacted the National Institute of Child Health and Human Development (NICHD)'s Pediatric, Adolescent and Maternal AIDS Branch to discuss how HRA might receive information and copies of clinical trial protocols that were being developed.[464] HRA hoped that advance notice of pending trials might allow the agency to decide on the appropriateness of foster child enrollment faster. A physician at the Pediatric, Adolescent, and Maternal AIDS Branch, John "Jack" Moye

[458] Memo, July 3, 1990, from Pat Burton, director, Hospital Baby Project, to Melinda Fields, acting assistant deputy commissioner for policy and planning, re: AIDS Medical Advisory Panel.
[459] Memo, August 16, 1990, from Barbara J. Sabol to Woodrow A. Myers, commissioner, NYC DOH, re: HRA Medical Advisory Panel.
[460] See, for example, letter, July 6, 1990, from Andrew Wiznia to Barbara Sabol, re: Creation of MAP.
[461] Vera staff reviewed copies of 22 letters dated December 28, 1990, from Barbara Sabol to physicians welcoming them to the MAP.
[462] Memo, June 25, 1990, from Cristina Palacio to Barbara Sabol, B. Ensminger, C. Marcus, A. Rothbaum, P. Burton, M. Swackhamer, re: Public Health Service AIDS-Related Policy Statement.
[463] Memo, July 24, 1990, from New York State Department of Social Services Division of Family and Children Services, Medical Assistance Transmittal 90 INF-36 to Commissioners of Social Services; Directors of Voluntary Child Care Agencies, subject: Medicaid Reimbursement of AZT for Foster Children.
[464] Vera key respondent interview.

Jr., sent regular updates on the status of NICHD's review of HIV/AIDS pediatric clinical trials—a practice he would continue through 1999. In an early letter, the NICHD expressed agreement with HRA's decision to consider enrolling foster children in clinical trials, noting that doing so was consistent with the position of the American Academy of Pediatrics and with "the intent of a forthcoming Public Health Service guidance document offering points to consider on involving HIV positive children who are wards of the state in research on HIV infection and AIDS."[465] The correspondence that Vera staff saw between Moye and HRA indicates that Moye understood that HRA needed to make its own determination on the trials: Each letter describing a new protocol contained a paragraph noting that NIH provided the information only to assist HRA/ACS in their decision making process.

Approving Clinical Trials, Not Individual Enrollments

On May 28, 1991, HRA commissioner Sabol sent a letter to foster care agencies and medical providers describing a new policy and process for deciding on clinical trials enrollment of HIV-positive children in foster care.[466] In the process spelled out in Sabol's letter, the MAP would review individual trials and recommend whether foster children generally should participate in specific trials, based on whether a trial would "offer each participating foster child a significant potential benefit, with a concomitant 'minimal' risk of injury or harm."[467] After weighing the advice of the MAP, OLA, and the PAU regarding a specific clinical trial, the commissioner would approve or disapprove of foster children participating in that trial. If the commissioner approved participation, the process called for HRA and the medical institutions conducting the study to sign a letter of agreement, after which enrollment could begin without the commissioner (or his or her designee) reviewing the individual circumstances of each child proposed for enrollment.[468] The following section describes this letter of agreement, a standard letter that remained unchanged until at least January 29, 1997—although in some trials, as described below, the commissioner inserted additional conditions for foster child enrollment.[469]

Elements of the New Policy and Process. The agreement called for the clinical trial researchers to obtain informed consent from a birth parent or legal guardian. When the parents or guardians whereabouts were unknown, the clinical trial researcher could ask the child's contract foster care agency to conduct a "diligent effort to locate the parents to obtain consent for participation" or to

[465] Letter, May 24, 1991, from Jack Moye, MD, Pediatric Adolescent and Maternal AIDS Branch, NICHD, to Pat Burton, director, Hospital Baby Project.
[466] Form letter, May 28, 1991, from Barbara Sabol to physicians re: New guidelines for HRA approval of foster child enrollment in clinical trials; letter, June 19, 1991; from Robert Little, executive deputy commissioner, to Executive Directors of Voluntary Agencies.
[467] Form letter, May 28, 1991 from Barbara Sabol to physicians, re: New guidelines for HRA approval of foster child enrollment in clinical trials.
[468] A sample letter of agreement is in Appendix 9.
[469] Letter, January 29, 1997, from Nicholas Scoppetta, Children's Services commissioner, to Mahrukh Barnji, MD, Metropolitan Hospital, that announces approval of PACTG 338 and includes a letter of agreement. Copies of this letter went out to several other principal investigators on the same date.

make "written certification of diligent search for those parents whose whereabouts remain unknown."[470] The search consisted of "at least one personal visit to the parent(s) last known address" and a mailgram to the last known address if the personal visit proved unsuccessful in locating the parent.[471] When a search did not locate a parent, the letter of agreement called for the agency to notify the clinical trial researcher that the search took place. The researcher then notified the PAU of the enrollment. The PAU could then formally approve the enrollment. If a foster care agency certified that the child's parents were deceased, the commissioner (via the PAU designee) consented to an approved trial upon receipt of a notification of enrollment from the doctor. Regardless of the consent process used, HRA required that copies of the signed consent forms be sent to the PAU, along with IRB approvals. The child's personal physician also had to consent to the enrollment, although the letter of agreement did not require documentation of this consent.

The letter of agreement contained some protections for children enrolled in trials. When a trial treatment showed positive results, the agreement required that participants be offered that treatment after the trial, if appropriate. Also, participants could not be precluded from other treatment that might help them while in the trial. HRA required that hospitals follow the relevant laws regarding confidentiality and obtain HRA's approval before publishing research on foster children as a separate group.

The HRA letter of agreement required that any approved study comply with federal regulations regarding the participation of wards of the state in research, saying, "The study should be conducted in compliance with 45 CFR 46.409."[472] Further, the agreement mandated that "serious consideration shall be given to the appointment of a person recommended by the National Medical Association" when appointing an independent advocate as "required by 45 CFR 46.409."[473] As Chapter 6 of this report noted, 45 CFR 46.409 requires an IRB to appoint an

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[470] "Diligent search" is a common term in child welfare but without a standard definition. According to Price, 2002, "Slightly more than half of the states have statutory language requiring a diligent search to identify and/or locate parents in the case of abandoned children or when the whereabouts of a parent is unknown. A few of these states (AK, AZ, WI) require a search for at least three months. The District of Columbia only requires a search for one month. Indiana, on the other hand, specifically states that a diligent search is *not* required if the judge determines that it is not in the best interest of the child." (Amy Price, *Expediting Permanency For Abandoned Infants: Guidelines For State Policies And Procedures.* (University of California at Berkeley: National Abandoned Infants Assistance Resource Center, 2002).

A search of the laws of New York State and the policy directives of the Office of Children and Family Services did not produce a definition of diligent search (see http://public.leginfo.state.ny.us/menuf.cgi and http://www.ocfs.state.ny.us/main/policies as of April 23, 2008). In the file review, Vera staff found different types of diligent searches that require workers to engage in more or less activity. For example, diligent searches for parents facing termination of parental rights hearings often included letters to the federal Bureau of Prisons, state and local corrections agencies, psychiatric facilities, the armed services, and other institutions. The Federal Parent Locator Service provides searches of many non-public databases, see http://www.acf.hhs.gov/programs/cse/newhire.

[471] Form letter, May 28, 1991, from Barbara Sabol to physicians; letter, June 19, 1991, from Robert Little, executive deputy commissioner, to Executive Directors of Voluntary Agencies. This is the same level of search used to locate parents for medical treatment consents.

[472] Undated sample letter of agreement sent to principal investigators with a form letter dated May 28, 1991, from Barbara Sabol.

[473] Ibid.

independent advocate for "wards of the state," which includes children in foster care, when the IRB determines that a trial falls into a specific category of research (45 CFR 46.406 or .407).

Implementing the Trial Approval Policy. Starting in 1991, the PAU received clinical trial protocols from hospitals and from the National Institutes of Health as soon as they became available.[474] If PAU staff knew the trial did not meet HRA's criteria for approval, they could reject it without consulting the MAP.[475] Otherwise, the PAU was to organize a MAP review. This meant asking three or four physicians on the MAP to provide written comments to HRA about the trial's appropriateness and to meet with PAU and OLA staff to discuss the trial.[476] A letter from HRA regarding the protocol for PACTG 152, for example, provided five questions to guide the analysis.[477] These questions, given below, remained in most of the letters that Vera reviewed from HRA/ACS to MAP members asking for a review of a specific trial.

- Are there specific treatment benefits, including diagnostic benefits, that would accrue to a foster child who may be enrolled in this study? If so, what are they?
- Would these benefits be generally available to the child outside this study?
- Are there any risks to the foster child who may be enrolled in this study? If so, what are they?
- In your professional opinion, do the benefits available to the child outweigh the risks or benefits?
- Are there other concerns or issues that you believe are noteworthy? If so, what are they?

Following a MAP meeting to discuss a specific trial, the MAP doctors made written comments about the trial and in most cases made a recommendation that the commissioner approve or disapprove of the trial. An OLA attorney would then summarize the discussion and forwarded a recommendation to the commissioner for a final decision. When the commissioner approved a specific trial, PAU staff notified the appropriate medical institutions and issued a standardized letter of agreement for the trial to each facility. Each clinical trial researcher signed

[474] Form letter, May 28, 1991, from Barbara Sabol to physicians, re: New guidelines for HRA approval of foster child enrollment in clinical trials. According to a letter of March 2, 2004, Moye sent 31 letters or faxes concerning approximately 40 protocols to HRA/ACS during the period 1991-1999.

[475] PAU staff rejected participation in Phase I trials without the MAP through 1997, but the MAP did review and in some cases recommend the Phase II part of a Phase I/II study. For example, in an October 25, 1995, memo from OLA attorney Fran Winter to Files, Winter, who had just started working on clinical trials policy following Carol Marcus's retirement, recorded that "In a discussion with Pat Burton on this date it was agreed that HRA would not convene a HIV Advisory Panel to review Protocol [265] because it involves a Phase I/II trial testing the safety and immunogenicity of chicken pox vaccine on HIV infected children…It was confirmed that the Commissioner's policy is not to consent to enrollment of foster children in the safety testing of a drug unless the child's parent or legal guardian specifically consents to the enrollment."

[476] Letter, December 28, 1990, from Commissioner Barbara J. Sabol to Elaine Abrams, MD, associate professor of pediatrics, Harlem Hospital Center..

[477] Letter, June 28, 1991, from Pat Burton to Winston Price, re: Pediatric AIDS Medical Advisory Panel Protocol 152.

the letter and forwarded the letter, informed consents, IRB approvals, and any other supporting documents to the PAU.

The new procedures accelerated the review and enrollment process. By the end of 1992, less than two years after the announcement of the new policy, HRA had approved several trials: PACTG protocols 144, 152, 182, 188, 190 and an observational protocol, titled Pediatric Pulmonary & Cardiovascular Complications (P2C2). Sometimes, HRA approved a trial with conditions, such as requiring parental consent or requiring a foster parent's assent (PACTG 188, for example).

By December 31, 1992, the PAU reported that 76 of the 621 HIV-positive children in care were enrolled in clinical trials.[478] A year later, the PAU reported 127 enrollments in four HIV/AIDS research studies, with 601 HIV-positive children in care.[479] Of the 119 children in treatment trials (as opposed to observational trials), the PAU reported that 40 percent (50 children) had enrolled with a signed consent from a birth parent. The commissioner consented to the remaining enrollments. Of the total enrollments, in one-third of the cases parents could not be located; in 21 percent, parental rights had been terminated or surrendered; and in 7 percent, both parents were known dead at the time of enrollment.[480]

Through 1994, when the agency modified clinical trials policy, HRA rejected participation of foster children in several trials, including PACTG 128, PACTG 170, PACTG 218, and five other trials that were not PACTG protocols.[481] (See Table 10.4 and 10.5 for information on MAP activity and for medication trials in which foster children were enrolled.). The MAP reviewed PACTG protocol 170, for example, which studied an experimental treatment for a common and at times lethal opportunistic infection, PCP pneumonia, in the spring of 1992. Physicians Karen Hopkins and Stephen Nicholas both recommended against participation.[482] In his review, Nicholas argued that the medication could be accessed outside of the trial, that Harlem Hospital decided not to participate in the study, and that he did not recommend enrollment for any children, whether in foster care or not, because the existing treatment (Bactrim) worked well.[483] Nicholas and the MAP also reviewed PACTG 218. Though members of the MAP, including Nicholas, acknowledged PACTG 218's possible benefits, the MAP did not recommend

[478] PAU quarterly report, February 3, 1993, from Deirdre Burke, MHRA grants manager, to Ann Currier, AIDS Institute, NYS DOH. The PAU wrote quarterly reports as part of its grant from the Medicines and Healthcare products Regulatory Agency, which then sent copies to NYS DOH. In later years, these reports went directly to the AIDS Institute. This report covers the period October 1, 1992, to December 31, 1992.
[479] PAU quarterly report, January 24, 1994, from Deirdre Burke, MHRA grants manager, to Maggie Mitchell, AIDS Institute, NYS DOH. This report covers the period October 1, 1993 to December 31, 1993.
[480] Ibid.
[481] Memo, March 16, 1994, from Carol Marcus to Commissioner Marva Livingston Hammons, re: Participation of Foster Children who are HIV Seropositive or who are HIV Infected in Clinical Trial Protocols.
[482] Letter, May 5, 1992, from Stephen Nicholas to Pat Burton; letter, October 7, 1992, from Karen Hopkins to Pat Burton.
[483] Letter, May 5, 1992, from Stephen Nicholas to Pat Burton.

enrollment of foster children and the commissioner refused to approve PACTG 218 for foster child participation.[484]

From its inception, HRA/ACS departed from the MAP approval process in some situations, relying instead on a single outside consultant to make a recommendation for the enrollment of a child. In July 1991, for example, a doctor at the National Cancer Institute (NCI) recommended a trial for a New York City child in foster care living in another state. At the same time, the PAU learned of another foster child receiving treatment at Kings County Hospital whose physician wanted the youth evaluated by NCI for enrollment in the same trial (NCI Recombinant G-CSF-Erythropoietin 91-C-01C). The PAU asked one physician, Stephen Nicholas, to review the trial and provide his recommendation, rather than convene a MAP meeting.[485]

The new MAP review policy required significant administration. Selecting and contacting MAP reviewers, scheduling meetings, writing summaries, tracking letters of agreement, and enrollments all placed demands on OLA and the PAU—especially as the number of trials increased: NIH sent HRA protocols and other information on five trials in 1991, six trials in 1992, and eight trials in 1993.[486] While the stream of protocols coming from NICHD and other trial sponsors increased, so too did the number of HIV-positive children in care, as did demands for testing and training of contract agency staff and foster parents. The staff of the PAU grew from two in 1991 to five in 1993, along with two additional part-time grant-funded staff.[487] The PAU also received funding from the New York State Department of Health's AIDS Institute to computerize its operations in 1992.[488]

1994 Policy Update

In a March 1994 policy bulletin regarding medical consents for foster children, HRA reiterated its clinical trials enrollment policy, with one change.[489] As discussed in Chapter 5, parents of children in foster care retain parental rights unless those rights are terminated or surrendered, or

[484] See letter, July 22, 1993, from Stephen Nicholas to Maria Favuzzi. The letter, which recommended against approving either PACTG 218 or 230, states "since it cannot at this time be considered a form of treatment and since the potential benefits and risks for children are unknown, I cannot provide a persuasive argument for the approval of this protocol for HIV-infected children in the custody of CWA."

[485] Letter, July 10, 1991, from Maria Favuzzi to Stephen Nicholas. Favuzzi cc'd the letter to Carol Marcus at OLA and her supervisor, Pat Burton.

[486] Letter, March 2, 2004, from Jack Moye, NIH, to Glenda Carroll, PAU.

[487] Memo, August 21, 1991, from Claude Meyers, director of foster care development, to Mildred Hare, director of CWA Labor Relations, re: Restructuring of the Office of Policy and Planning/Redeployment of Staff from Eliminated Units; Description of the PAU staffing dated March 23, 1993.

[488] Memo, November 18, 1992, from Claude Meyers, assistant deputy commissioner for policy and planning, to PAU Liaisons.

[489] Memo, March 15, 1994, from Claude Meyers, acting executive deputy commissioner of CWA, to Staff, CWA; Executive Directors, Voluntary Child Caring Agencies, re: CWA Procedure No. 94/Bulletin No. 94-1, Medical Consents for Children in Foster Care. Section IV-A of the bulletin cited clinical trials for children with HIV as an exception to the general policy prohibiting foster child participation in clinical research. The bulletin did not describe the policy in detail, but contained four paragraphs describing HRA policy and referred questions to the Pediatric AIDS Unit.

the parents die.[490] Unless parental rights have been severed, children in foster care are in the "care and custody" of the commissioner of social services (the commissioner of HRA in the case of New York City in 1994). When children fall into this category, birth parents who are available and have retained their parental rights have the right to sign informed consents for clinical trial participation and other non-routine medical care and to remove children from clinical research. When parental rights have been severed, on the other hand, a child is considered to be in the "care and guardianship" of the commissioner. In these cases, the commissioner or his designee make most decisions that would otherwise be made by a parent.

The March 1994 policy presumed that children in the care and guardianship category had the commissioner's consent for approved trials, but it made clear that the PAU still needed to receive a request for enrollment from a doctor and issue an approval.[491] For the first time, however, the policy introduced the term "joint guardianship" in the clinical trials context. Prior to issuance of the March 1994 policy, HRA's standard petition forms used for terminating parental rights in family court proceedings asked the court to place the child in the joint guardianship of the commissioner and the contract foster care agency.[492] Outside of the clinical trials context, joint guardianship allowed the contract foster care agency to proceed with adoptions and to approve routine medical decisions without waiting for approval from HRA.[493] According to the March 1994 policy bulletin, contract agencies had legal authority to consent to enroll those children who were in joint guardianship into a commissioner-approved "experimental protocol," but "when the agency is co-guardian, the [contract foster care] agency may not give such consent *without prior approval* from the CWA Pediatric AIDS Unit." [italics added][494] This requirement, in essence, meant that HRA retained the right to approve all clinical trial enrollments.[495]

In April 1994, CWA issued corrections to the March 1994 policy bulletin.[496] The corrections changed the policy affecting co-guardianship by removing the words "without prior approval" and adding "it is HRA policy that the voluntary agency [the contract foster care agency] must

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[490] For an explanation of this process, see Chapter 5.

[491] Bulletin, March 15, 1994, from Claude B. Meyers, acting executive deputy commissioner, CWA, to All Staff, CWA, Executive Directors, Voluntary Child Care Agencies, Pediatric AIDS Unit Liaisons, Voluntary Child Care Agencies; subject: CWA Procedure/Bulletin: *Medical Consents for Children In Foster Care.*

[492] Vera staff asked Children's Services legal staff to define joint guardianship and explain its use in termination of parental rights proceedings. This sentence relies on their explanation which is consistent with documents in child welfare files that Vera reviewed.

[493] This account is based on Vera staff's correspondence with Children's Services legal staff.

[494] April 27, 1994, statement from Claude B. Meyers, acting executive deputy commissioner, CWA, to All Staff, CWA, Executive Directors, Voluntary Child Care Agencies, Pediatric AIDS Unit Liaisons, Voluntary Child Care Agencies; subject: Pen and Ink Corrections to CWA Procedure No. 94/Bulletin No. 94-1, *Medical Consents for Children in Foster Care*.

[495] The March 15, 1994, policy also emphasized that the commissioner could not provide consent under any circumstances for children in the care of contract foster care agencies as a result of delinquency or status offenses (referred to as Persons In Need of Supervision (PINS) in New York State).

[496] April 27, 1994, statement from Claude B. Meyers, acting executive deputy commissioner, CWA, to All Staff, CWA, Executive Directors, Voluntary Child Care Agencies, Pediatric AIDS Unit Liaisons, Voluntary Child Care Agencies; subject: Pen and Ink Corrections to CWA Procedure No. 94/Bulletin No. 94-1, *Medical Consents for Children in Foster Care*.

immediately *notify* the CWA Pediatric AIDS Unit" of a clinical trial enrollment when the agency is co-guardian. [italics added]." A PAU quarterly report issued in August 1994 noted the change:

> *Situations occasionally occur in which an HIV-infected child is in the joint guardianship of the Commissioner of Social Services and a Voluntary Child Care Agency (VCCA), and the child is medically recommended for enrollment in a clinical trial or research protocol that has not been reviewed, or was not approved because of legal constraints, for foster child enrollment. In these situations, the VCCA having joint guardianship is legally permitted to consent on behalf of the child to enrollment. The Child Welfare Administration's revised Medical Consent Bulletin describes this circumstance and the "right" of VCCAs to consent when this circumstance exists. The PAU has designed a document to serve as notification from VCCAs to the PAU of the Agency's intent to consent to the child's enrollment in the trial/protocol, and to further serve as the PAU's acknowledgement to the VCCA of receipt of notification.*[497]

In sum, this change gave authority to contract foster care agencies to make clinical trials enrollment decisions for children whose parents' rights were terminated—without review or approval from HRA. This included decisions to enroll children into clinical trials that the commissioner refused to approve as appropriate for children in foster care. The notification form created by the PAU, however, also called for the signature of a foster parent. Children whose parents' rights are terminated are legally freed for adoption. Once an adoption is completed, an adopted child's new parents have the same legal rights afforded to birth parents, including the right to approve or reject a clinical trial enrollment for their child. However, the new HRA policy did not set any criteria to indicate that adoption was imminent or in progress.

This change in the policy created a window of time between the severing of parental rights and an adoption when a contract agency could approve the enrollment of a child in a clinical trial without approval by HRA. In the same month the new policy went into effect, April 1994, the contract foster care agency St. Christopher Ottilie (now SCO Family of Services) approved Stephen Nicholas's request for the enrollment of a child at ICC into PACTG 218, a Phase I HIV vaccine trial conducted at several sites in the United States.[498] The child's foster parent signed the notification of enrollment form. Two other children in foster care were enrolled through the joint guardianship provision in PACTG 218 at ICC in 1994.[499]

Other contract agencies provided consent to clinical trials that HRA had not approved. For example, a physician and pediatric HIV clinical trial researcher at SUNY Downstate in Brooklyn

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[497] PAU quarterly report dated August 4, 1994, covering the period April 1, 1994, to June 30, 1994. Quote marks are from original text.

[498] This information comes from Vera's review of child welfare files.

[499] Vera medical reviewers did not find any adverse events experienced by the three children, though in two of the three cases the files did not contain sufficient medical information. A peer-reviewed journal article on the study found no adverse events or treatment benefits from the trial. The article noted a shortfall in recruitment that led to a change in eligibility criteria. See John S. Lambert et al, "Safety and Immunogenicity of HIV Recombinant Envelope Vaccines in HIV-Infected Infants and Children," *Journal of Acquired Immune Deficiency* 19 no. 5 (December 15, 1998): p. 451-461.

requested approval from a foster care agency to enroll a child in PACTG 245 in late 1994. A note in the case planning records describes a telephone call to the PAU director. The note indicates that the PAU director said that PACTG 245 was not approved by HRA and the child could only participate if the foster mother and the agency director consented. The agency director, the two clinical trial researchers and witnesses signed a Report of Enrollment of Foster Child in Clinical Trial several months later. HRA approved PACTG 245 after the consent and enrollment dates.[500]

The PAU quarterly report for October to December 1994 indicated that "seven foster children were enrolled in clinical trials not approved by CWA."[501] The report noted that either the birth parent or a contract foster care agency with joint guardianship had consented.[502] A subsequent report for the period April to June 1995 noted 14 such enrollments, though the report did not indicate if these were cumulative enrollments or enrollments only of children currently in foster care.[503] Subsequent reports did not contain this information.

In July 1995, HRA contracted with Stephen Nicholas to be the medical consultant to CWA for the period from August 1995 through July 1998.[504] Nicholas, at the time an assistant professor of pediatrics at Columbia University Medical School and the executive director at the Incarnation Children's Center, had reviewed at least six clinical trial protocols as a MAP member before this contract, had participated in training foster care agencies and foster parents, and had consulted free of charge for several years.[505] He also served as a principal investigator (the lead clinical trial researcher at a site) on several clinical trials and was well-regarded by many of his peers and PAU staff.[506] Nicholas became the PAU's primary medical consultant for HIV-related issues. His contracted services included: a) making requests for emergency medical consents for HIV-positive children in care, b) providing medical updates that may affect CWA policy concerning HIV-positive children in foster care, c) ensuring current clinical standards of care for HIV-positive kids, including medical therapies and diagnostic tests that might be recommended for a child in foster care, and d) consulting on experimental alternative therapies for HIV-positive children and assessment of the relative risks and benefits of particular clinical

[500] The information in this paragraph comes from Vera's review of child welfare files. According to a PAU quarterly report for the period October 1, 1995, to December 31, 1995, on November 9, 1995, HRA approved enrollment in "Stage II of ACTG 245 only," a Phase I/II trial.
[501] PAU quarterly report dated January 26, 1995 for the period October 1, 1994, to December 31, 1994, p. 5.
[502] Ibid.
[503] PAU quarterly report (undated) for the period April 1, 1995, to June 30, 1995. The next two quarterly reports did not contain breakdowns by approved and unapproved trials, and thereafter the PAU quarterly reports became unreliable.
[504] Nicholas was paid $7,200 over three years—see contract dated July 6, 1995, between City of New York Department of Social Services of the Human Resources Administration ("Department"), and Dr. Stephen Nicholas ("Contractor").
[505] Information in this sentence comes from clinical trials policy documents and Vera staff's interview with Stephen Nicholas.
[506] The characterization of Nicholas as well regarded by his peers and CWA staff is based on Vera staff's interviews of other principal investigators and CWA staff, as well as CWA's support of Nicholas for a National AIDS Caregiver award (see letter, February 4, 1994, from HRA Acting Executive Deputy Commissioner Claude Meyers to Sister Una McCormack, Executive Director, Catholic Home Bureau).

trials and research protocols.[507] Nicholas did not replace the MAP—which continued to meet and make recommendations concerning specific clinical trials as it had previously.

From 1995 to 1996, several changes took place that affected the PAU and the implementation of the clinical trials policy. Maria Favuzzi and her supervisor, Pat Burton, left the child welfare agency. Favuzzi had directed the PAU since 1989 and reported to Burton. Favuzzi, a nurse, had longstanding relationships with MAP members, OLA lawyers, the AIDS Institute and the contract foster care agencies.[508] Both Burton and Favuzzi had years of experience with HRA's clinical trials review process, federal research regulations, and HIV/AIDS medical terminology. Carol Marcus, an OLA lawyer who had played an active role in clinical trials policy since January 1990, also departed. New staff were unfamiliar with how parts of the clinical trials review process worked, in part because of a lack of documentation of the process.[509]

With the creation of the Administration for Children's Services in 1996 (see Chapter 3), the city removed responsibility for child welfare from HRA. A 2004 internal review of the PAU by Children's Services, along with interviews and document review by Vera staff indicate that personnel changes and the move to Children's Services new offices disrupted the functioning of the PAU. In 1996, the PAU's electronic record keeping system crashed and never properly functioned thereafter.[510] The unit quarterly reports to the AIDS Institute and MHRA, for example, showed that *cumulative* totals of children enrolled in clinical trials and approved clinical trials had declined, a mathematical impossibility.[511] Records were lost in the move and in one account, some files were shredded.[512] The number of PAU staff decreased as well. By 2004, the PAU had only one full-time employee to consent to HIV testing, track HIV test results, train contract agency staff, monitor clinical trial reviews and individual enrollments, and produce reports. That staff member had no formal training in administration or health related areas and did not have a bachelor's degree.

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[507] Contract dated July 6, 1995, between City of New York Department of Social Services of the Human Resources Administration ("Department") and Dr. Stephen Nicholas ("Contractor").

[508] This characterization is based on the notes and correspondence Vera staff reviewed and on the interviews that Vera staff conducted.

[509] See memo, July 14, 1997, from Michele Weinstat, Legal Counsel Unit, to Hee Sun Yu, assistant commissioner, Medical Services Unit, re: Enrollment of Foster Children in AIDS Clinical Trials Group Protocol 247: ACS HIV Advisory Panel. Weinstat writes, "I have spoken with Fran Winter, who informed me that there is no written protocol and only an informal set of common sense ground rules by which the Advisory Panel functions."

[510] PAU quarterly report, August 1, 1996, notes "a computer failure" on page 3. This statement is repeated in subsequent reports which ascribe the absence of certain data to the computer failure. When the data start being reported again, they include anomalies such as no missing demographic data—though there had always been at least some missing demographic data in every prior reporting period.

[511] PAU quarterly report, January 31, 1997, reports 252 cumulative enrollments, while PAU quarterly report dated August 3, 1998, reported 86 cumulative enrollments. PAU quarterly report dated January 31, 1997, reports 13 approved trials, while PAU quarterly report dated August 3, 1998, reported eight approved trials. There is no discussion of this discrepancy in any report. "Cumulative" means the total ever recorded, so reductions in cumulative totals are not possible. The quarterly reports do not discuss this discrepancy.

[512] Memo draft, February 14, 2005, from Joan Siegel to John Mattingly, cc: Joseph Cardieri; Jennifer Jones Austin; Martin Baron; Francene Mann, re: HIV Clinical Trials

The MAP continued to meet after 1995 and recommended the approval of some trials, such as PACTG 327 and PACTG 338. A MAP panel recommended against approving other trials without birth parent consent. The panel did not recommend approval of PACTG 247, for example, which tested the effectiveness of enhanced calorie feeding formula in improving weight gain among HIV-exposed infants. The MAP comments noted that the trial did not offer any special benefit not otherwise available, as pediatricians could prescribe the enhanced formula outside of a clinical trial if they felt it appropriate.[513] In general, the Children's Services' standard that a trial should offer a benefit not otherwise available to foster children became harder to meet as the FDA approved more pediatric HIV treatments.

In the files Vera staff reviewed, PACTG 377 (377) generated the most discussion during the period from 1996 to 1999. Children's Services initially rejected 377 without convening the MAP because NIH deemed it a Phase I/II trial. While Children's Services and its predecessor, HRA, had approved enrollments into Phase I/II trials in the past, the agency had only approved enrollments in the second phase of such trials, because Phase I trials, which tested safety, toxicity, and tolerance, did not meet New York City's child welfare criteria for treatment.[514] The request for the commissioner's approval of 377 was for the Phase II part of the study, which tested four combinations of drugs each previously approved individually for treatment of pediatric HIV. Not long before, the AIDS Institute had recommended combination therapy from the moment of diagnosis; a fact mentioned by MAP members Herman Mendez and Stephen Nicholas and confirmed directly with the AIDS Institute by a Children's Services attorney.[515]

Following a meeting to discuss 377 on March 5, 1998, the Children's Services lawyer assigned to the MAP, Michele Weinstat, asked the MAP doctors many questions.[516] She asked if the doctors would choose any of the triple drug combinations for a child not enrolled in the study, and if so, if one combination was clearly preferred over any of the other three. She also asked if adults used any of the combinations and if the 377 combinations were at least as

[513] Memo, October 10, 1997, from Michele Weinstat to Nicholas Scoppetta, re: Enrollment of Foster Children in AIDS Clinical Trials Group ("ACTG") Protocol 247, "Randomized, Double Blind, Controlled Study of An Increased Caloric Density Infant Formula and Its Effect on Growth and Nutritional Status in HIV-Infected Infants."
[514] Vera staff found documentation that HRA did not approve Phase I trials. For example, a memo dated October 25, 1995, from Fran Winter (the OLA lawyer who replaced Carol Marcus) to Files re: HIV Protocol 265 said "In a discussion with Pat Burton on this date it was agreed that HRA would not convene a HIV Advisory Panel to review Protocol because it involves a Phase I/II trial testing the safety and immunogenicity of chicken pox vaccine on HIV infected children…It was confirmed that the Commissioner's policy is not to consent enrollment of foster children in the safety testing of a drug unless the child's parent or legal guardian specifically consents to the enrollment."
[515] Memo, March 27, 1998, from Michele Weinstat, Legal Counsel Unit, to Nicholas Scoppetta, commissioner, re: Enrollment of Foster Children in AIDS Clinical Trial Group ("ACTG") Protocol 377, "PRAM-2: A Phase I/II Randomized Multicenter Protocol Comparing Four Antiretroviral Regimens Containing Combination of Protease Inhibitors, Nucleoside Reverse Transcriptase Inhibitors (NRTI's), and a Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI); facsimile, March 19, 1998, from Michele Weinstat to Sheila Hackel, New York State Department of Health AIDS Institute; "Criteria for the Medical Care of Children and Adolescents with HIV Infection." NYS DOH AIDS Institute, June 1997.
[516] Memo, March 5, 1998, from Michele Weinstat to Steven Nicholas and Herman Mendez, re: ACTG 377-Additional Questions.

successful as any other combination used in adults. Finally, Weinstat asked about risks and discomforts attendant to entry testing and monitoring.

The MAP doctors answered Weinstat's questions and asserted that the AIDS Institute directive meant that all HIV-positive children in foster care were likely to receive combination therapy whether they were in a clinical trial or not.[517] They also suggested that 377 offered a safer way to provide children in care with combination treatment because the children would receive closer monitoring: 377 provided for monthly laboratory tests of CD4 counts, viral loads, and other tests as opposed to quarterly testing paid for by Medicaid. In her subsequent memo to the commissioner, Weinstat reported that although each individual drug had known side effects, some of them serious in some patients, doctors knew less about the side effects involved in combinations of the drugs in children. (Early data from adult Phase I trials showed no unanticipated effects. Andrew Wiznia, a pediatrician at Bronx Lebanon hospital, 377's co-chair and a former MAP member, reported that in the first 12 weeks of Phase I of 377 only one of 80 children enrolled nationwide developed a skin rash, and the rash had disappeared after the child stopped the trial medications.) Weinstat reported that the doctors worried most about adherence: if foster parents failed to insure that children adhered strictly to the medication schedule in the protocol, children might develop resistance to the protease inhibitor in the trial and possibly to protease inhibitors generally.

Weinstat recommended that the commissioner approve the enrollment of foster children in 377 with the following conditions. The child's pediatrician must recommend the trial as the best treatment available for the child, and a second physician designated by Children's Services must review the case of each proposed participant and agree that the protocol treatment is the best available. Both physicians would then have to agree that the potential benefits outweighed the risks to the child. In other words, enrollment in 377 would be done on a case-by-case basis, not on a trial basis. Commissioner Scoppetta approved enrollments for foster children in the trial on April 9, 1998.

1998 Clinical Trials Policy

In December 1998 Children's Services issued a revised clinical trials policy—prompted, in part, by concerns raised during the review of 377.[518] The new policy confirmed the existing policy but added specific guidance on Phase I and Phase II trials. The 1998 addition stated:

[517] Memo, March 27, 1998, from Michele Weinstat, Legal Counsel Unit to Nicholas Scoppetta, commissioner, re: Enrollment of Foster Children in AIDS Clinical Trial Group ("ACTG") Protocol 377, "PRAM-2: A Phase I/II Randomized Multicenter Protocol Comparing Four Antiretroviral Regimens Containing Combination of Protease Inhibitors, Nucleoside Reverse Transcriptase Inhibitors (NRTI's), and a Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI)." This memo summarizes the discussions referenced elsewhere in this paragraph.

[518] See memo, October 27, 1997, from Michele Weinstat to Gerald Harris, Children's Services general counsel, re: HIV Research Studies: Response to NIH Announcements; memo, November 26, 1997, from Michele Weinstat to Gerald Harris, re: ACS Policy on Participation of Foster Children in HIV Clinical Trial Groups.

- For Phase I or Phase II Children's Services-approved trials where "dosage and toxicity has already been tested in previous studies," separate consent from the Commissioner is not necessary. The physician must *notify* the PAU (with applicable documentation attached) that a child is being enrolled in the trial and that all required steps have been completed, including parental consent secured and/or certification of a completed diligent search.
- For Phase I or Phase II trials designed to test dosage and toxicity, the commissioner needed to consent for the participation of individual children. The physician must proceed through all previously required steps and then submit to the PAU a *request* to enroll an individual child in the trial. Children's Services would then employ an independent physician to review the child's medical record; if this independent physician determined that trial enrollment was the best available treatment for the child, the Commissioner would issue an individual consent for that child, and only then would the child enter the clinical trial.[519]

The new policy codified the decisions made during the discussion of PACTG 377.

Though Children's Services issued a policy bulletin that covered clinical trials (among other HIV-related issues) in December 1998, internal discussions of the policy continued in 1999. The MAP met in February 1999, and recommended that the commissioner approve several new clinical trials for the enrollment of foster children, but Vera staff found no evidence that the commissioner approved these trials. Instead, PACTG protocols 345, 366, 382, 397 and 403 were considered "pending." Vera staff found no indications that the MAP met again or that the trials pending at the time (345, 366, 382, 397 and 403) were approved by the commissioner.[520]

In a memo several months later from Weinstat to Hee Sun Yu, then the assistant commissioner for medical services, Weinstat recommended that Children's Services no longer approve clinical trials, in part "due to the unreliability of the MAP format."[521] The memo cited two arguments attributed to Steven Nicholas and his successor as medical director at Incarnation Center for Children, Catherine Painter.[522] Citing Nicholas and Painter, Weinstat wrote "that study trials tend to offer medication available off-study and include Phase I aspects that are

[519] December 30, 1998, Bulletin from Nicholas Scoppetta, commissioner, Children's Services, to All Staff, ACS; Executive Directors, Contract Foster Care Agencies; Pediatric AIDS Unit Liaisons, Contract Foster Care Agencies; subject: Bulletin 98-2/Procedure 101: HIV-Related Assessment, Testing, Counseling and Clinical Trial Enrollment of Children and Youth in Foster Care.

[520] The first quarter 2003 PAU report says that PACTG 1010 and 1020 "were reviewed by our medical panel. The Panel recommended that both trials involved risks too great for ACS children and determined that foster children should not participate in either of these studies at this time." We found no other evidence that the panel met. Instead, the documentation suggests that both protocols were sent to the PAU's medical consultant, Dr. Jonathan Horwitz, who wrote a letter recommending against foster children participating in the protocols.

[521] Memo, June 3, 1999, from Michele Weinstat to Hee Sun Yu, re: Reformulation of ACS Policy Regarding HIV Clinical Drug Trials.

[522] Ibid.

riskier than we historically favored."[523] Weinstat contended that "the current use of the Medical Advisory Panel, composed primarily of physicians with vested, financial interests in recruiting children for their studies, has become an undependable vehicle for analyzing whether to allow enrollment in clinical studies." Weinstat also cites Painter and Nicholas in pointing out that fewer HIV-positive foster children were parentless and unadopted than in the past, and therefore the need for commissioner's consent—as opposed to parental consent—"rarely arises." The memo reported that "Drs. Nicholas and Painter suggest that the study inclusion now be limited to foster children whose parents or legal guardians consent to inclusion." Weinstat worried that Children's Services' approval of a study for enrollment might be construed as *endorsement* of the study—an interpretation that might lead to legal liability should a study prove harmful.

These concerns were noted in the PAU report for the second quarter of 1999, which said "the ACS Division of Legal Services is proposing a reformulation of ACS policy vis-à-vis HIV clinical trials, based on comments submitted by two of the doctors from the PAU MAP."[524] However, Vera staff did not find documentation that Children's Services issued a new policy bulletin or put changes in writing. In the fall of 1999, a policy bulletin on providing medical consents for children in foster care cited Bulletin 98-2 as Children's Services' clinical trials policy.[525] Training of contract foster care agency staff on 98-2 continued throughout 1999.[526] A PAU report for the third quarter of 2001 announced the rejection of PACTG 381 and said that Children's Services is "still considering the reformulation of HIV clinical trial enrollment policy."[527] To the knowledge of Vera staff, no formal changes to clinical trials policy took place until after Children's Services asked Vera to conduct this study. Children's Services has a new clinical trials policy in draft form that will apply until the completion of Vera's final report.

Conclusion

New York City's child welfare agency considered many issues in response to the initial request to enroll children in foster care in clinical trials in the late 1980s. Once HRA decided to allow foster children to participate in clinical trials under certain conditions, policy revisions in 1991 and 1994 aimed to speed the decision-making process. The policy revision in 1998 kept most aspects of the policy in place and also allowed Children's Services to consider trials that it had not approved in the past, but with an added review by an independent physician.

Compliance with the agency's clinical trials policy and regulations regarding research are discussed in Chapter 10 of this report. Before discussing compliance, an understanding of how

[523] Painter raised these and other concerns cited by Weinstat in a letter dated March 15, 1999, to Hee Sun Yu re: [MAP] review of PACTG 366, PACTG 382, and PACTG 403.
[524] PAU quarterly report for the period April 1 to June 30, 1999.
[525] New York City Administration for Children's Services' Bulletin No. 99-1, October 18, 1999, "Guidelines for Providing Medical Consents for Children in Foster Care." The bulletin was distributed to foster care providers and signed by the commissioner.
[526] Memo, September 24, 1999, from Hee Sun Yu to Executive Directors of Contract Agencies and PAU, re: Bulletin 98-2 Training Plans.
[527] PAU quarterly report for the period April 1 to June 30, 1999.

pediatric HIV/AIDS clinical trials were conducted and the experience of foster children in those trials will provide a better understanding of the issues involved. These two topics are the subject of the next two chapters.

Chapter 8: The Clinical Trials

Chapter Summary

Vera reviewers identified 88 clinical trials related to HIV/AIDS that enrolled New York City foster children between 1987 and 2005. There were 532 children in New York City foster care for whom Vera reviewers found documentation of enrollment in clinical trials or observational research studies. Some children were enrolled in more than one research study. The file review found documentation of a total of 832 enrollments.

Among those 88 trials were 65 trials that involved treatments for HIV/AIDS or treatment/preventive regimens for AIDS-associated conditions, such as opportunistic infections and bacterial infections. Fifteen of these trials account for 80 percent of the enrollments in medication trials.

Of the 88 clinical trials, 35 involved testing treatments to suppress HIV, 20 tested treatments to prevent or treat opportunistic infections and other HIV-associated conditions, seven trials were expanded access programs that allowed access to antiretroviral medications before they had been approved by the Food and Drug Administration (FDA) for pediatric use. Two trials tested whether treating pregnant women and their newborn infants prevented transmission of HIV from mother to baby. There were approximately 20 research studies about pediatric HIV/AIDS that involved observation only, without an intervention. In four trials reviewers could not determine the type of research or clinical trial; although there was documentation for one of these trials indicating it involved medication.

One of the outcomes from the trials that included New York City foster children is that 15 antiretroviral medications are now approved by the FDA for treatment of children with HIV/AIDS. Discussion of how the children experienced those trials has been reserved for Chapter 9. A description of each of these trials is found in Appendix 10.

Introduction

This chapter begins with background information on why clinical trials are conducted, how they are regulated and monitored, and how they are funded. This information is offered to give readers an understanding of clinical trials generally. It is followed by a discussion of the specific trials in which foster children in the Vera Institute study participated.

Federal Regulations for Testing and Marketing New Drugs

A drug or medical device cannot be sold in the United States until it has been approved by the FDA. FDA approval almost always specifies the diseases or medical conditions for which the drug or device may be applied, specific populations for whom the drug has been approved based on data that proves both safety and efficacy (for example, adults, or children older than three years), and the appropriate doses for the medication's use. This information is included in the

drug labeling, which the agency must also approve.[528] Once the FDA approves a drug, however, doctors are free to prescribe it in ways the FDA has not specified, such as prescribing medication to children that only has adult labeling. This is called "off label" prescription.

Two concerns that shaped the way the federal government regulates the pharmaceutical industry were the demand for consumer protection from potentially dangerous products and the demand for new products to meet pressing medical needs. Congress passed early regulations such as the 1938 Food, Drug, and Cosmetic Act (FDCA) and the 1962 Kefauver-Harris Amendments to the FDCA in response to large-scale tragedies brought about by the marketing of unsafe products.[529]

The FDCA required manufacturers to adhere to a new drug application process that entailed providing evidence that a drug was safe before it could be marketed.[530] The 1962 amendment established the current regulations that require three phases of testing to demonstrate safety and efficacy before an NDA can be approved.[531]

Of the 88 clinical trials Vera staff identified, 65 involved the use of a new drug or combination of drugs on children with HIV—the others were observational research studies.[532] Before testing a new drug in people, a product sponsor—usually the manufacturer—must submit an Investigational New Drug (IND) application to the FDA. The application includes results of laboratory studies and other evidence suggesting that a substance might be effective and safe. The applicant must receive permission from the FDA to begin testing. All research carried out to support an application for approval of a new drug must comply with the regulations found in the

[528] Information on the approval of new drugs can be found on the FDA web site at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.

[529] In 1937 the Tennessee pharmaceutical Massengill and Company manufactured an elixir version of a new antibiotic called sulfanilamide. This product resulted in the death of 106 people, mostly children, because ethylene glycol, the ingredient in car anti-freeze, was used in the formulation. Thalidomide, a sedative promoted to induce sleep and reduce nausea in pregnant women, was first introduced in the European market. The American distributor, Richardson-Merrell, applied for FDA approval despite increasing evidence from Europe linking thalidomide with peripheral neuropathy and severe birth defects of the limbs (seal limbs or phocomelia). By the time the FDA, in response to European data, ordered the retrieval of all the thalidomide that had been distributed on an investigational basis, this included some 2.5 million tablets to over 1,000 physicians as well as tens of thousands of unlabeled tablets, liquids, and powders containing the drug. At least 17 known cases of phocomelia were recorded in the United States and at least 10,000 children overseas were born with thalidomide-induced deformities. See U.S. Food and Drug Administration, *Taste of Raspberries, Taste of Death: The 1937 Elixir Sulfanilamide Incident* (June 1981) from http://www.fda.gov/oc/history/elixir.html, accessed June 12, 2007.
U.S. Food and Drug Administration, "Frances Oldham Kelsey: FDA Medical Reviewer Leaves Her Mark on History," *FDA Consumer Magazine* (March-April 2001) from http://www.fda.gov/fdac/features/2001/201_kelsey.html, accessed September 24, 2008.

[530] CATO Institute, *Compassion vs. Control: FDA Investigational-Drug Regulation* from http://www.cato.org/pubs/pas/pa072.html, accessed June 12, 2007.

[531] . M. Santoro and T. Gorrie, *Ethics and the Pharmaceutical Industry* (New York: Cambridge University Press, 2005), 14.

[532] All medications in the trials in which children in the Vera review were involved had been previously tested or were undergoing simultaneous testing in adults with HIV. Vera staff identified three additional research studies but did not have enough information to determine the type of trial or research they involved.

Code of Federal Regulations-21 CFR 50, 21 CFR 56, and 21 CFR 312.[533] If the research is carried out at institutions that received federal research funding (as in the case of the clinical trials being examined in the Vera review), each Institutional Review Board (IRB) must also ensure that the research complies with the federal regulations found in 45 CFR 46, that protect human subjects involved in research and includes special provisions for the protection of children and "wards of the state."[534]

Testing involving human subjects to establish the safety and efficacy of new drugs is carried out in three phases. Phase I trials usually establish the safety of the drug in humans, usually adults. Phase II trials usually test whether a drug is effective in a small number of adults after a tolerable dose has been identified in Phase I. Phase III studies continue to test a drug's effectiveness, often by comparing it with the current best treatment. Phase I studies typically have the fewest participants (20 to 80), Phase II studies usually involve a small number of participants (at most several hundred), and Phase III studies may have hundreds or thousands of participants.[535] During testing, the investigators must notify the FDA of any "serious or life-threatening" reactions to the drug in adverse event reports.[536] The regulations also require trial sponsors to have research approved by an IRB and to document trial participants' informed consent, which must be obtained prior to a person's involvement in the trial.[537] In some circumstances—usually involving a life-threatening condition—drugs that are undergoing testing or have been tested, but not marketed can be made available to people with that condition who have no other treatment options, on a "compassionate use" before FDA approval or before the drug is available for marketing.

Clinical trial designs are complex and often combine Phases I and II or Phases II and III. Trials often begin with the earlier phase and add additional enrollments once the earlier phase has been completed. Participants in the earlier phase often have the option of remaining in a trial through the next phase and receiving the experimental treatment for a longer period of time.

Once Phase III testing is complete, if the product sponsor believes the results indicate that the product is safe and effective, the manufacturer must apply to the FDA for the drug's approval. An FDA panel reviews the data generated by the clinical trials and issues a recommendation that the drug be approved or disapproved, or that more information is needed. Until a new drug is approved by the FDA, it is available only to clinical trial participants or through special

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[533] 21 CFR 50 and 21 CFR 56 apply to all clinical investigations regulated by the FDA under the Federal Food and Cosmetic Act and clinical investigations that support applications for research or marketing permits for products regulated by the FDA. 21 CFR 56 was amended on April 24, 2001, to provide additional safeguards to protect children. Prior to this date, for institutions *not* receiving federal research funding, special protections for children and wards of the state did not apply. 21 CFR 56 describes IRB requirements for research. The regulations can be found at http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&tpl=%2Findex.tpl.

[534] As discussed in detail in Chapter 6, 45 CFR 46.409 includes special protections for children and "wards of the state" who participate in research. The regulations can be found at http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&sid=d5e5003d900a4f41f3af7fe981d0a3bb&tpl=/ecfrbrowse/Title45/45cfr46_main_02.tpl.

[535] Code of Federal Regulations, 21CFR312, from http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.21 (accessed August 23, 2007).

[536] 21 CFR 312.32.

[537] 21 CFR 56.103 and 21 CFR 50.20.

expanded access programs (described below). The FDA may also require a specific product to undergo "post-marketing studies"—studies of a product's safety and efficacy—after the FDA approves its use. Post-marketing studies may be required of any new product. Those approved through the fast-track mechanism are required to undergo such studies. The FDA may withdraw approval if post-marketing studies are incomplete or fail to demonstrate efficacy.[538]

Beginning in the 1980s, AIDS activists who wanted increased access to antiretroviral medications and other AIDS treatments and pharmaceutical companies pressured the FDA to accelerate the process of licensing new AIDS drugs. The activists saw participation in clinical trials as a means to receive life-saving treatment and disagreed with the viewpoint that the public needed protection from clinical trials of new treatments.[539] Prisoners' rights advocates and public health officials also sought to increase access to experimental HIV/AIDS treatment for incarcerated people with HIV/AIDS. Some advocacy organizations for children with HIV/AIDS, including the Elizabeth Glaser Pediatric AIDS Foundation, argued for increased clinical trials of drugs to treat children with HIV/AIDS.[540]

Two mechanisms were implemented by the FDA to increase access to newly-developed treatments for HIV/AIDS: decreasing the amount of time needed for a drug to be tested and approved by the FDA, and increasing access to drugs while they were in the testing process but had not yet been approved for marketing. The FDA implemented new accelerated approval regulations in 1992 and fast tracked drug development programs in 1997.[541]

Expanded access to new drugs occurred through the approval of "Treatment IND" in 1987 and the "Parallel Track" initiated in 1992.[542] The Treatment IND mechanism makes promising new drugs available to medically fragile patients while phase II and III trials are in progress.[543] Only patients ineligible for, or without access to, ongoing clinical trials may receive the new drugs under the treatment IND system.[544] Treatment INDs must be approved by the FDA, and

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[538] Fast track mechanisms were developed in 1992 as part of the effort to bring HIV drugs to the market. More information about post-marketing studies can be found at http://www.fda.gov/cber/fdama/pstmrktfdama130.htm. Regulations related to post-marketing requirements and withdrawal of approval are found in 21 CFR 601 314.530.

[539] H. Edgar and D.J. Rothman, "New Rules for New Drugs: The Challenge of AIDS to the Regulatory Process," *The Milbank Quarterly* 68 (1990): 111-42; and CATO Institute, *Compassion vs. Control: FDA Investigational-Drug Regulation* from http://www.cato.org/pubs/pas/pa072.html, accessed June 12, 2007.

[540] Nancy Dubler, Nancy Neveloff, and Victor W. Sidel, "On Research on HIV Infection and AIDS in Correctional Institutions," *The Milbank Quarterly* 67, no. 2 (1989): 171-207; and Elizabeth Glaser, "Pediatric AIDS Foundation, Pediatric Drug Testing" from http://www.pedaids.org/YouCanHelp/Advocacy/ChildrensHealth/Pediatric%20Drug%20Testing.aspx, accessed September 1, 2007.

[541] Food and Drug Administration, "Expanded Access and Expedited Approval of New Therapies Related to HIV/AIDS, 1998," from http://www.fda.gov/oashi/aids/expanded.html, accessed September 3, 2007.

[542] Throughout this report, use of drugs through the treatment INDs or through the Parallel track mechanism will be referred to as expanded access programs.

[543] The term IND or Investigational New Drug refers to any substance that has been approved for testing by the FDA but has not yet been approved. The use of an IND in a clinical trial is for testing purposes—it may or may not offer the benefit of treating the participants' condition. In a Treatment IND, the medication has not yet been approved for marketing, so the drug is still an IND, but the *purpose* of giving the drug is to treat the patients' condition.

[544] Food and Drug Administration, "Treatment IND," from http://www.fda.gov/cder/handbook/treatind.htm, accessed June 15, 2007.

the criteria for approval are described in 21 CFR 312.34. The FDA approved a Treatment IND for Zidovudine (AZT) for children with HIV in October 1989.[545] Because a Treatment IND involves the use of unapproved medications, the treatment INDs are considered research and must be approved by local IRBs; informed consent for participation is required.

The Parallel Track policy expanded the availability of investigational drugs to people with HIV/AIDS who could not participate in clinical trials. The policy differs from the Treatment IND primarily in that it applies only to AIDS and HIV-related diseases. Generally, parallel-track drugs can be made available earlier in the development process than drugs used in Treatment INDs.[546] The Vera review identified 68 children who received treatment through these expanded access programs.[547]

Because of the strict regulation of research involving children (45 CFR 46 Subpart D) and because the pediatric market is limited, pharmaceutical companies, for many years, shied away from conducting clinical trials in children.[548] This means that although physicians could and did prescribe medications to children that the FDA had only approved for adults, they were doing so off label, without the benefit of research on the safety, dosing, and effectiveness of the medication in children. A 1999 review revealed that between 1973 and 1994, 71 to 80 percent of "approved new molecular entities or products listed in the *Physician's Desk Reference* (PDR) did not have sufficient pediatric drug labeling." This means that the labeling did not describe the best way to prescribe these drugs for children, based on research conducted on children.[549] The American Academy of Pediatrics is one of several organizations that advocated for increased testing of drugs for use in children, commenting that "the lack of drug studies in children presents the treating physician with an ethical dilemma. The physician must frequently either not treat children with potentially beneficial medications or treat them with medications based on adult studies or anecdotal empirical evidence in children."[550] This advocacy resulted in legislation. The Food and Drug Administration Modernization Act of 1997 included financial incentives to pharmaceutical companies that conducted pediatric studies. The Best Practices for Children Act, passed in 2002, extended the incentives of the 1997 Act. The Pediatric Research

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[545] Food and Drug Administration, Timeline HIV/AIDS Historical Time Line 1991-1994, retrieved September 26, 2008 from http://www.fda.gov/oashi/aids/miles.html. AZT is also known by the name Zidovudine (ZDV) and by the brand name Retrovir.

[546] Food and Drug Administration, "Expanded Access and Expedited Approval of New Therapies Related to HIV/AIDS, 1998," from http://www.fda.gov/oashi/aids/expanded.html (accessed September 30, 2007).

[547] The Vera review identified seven clinical trials that appeared to meet the criteria for expanded access programs. Some were clearly treatment INDs. Others were open label trials whose stated goals were to make medication available to children who were intolerant of or had worsening disease on other available therapy. These were classified as expanded access programs in this review.

[548] Institute of Medicine, *Ethical Conduct of Clinical Research Involving Children* (National Academies Press: Washington DC, 2004), 60-1.

[549] J.T. Wilson, "Update of the Therapeutic Orphan," *Pediatrics* 104 (1999):585-90, as cited in M.D. Murphy and S.F. Goldkind, "The Regulatory and Ethical Challenges of Pediatric Research," in M. A. Santoro & T. M. Gorrie, eds., *Ethics and the Pharmaceutical Industry* (New York: Cambridge University Press, 2005), p. 49-50.

[550] American Academy of Pediatrics, "Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations," *Pediatrics* 95, no. 2 (February 1995), available electronically at http://aappolicy.aappublications.org/cgi/reprint/pediatrics;95/2/286.pdf.

Equity Act of 2003 gave the FDA the authority to require pediatric studies of certain drugs and biological products.[551]

Pediatric trials of the first drug to treat HIV—Zidovudine (AZT)—started after the drug had been approved for adults. AZT was licensed for adults in 1987 and for children in 1990.[552]

NIH-Sponsored Clinical Trials of Pediatric HIV Treatment

Two branches of the National Institutes of Health sponsor extramural clinical trials of treatments for children with HIV/AIDS: the National Institute for Child Health and Human Development (NICHD) and the National Institute for Allergy and Infectious Disease (NIAID).[553] After 1991, both of these agencies worked through a network of physicians and researchers called the Pediatric AIDS Clinical Trials Group (PACTG).[554]

The first clinical trial of a treatment for children with HIV/AIDS was sponsored before the PACTG was founded. NICHD sponsored ACTG 045 to evaluate whether children with HIV who received monthly infusions of intravenous immunoglobulin (IVIG) were less likely to contract serious bacterial infections—an often fatal development in children with AIDS. The study protocol randomly assigned participating children to one of two groups.[555] One group received IVIG infusions; the other received a placebo.[556] The study enrolled 376 children at 42 sites across the United States., including 17 sites in the New York metropolitan area.[557] Vera researchers identified 21 New York City foster children who participated in this trial.

The PACTG was founded while the IVIG trial was underway. The PACTG is a cooperative clinical trials network funded by the NIAID and the NICHD to evaluate clinical interventions, including the efficacy of drugs and drug combinations for treating HIV infection and HIV-

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[551] Institute of Medicine, *Ethical Conduct of Clinical Research Involving Children* (Washington, DC: National Academies Press, 2004): 90. Information on these laws and on clinical trials and children can also be found at: http://www.fda.gov/consumer/updates/pediatrictrial101507.html#children.

[552] Food and Drug Administration, from http://www.fda.gov/oashi/aids/pedlbl.html, accessed June 2, 2008.

[553] Extramural research refers to research funded by the NIH but conducted at other institutions. Intramural research is conducted at the NIH in Bethesda, Maryland. During the period under review, the National Cancer Institute (NCI), a branch of the NIH, conducted intramural pediatric HIV research. A few New York City foster children participated in the NCI pediatric HIV protocols.

[554] Vera staff obtained information about the structure of the NIH-funded trials by reading the protocols, reviewing electronically available information from the National Institutes of Health, and interviewing principal investigators and other scientists involved with the clinical trials. Westat provided written responses to questions. The AIDS Clinical Trials Group (ACTG) was launched in 1987 by the NIAID to conduct clinical trials of AIDS treatments, mainly in adults. In 1991 the PACTG was launched as a separate entity to conduct research on treatment for HIV/AIDS in children. More information on the ACTG can be found at: http://www.aactg.org. Information on PACTG retrieved from http://www.nichd.nih.gov/research/supported/pphsn.cfm and from http://pactg.s-3.com/.

[555] Randomization in a clinical trial means that participants are assigned randomly, as in a coin toss, to an arm of the study. This two-armed study (placebo vs. treatment with IVIG) provided a 50 percent chance that the participant would receive the placebo and a 50 percent chance that he or she would receive the treatment.

[556] NICHD, Clinical Trial Efficacy of Intravenous Gamma Globulin in the Treatment of Symptomatic children Infected with Human Immunodeficiency Virus (HIV), September 1987.

[557] Westat, communication to Vera Institute of Justice, received October 8, 2008. Two sites outside of New York City—New York Medical College/Westchester County Medical Center and the State University of New York at Stony Brook—are included here because children in the Vera review were enrolled in clinical trials at these sites.

associated illnesses in infants, children, adolescents, and pregnant women.[558] It developed and implemented Phases I, II, and III clinical trials, working collaboratively with the FDA, other federal agencies, community representatives, and pharmaceutical companies.[559]

The PACTG-sponsored trials described in the Vera review were conducted at medical institutions across the country. Funding and monitoring mechanisms for a trial depended on whether the site was sponsored by the NICHD or the NIAID. In either case, the study protocols were the same and scientists from both NIH institutes were involved in developing and implementing the trials. In PACTG studies, conducted at sites funded by both the NICHD and the NIAID, the NIAID held the Investigational New Drug permit, issued by the FDA, and served as the liaison with the pharmaceutical companies that supplied the protocol drugs. For each PACTG-sponsored clinical trial, an agreement was drawn up between the NIAID and the pharmaceutical company.[560]

The NICHD sponsored a network of Pediatric and Perinatal HIV Clinical Trials Centers, and contracted a private company, Westat, to coordinate the network.[561] The contract between the NICHD and Westat is awarded through a competitive process that recurs every five years. Contracts between Westat and individual sites are also awarded competitively at five year intervals. NICHD-sponsored sites receive payment from Westat for each clinical trial-related patient visit, as well as funding to cover staff and miscellaneous costs.

The NIAID uses a different funding mechanism which is designed to maintain an infrastructure for conducting clinical trials. Medical centers apply to the NIAID to become a research site, called a Pediatric AIDS Clinical Trials Unit (PACTU). Each PACTU is expected to enroll an agreed upon minimum number of patients each year, but unlike NICHD-sponsored sites, payment is not based on the number of participant visits—although incentive funding was available to sites that enrolled more than the expected number of participants in high-priority protocols and to sites whose investigators contributed a substantial amount of uncompensated time and effort to PACTG committees and other activities. The NIAID funded 18 to 25 PACTUs around the country as well as a coordinating and operations center and a statistical and data management center. The coordinating and operations center for the PACTG was a private company called Social and Scientific Systems (SSS).[562] The Center for Biostatistics in AIDS

[558] NIAID, *Resource Guide for the Development of AIDS Therapies*, from http://www.niaid.nih.gov/daids/pdatguide/pactg.htm, accessed November 4, 2008.
[559] The PACTG was subsequently renamed the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) and expanded to include sites outside of the United States. More information on IMPAACT can be found at: http://pactg.s-3.com/Iinfo.htm.
[560] The Pediatric AIDS Clinical Trials Group, *AIDS Clinical Trials Unit, Terms of Award*, from http://www.niaid.nih.gov/daids/terms/pactuter.htm, accessed June 16, 2007. A copy of a sample agreement between NIAID and a pharmaceutical company can be found at http://www3.niaid.nih.gov/about/organization/odoffices/omo/otd/pdf/CTA-DIR.pdf.
[561] U.S. Department of Health and Human Services, "NIH Guide For Grants and Contracts," 20, no. 25 (June 28, 1991). Westat's responses to questions from Vera staff (April 10, 2008) indicate that Westat is responsible for negotiation and management of clinical center budgets and subcontracts; protocol and case form development; ensuring regulatory compliance; training, site monitoring; data management; data analysis; and DSMB presentation.
[562] More information about SSS can be found on its web site at http://www.s-3.com.

Research (CBAR) at the Harvard School of Public Health served as the statistical and data management center.[563] Funding for the PACTU's was competitive—institutions had to reapply every five years, and evidence of successful enrollment of participants in clinical trials during previous funding cycles was one of the criteria for continued funding.[564]

The clinical trials sponsored by the PACTG—including both NIAID-funded sites and NICHD-funded sites—were conducted at over 70 medical institutions around the country.[565]

Site Monitoring. In addition local IRBs reviewing and monitoring clinical trials, NIH-sponsored clinical trials of new drugs usually had an independent panel of experts called the Data and Safety Monitoring Board (DSMB), charged with monitoring their progress. The DSMB reviewed data periodically during the trial to monitor participants' safety and the efficacy of the treatments being tested. The DSMB can recommend that a trial protocol be amended or ended, based on any beneficial or adverse effects that may be observed. The panel is funded separately by NIAID.[566] Among the trials in which New York City foster children were enrolled, at least three—PACTG 152, PACTG 240, and PACTG 076—were ended early or were significantly modified based on the findings of their DSMB. The changes in each are described in Appendix 10.

While the DSMBs monitored trial *results*, Westat and other contractors monitored the *conduct* of the clinical trials. This monitoring included regular site inspections to check the handling and storage of medication, record keeping, compliance with the trial protocol, and compliance with federal research regulations for the protection of human subjects. In response to written questions from the Vera Institute, Westat officials reported that for PACTG clinical trials at sites funded by the NICHD, Westat staff conducted reviews of research records to verify that all participants met enrollment criteria, that the source of all reported data was documented, and that adverse events and toxicities were noted and acted upon according to protocol.[567] Westat also reported that the monitoring process included verifying the presence of a signed informed consent document obtained for each participant enrolled in a clinical trial and required that the clinical sites maintain documentation in research files that the person signing the consent was legally authorized to do so. If the Westat site monitor was aware that a child was in foster care, he or she sought documentation showing that the study had been approved by HRA or Children's Services. Westat could not definitively recall the documentation that it accepted for informed consent, but some of their staff who were involved during that period believed that they had accepted informed consent by a biological parent whose rights had not been terminated or a letter

[563] More information about CBAR can be found on its web site at http://www.hsph.harvard.edu/cbar.
[564] U.S. Department of Health and Human Resources, "NIH Guide for Grants and Contracts," 20, no. 25 (June 28, 1991).
[565] Appendix 10 includes the number of sites at which each trial was conducted and lists the medical centers in New York City where the trial was conducted.
[566] PACTG Full Text AI-96-001, "NIH Guide," 25, no. 4 (February 16, 1996), RFA: AI-96-001.
[567] Westat Institutional responses to Vera Institute of Justice Questions April 10, 2008.

from the commissioner of child welfare that the child had been approved to participate in the research.[568]

New York City Clinical Trials Sites

NICHD funded 27 PACTG sites across the U.S. and Puerto Rico, including 12 sites in the New York City area.[569] NIAID funded four PACTUs in New York City: Columbia University, Mount Sinai Medical Center, Bronx Lebanon Hospital Center, and New York University Medical Center.[570] Incarnation Children's Center was a sub-site of Columbia University. Some sites were funded by NICHD during some funding cycles and by NIAID during other cycles. Children on the Vera review list were enrolled in clinical trials at sites funded by both branches of the NIH.

Vera staff were able to obtain information about total New York City enrollment in 19 PACTG clinical trials.[571] The total number of New York City enrollments in the 19 trials is 2,341. The number of children in the Vera review who were enrolled in those same 19 trials is 432 (18 percent of all New York City children enrolled). PACTG 240 had the largest proportion of foster children enrolled (43.8 percent of all New York City enrollments). In 16 medication trials, New York City foster children made up 366 of 1,214 New York City enrollments (30.1 percent). The list of 19 trials includes two observational research studies—PACTG 219 and PACTG 188—in which New York City children made up 6.5 percent of 1,006 enrollments.[572] PACTG 076, also included in this list, is a study of prevention of maternal-child transmission. Mothers consented to the enrollment of their infants during the pregnancy. Only one child in the Vera review was enrolled (see Figure 8.1).

[568] The information about monitoring applies only to NICHD-funded sites monitored by Westat. Sites funded through NIAID were monitored by other contractors. Vera staff only requested information for this report from Westat.

[569] Westat, communication to Vera Institute of Justice received October 8, 2008.

[570] Not all sites received funding throughout the period that Vera staff studied, as NIAID released RFPs every five years. Columbia University received funding in 1988, 1989, 1992, 1997, 2002, Mount Sinai Medical Center in 1988 and 1989, Bronx Lebanon Hospital Center in 1992, 1997, 2002, and New York University Medical Center in 1997, 1989-1990 and 1993 cycles from DHHS, Institutions Added to AIDS Clinical Trials Group, June 28, 1993, retrieved November 3, 2008 from http://www.dhhs.gov/news/press/pre1995pres/930628a.txt, accessed November 3, 2008; 1997 funding cycle from NIH News, February 1997, from http://www3.niaid.hih.gov/news/newsreleases/1997/pedactg.htm, accessed November 3, 2008; and 2002 funding cycle from NIH News, March 7, 2002, from http://www3.niaid.nih.gov/news/newsreleases/2002/pactg02.htm, accessed November 3, 2008.

[571] Dr. John Moye, NICHD, "List of New York City and National Enrollments for Selected PACTG Trials," Communication to the Vera Institute of Justice, January 15, 2009.

[572] The Commissioner required birth parent consent and foster parent assent for enrollment in these observational research studies. See Chapters 7 and 10 for a discussion of policy and policy compliance.

Figure 8.1: Foster Children as a Percentage of all New York City Enrollments in 17 NIH-sponsored Clinical Trials and Two NIH-sponsored Observational Research Studies

Trial	NYC Enrollment*	Enrollment of Children in Vera Review**	Enrollment in Vera review as a Percentage of New York City Enrollments
PACTG 240	73	32	43.8
PACTG 152	288	123	42.7
PACTG 051	89	35	39.3
PACTG 327	29	11	37.9
PACTG 239	9	3	33.3
PACTG 292	14	4	28.6
PACTG 144	105	29	27.6
PACTG 190	69	19	27.5
PACTG 300	170	46	27.1
PACTG 338	74	19	25.7
PACTG 377	55	14	25.5
PACTG 138	48	11	22.9
PACTG 245	130	16	12.3
PACTG 265	23	2	8.7
PACTG 225	18	1	5.6
PACTG 179	20	1	5.0
Total for 16 medication trials	**1,214**	**366**	**30.1**
PACTG 219	680	50	7.4
PACTG 188	326	15	4.6
Total for two observational studies	**1,006**	**65**	**6.5**
PACTG 076	121	1	0.8
Total for NYC data	**2,341**	**432**	**18.5**

*Source: Dr. John Moye, NICHD, "List of New York City and National Enrollments for Selected PACTG Trials," Communication with the Vera Institute of Justice, January 15, 2009.
**Includes 36 enrollments that occurred before the child entered foster care and 15 enrollments for which Vera reviewers could not determine if the enrollment took place while the child was in foster care.

How Vera Identified Children Participating in Clinical Trials

This section describes the process reviewers followed to collect information and how this information was used to identify specific trials. It offers a brief overview of the trials themselves.

Determining Trial Participation. Vera's medical review staff collected information about clinical trial enrollment from child welfare files.[573] Whenever information indicating trial participation appeared in a file, reviewers recorded all relevant trial information, including the trial's name and number, the medical center where it was conducted, the trial's sponsor, the physician in charge of the study at the site where the trial was conducted (also referred to as the principal investigator or PI), the medications involved in the trial, the enrollment dates, any

[573] See Chapter 2 for a description of how Vera staff conducted the review.

adverse events or toxicity, the type of documents used for consent, and the participating child's independent advocate (a person appointed by the IRB, for certain clinical trials, to look out for the child's interests while they are enrolled in a clinical trial).[574] In some cases, reviewers found detailed information about a trial, including dozens of pages of medical and child welfare notes. In others, reviewers found only copies of informed consent forms, a reference to trial participation in a progress note or correspondence, or a laboratory report with clinical trial identifying information.

Vera reviewers had to exercise judgment in determining whether a child was enrolled in a clinical trial. They were trained to give more weight to certain types of documentation. For example, laboratory reports with the child's name and a clinical trial name were considered strong evidence that a child was enrolled, as were copies of medical records related to clinical trial enrollment and monitoring, completed consent forms, Pediatric AIDS Unit notification of enrollment forms signed by principal investigators, and letters written by health care providers that discuss trial participation.

In some cases, there is mention in the child welfare casework notes of a clinical trial, but no confirming medical documents were found. Vera reviewers were instructed to place more weight on casework notes that mentioned enrollment in a specific trial at a specific hospital as opposed to vague information that did not indicate enrollment actually occurred (e.g., "child taken to doctor, clinical trial discussed"). Occasionally, reviewers found documentation stating that the child was in a "study," "trial," or "research protocol," but the name of the study was not found. These were counted as enrollments in unidentifiable trials.[575]

If after reviewing all available files Vera reviewers could not make a determination, a senior Vera staff member reviewed the case and made a final determination.

Clinical Trial Information. In addition to gathering information about clinical trials in the child welfare files, the medical team gathered information to classify the phase of the trial, identify the medications being tested, identify the trial sponsor, the trial objectives, and the procedures followed.

Because no central registry of clinical trial information exists, Vera staff retrieved information on the trials from several sources.[576] Most information was collected from government, medical center, and pharmaceutical company web sites.[577] In addition, Vera staff

[574] See Chapters 6 and 10 for a discussion on independent advocates and children in clinical trials.

[575] References to participation in a "protocol" were the most difficult to interpret because protocol can refer to a clinical trials protocol or to any standardized procedure used to treat a specific disease or condition. One such mention of a "protocol" was not counted as a clinical trial because it involved only one medication which had been approved several years before and there was nothing in the notes to indicate that the medication was being used on an experimental basis.

[576] Information on clinical trials is often difficult to obtain. One article noted that only half of the results of clinical trials are reported and that not all of those reports are retrievable in Medline, the largest online database of medical articles. See E. Manheimer and D. Anderson, "Survey of Public Information about Ongoing Clinical Trials Funded by Industry: Evaluation of Completeness and Accessibility," *British Medial Journal* 325 (2002):528-31.

[577] Online sources included www.clinicaltrials.gov, http://www.clinicaltrialssearch.org/, http://clinicalstudyresults.org/, http://www.acria.org/index.html, and

requested and received copies of many clinical trials protocols from the Pediatric AIDS Clinical Trials Group and the National Institutes of Health through the Freedom of Information Act.[578] Written (electronic or paper) and/or phone inquiries were made to pharmaceutical companies for information about pharmaceutical company-sponsored trials. If these efforts failed to produce any information about a specific trial, Vera staff requested a copy of the trial protocol and other information from a trial site's office of sponsored research, the Institutional Review Board, and/or the individual investigator. Similarly, Vera staff searched MedLine, an online database, using titles or identifiers to identify and review published reports on each clinical trial.

Figure 8.2 summarizes the sources Vera staff relied on to identify and learn about the trials. Information frequently came from more than one source. For some trials, the only information available about a trial was the informed consent form found in the child welfare file of a child enrolled in that trial. For 36 NIH-sponsored clinical trials of medications or treatments, Vera staff obtained the full trial protocol. There were several trials for which Vera staff obtained little or no information. In some cases, pharmaceutical companies declined to provide protocols, but did send Vera staff information about the medications or published reports about a trial. Some hospitals provided information about clinical trials; others declined to share any information.

Figure 8.2: Clinical Trial-Specific Information Accessed by Vera Staff

Available Information about a Trial	**Number of Clinical Trials and Observational Research Studies**
Full protocol	36
Synopsis from www.clinicaltrials.gov	58
Synopsis from other electronic site	10
Synopsis from ACRIA[579]	7
Peer reviewed published report	34
Informed consent or patient information sheet	38

Foster Child Enrollment in Clinical Trials and HIV-Related Observational Research Studies

This report examines the enrollment of New York City foster children in clinical trials of HIV-related treatments as well as enrollment in observational research studies about pediatric HIV that did not involve treatment. Although the observational studies did not involve any medication or other intervention, they are included because they are considered research and require IRB approval and informed consent. Children enrolled in observational studies could also be enrolled

http://www.aidsinfo.nih.gov/ClinicalTrials/Default.aspx?MenuItem=ClinicalTrials. When these specific sites contained no information on a trial, Vera staff conducted Internet searches. If a pharmaceutical company sponsored a study, Vera staff searched the company's web site.

[578] Vera staff made its Freedom of Information Act request to the NIH at the beginning of this research project, before all of the clinical trials in which children in the review participated had been identified. Therefore we did not request protocols for every trial.

[579] ACRIA stands for the AIDS Community Research Initiative of America. ACRIA maintains an electronic database of clinical trials that can be accessed at http://www.acria.org/clinical_trials/.

in medication clinical trials and/or have received medication and other treatment from their physician.

Our review covered a span of 20 years, from 1985 to 2005.[580] Of the 796 children whose files Vera staff reviewed for this study, 532 participated in a clinical trial or observational research studies while in foster care. Vera reviewers found 846 enrollments; some children participated in more than one trial.[581] Of the 88 trials, 37 enrolled only one foster child on the Vera review list. One trial, PACTG 152, accounted for 123 (14.6 percent) of all enrollments. This trial was one of the earliest Phase III trials and compared monotherapy with either AZT or ddI to combination therapy using both drugs.

As Figure 8.3 shows, 65 of the 88 research studies identified (73.9 percent) were medication trials, meaning that they involved testing or using a medical treatment or drug.[582] This number includes both trials of new medications or new medication combinations and expanded access programs (Treatment INDs and Parallel Track programs). Approximately 20 observational studies accounted for 22.7 percent of the research studies but accounted for 32.4 percent of all enrollments.[583] In observational research studies, researchers followed a child over time to learn more about specific aspects of HIV, such as transmission from mother to child or the effect of the virus on different parts of the body.

There were three clinical trials (3 percent of the 88 studies) with four enrollments (0.5 percent of all enrollments) for which Vera staff could not obtain sufficient information to determine whether it was an observational research study or a medication trial. There was one medication trial (1.1 percent of 88 studies), with one enrollment (0.1 percent of 846 enrollments), for which Vera reviewers could not determine the name. Vera reviewers sometimes found evidence of a child's enrollment in a clinical trial but could not identify the specific trial. This might occur when a medical or nursing note said that the child was enrolled in a clinical trial or study but did not say which study. For some enrollments the records contained a partial name of a clinical trial or the identification number of the trial for a specific institution, but reviewers were not able to determine the exact name of the trial and therefore could not locate additional information about the trial, including the phase or sponsor.[584]

[580] Vera staff's original research plan covered the period between 1988 and 2001. However, in the course of the review, a few trial enrollments that occurred earlier or later were found and included in the analysis.
[581] This number includes a small number of situations where a child enrolled twice in the same study. This was done when the child moved and re-enrolled in the same trial at another medical facility.
[582] For this report, a medication trial refers to any trial that involved an intervention. Most of these involved antiretrovirals or drugs used to treat complications of HIV. Some trials involved biological products, such as intravenous immunoglobulin (IVIG), or vaccines.
[583] Several observational research studies examined transmission of HIV infection from mother to infant. Vera reviewers were able to obtain information—full study titles, sponsors, protocols—for some but not all of the transmission studies. The studies for which full information was available are counted separately. The studies for which information was scant are counted together as "transmission studies."
[584] The steps taken to determine the name of a trial or learn more about it were described earlier in the methods section of this chapter.

Figure 8.3 Enrollment in Observational and Medication Trials

Trial Type	Trials that included children in Vera's review		Enrollments of children in Vera's review	
	No. of trials	Percentage	No. of enrollments	Percentage
Medication trials	65	73.9	568	67.1
Observational research studies[56]	20	22.7	274	32.4
Unable to determine	3	3.4	4	0.5
Total	88	100	846	100

The following sections provide detailed analyses of each of these two categories, medication trials and observational trials. A detailed description of each observational research study and medication clinical trial is found in Appendix 10.

Medication Clinical Trials

The Vera review found 568 enrollments of children in 65 medication trials, including expanded access programs. Only 15 of these trials enrolled 10 or more children from the review list; their enrollments accounted for 80 percent of all enrollments in medication trials identified in the Vera review. Fourteen of the 15 medication trials were sponsored by the NIH. One was the Burroughs Wellcome AZT Treatment IND, an expanded access program for Zidovudine (also known as ZDV or AZT).[585] The medication trial with the largest enrollment of children from the Vera review, PACTG 152, accounted for 21.7 percent of those who were enrolled in medication trials (see Figure 8.4).[586]

[585] This trial will be referred to as "B-W AZT IND" in tables throughout the chapter. (For details see Appendix 10.)
[586] PACTG 152 was one of the earliest Phase III trials in children and one of the first to evaluate a combination of two drugs. The study compared the efficacy of ZDV vs. ddI vs. ZDV+ ddI. It is described in detail in Chapter 10.

Figure 8.4: Medication Trials with 10 or More Enrollments

Trial	Phase	Number of enrollments	Percentage of all enrollments in medication trials*
PACTG 152	III	123	21.7
B-W AZT IND	Treatment IND	53	9.3
PACTG 300	II/III	46	8.1
PACTG 051	III	35	6.2
PACTG 240	II	32	5.6
PACTG 144	II/III	29	5.1
PACTG 045	II/III	21	3.7
PACTG 190	II	19	3.3
PACTG 338	II	19	3.3
PACTG 245	I/II	16	2.8
PACTG 128	III	15	2.6
PACTG 377	I/II	14	2.5
PACTG 138	II	11	1.9
PACTG 327	II	11	1.9
PACTG 247	UTD	10	1.8
Enrollment in trials with 10 or more enrollments		**454**	**79.8**
All other enrollments		114	20.1
Total enrollment in medication trials		**568**	**99.9**

* These percentages are based on total enrollments in medication trials (N=568). Does not total 100 percent because of rounding.

Figure 8.5 presents these trials according to their aims, such as developing new treatments for HIV/AIDS or treating or preventing HIV-associated conditions. When the name of a trial could not be determined, neither could the purpose be determined. Each of these categories is discussed below.

Figure 8.5: Types of Medication Trials by Purpose of Trial

Type of Medication Trial	Clinical Trials in which children in Vera review were enrolled		Enrollment of children in Vera review in interventional trials	
	Trials	Percent of Medication trials	Enrollments	Percent of enrollments in medication trials*
New Treatments for HIV/AIDS	35	53.8	447	78.7
Expanded Access Programs for HIV/AIDS Treatments	7	10.8	68	12.0
Treatment/Prevention of HIV-associated conditions and complications	20	30.8	50	8.8
Prevention of Mother-Infant Transmission	2	3.1	2	0.4
Unable to determine name of medication trial	1	1.5	1	0.2
All Medication Trials	**65**	**100**	**568**	**100.1**

*Percentages do not total 100 percent because of rounding.

New Treatments for HIV/AIDS. Of the 65 medication trials, 35 (53.8 percent) were for medications, or combinations of medications, to suppress viral production. One trial (PACTG 218) tested vaccines to determine whether increasing the immune system's response to HIV could decrease the impact of the virus in children who were already infected.

Expanded Access Programs. Expanded access programs (Treatment INDs and Parallel Track Programs) allow non-FDA approved medications to be used by patients with life-threatening illnesses who cannot be enrolled in a clinical trial. Twelve percent of enrollments in medication trials were in seven trials conducted under the expanded access programs.[587] The earliest of these programs—and the one with the highest enrollment—was the Burroughs Wellcome AZT Treatment IND. Of the 68 enrollments in expanded access programs, 53 (78 percent) were enrolled in this Treatment IND. Five children in the Vera review were enrolled in the Bristol Meyers Squibb Stavudine Parallel Track, the first use of the parallel track mechanism for expanded access. [588]

Treatment and Prevention of Opportunistic Infections and Other HIV-Associated Conditions. Twenty of the 65 medication trials tested new drugs or methods for preventing and treating opportunistic infections and other conditions associated with HIV infection. Ten of these studies involved routinely used childhood vaccines and vaccines used in adults and children with specific medical conditions that put them at risk for certain infections, such as pneumonia caused by the pneumococcus bacteria.[589] One study, PACTG 247, compared a high calorie, concentrated infant formula with standard infant formula to see if a higher calorie formula increased weight gain and growth in newborns and prevented failure to thrive. Four trials tested interventions to *prevent* opportunistic infections or serious bacterial infection in children with HIV, and four trials tested *treatment* for opportunistic infections or other complications (severe anemia, low

[587] For some trials, Vera reviewers had difficulty determining if the trial was a Phase III or Expanded Access Program. This was particularly true when Vera did not see a copy of the informed consent document or the trial protocol and relied only on a description of the trial in a progress note or approval letter. For one child, the approval letter for enrollment states that the child may receive a medication on a "compassionate use" basis, however it is not clear if this is through an expanded access program or as off-label prescribing. It is included in the data analysis as an expanded access enrollment. Another child was enrolled to receive Amprenavir in a trial that was either expanded access or Phase IIIB. It is included in this analysis as an expanded access, although, in this case, the child died before receiving the medication. In general, trials were considered expanded access if they were open label and described as having a goal of making the medication available to children who had no other therapeutic options and/or did not qualify for existing trials.

[588] This trial will be referred to as "BMS d4t Parallel Track" in tables throughout the chapter. (For details see Appendix 10.)

[589] Many routine vaccines protect against disease by exposing the person to a live but weakened form of a virus or bacteria (live attenuated vaccines) or to a portion of the bacteria or virus so that his or her immune system can develop antibodies that will fight off an infection if he or she is exposed in the future. Children with HIV often do not respond to routine immunizations in the same way that other children do, and therefore may not be adequately protected. We found two types of clinical trials using routine childhood immunizations: earlier studies that sought to find the effective dose for children with HIV and later trials that used routine immunizations to help measure the degree to which HAART therapy had "reconstituted" the child's immune system. Both types are included in this section.

white blood cell count, and low platelet count) of HIV in children. One trial was for treatment of lymphoma—a cancer often developed by people with HIV infection.

Prevention of Mother-to-Infant Transmission. Only two children in the Vera review were enrolled in clinical trials of pre-natal interventions during pregnancy to prevent the transmission of HIV from mother to infant. The first study, PACTG 076, began in 1991 and was stopped early because of favorable results. The study showed that administering Zidovudine (AZT) to HIV-positive women during pregnancy and while in labor and to their newborn children for the first six weeks of life reduced transmission of HIV infection by two-thirds.[590] Shortly after the trial was ended, in April 1994, the U.S. Public Health Service (PHS) recommended that the treatment be offered to all pregnant women with HIV.[591] PACTG 076 was followed by several other studies that tried different combinations of treatment to decrease mother-to-infant transmission. One of the children in the Vera review participated in a later transmission study, PACTG 316, in 1997, which tested the efficacy of Nevirapine in preventing mother-to-baby transmission.

Medication Trials by Trial Phase. Children in the Vera review participated in all phases of drug testing. Figure 8.6 groups the trials according to their phases, showing the children's participation rates according to phase. Of children enrolled in medication trials, the smallest number (3) were enrolled in Phase I clinical trials and the largest number (189) were enrolled in Phase III trials. Vera reviewers were unable to determine the phase of drug testing for 18 medication trials involving 39 children.

[590] E. Connor, R. Sperling, R. Gelber, P. Kiselev, G. Scott, M. O'Sullivan, et al., "Reduction of Maternal-Infant transmission of Human Immunodeficiency Virus Type 1 with Zidovudine Treatment," *New England Journal of Medicine*, 331 (November 3, 1994):1173-80.

[591] PACTG included only women who did not need to be on antiretroviral therapy for their own health and had CD4 counts greater than 200 cells/μl. The only indication for treatment was to prevent mother-to-infant transmission of the HIV virus, not to treat the mothers' infection. The USPHS recommendations applied to women in this same category.
Centers for Disease Control, "Zidovudine for the Prevention of HIV Transmission from Mother to Infant," *Morbidity and Mortality Weekly Report*, 43, no. 16 (April 29, 1994).

Figure 8.6: Medication Clinical Trials by Phase of Drug Testing

Phase of medication clinical trials	Clinical trials		Trial enrollments in Vera's review	
	No. of trials	Percentage	No. of enrollments	Percentage
Phase I	1	1.5	3	0.5
Phase I/II	14	21.5	65	11.4
Phase II	11	16.9	100	17.6
Phase II/III	4	6.2	104	18.3
Phase III	10	15.4	189	33.3
Expanded access programs	7	10.8	68	12.0
Unable to determine phase of trial	18	27.7	39*	6.9
Total	**65**	**100**	**568**	**100**

* Three trials in this group are the same trial (with two extensions) and involved only one child. Because the trial sponsor (Merck) assigned a different identification number for each extension, Vera staff counted them as three trials. One child was enrolled and informed consent forms were found for the original trial and each of the two extensions.

The Vera review found that three children participated in one NIH-sponsored Phase I clinical trial and 64 children participated in Phase I/II trials by the NIH.[592] There were six enrollments (of five children) in a study of Nelfinavir (Viracept) sponsored by Agouron Pharmaceuticals (Agouron Nelfinavir 1343-524).[593] While the consent forms indicate that this was a Phase I trial, three enrollments occurred after the drug had been approved by the FDA for use in children.[594]

All of the Phase I/II trials were sponsored by the NIH and most involved testing new combinations of antiretroviral medications, rather than the testing of new drugs. These trials generally included one or two new medications used in combination with other medications that had already been approved for either pediatric or adult use.

Medication Clinical Trials by Sponsor. As Figure 8.7 shows, the NIH sponsored 41 (63.1 percent) of the 65 interventional clinical trials identified in the Vera review. Pharmaceutical companies sponsored 17 (26.2 percent) of the 65 trials. In seven trials (10.8 percent), the sponsor could not be determined. Some of the trials for which Vera reviewers could not verify the sponsor appeared to have been small trials conducted at one medical center without outside sponsorship. Eighty-one percent of all enrollments in interventional trials were in clinical trials sponsored by the NIH. There were 93 enrollments (16.4 percent) in trials sponsored by

[592] The Children's Services policy about participation of children in Phase I trials is discussed in Chapter 6. Briefly, participation in Phase I trials was generally not permitted. Participation in Phase I/II trials was permitted if the child entered the trial during Phase II. Vera medical reviewers were unable to determine the phase in which a child participated based on information available in the child welfare files.

[593] This trial will be referred to as "AG Nelfinavir" in tables through out the chapter. (For details see Appendix 10.)

[594] Vera staff did not obtain a protocol for this trial. All information on the trial comes from a consent form found in the PAU files and from Agouron Pharmaceuticals' application to the FDA for licensing of Viracept (Nelfinavir), from www.FDA.gov, accessed September 18, 2008. Viracept was approved via the fast track mechanism, and the ongoing clinical trials may have been required post-marketing studies. For this report, this trial was classified as a phase-unable to determine. One child was enrolled twice, an original enrollment and one extension.

pharmaceutical companies. The majority of these enrollments—68 (73.1 percent)—were in expanded access programs (see Figure 8.6 above).

Figure 8.7: Medication Clinical Trials by Sponsorship

Sponsor of medication clinical trials	Clinical trials		Enrollments from Vera review	
	No. of trials	Percentage*	No. of enrollments	Percentage
National Institutes of Health	41	63.1	462	81.3
Pharmaceutical companies	17[595]	26.2	93	16.4
Unable to determine sponsor	7	10.8	13	2.3
Total	65	100.1	568	100

*Does not total 100 percent because of rounding.

Observational Studies

Of the 846 enrollments that Vera reviewers identified, 274 were enrollments in observational research studies. Of the 532 foster children who were enrolled in any study or trial, 103 were enrolled in observational research studies only. Observational studies often involve diagnostic tests, but do not test new medications or other interventions. Observational study participants are seen at regular intervals by the researcher and undergo a standardized series of evaluations, including physical examinations, blood tests, x-rays, and questionnaires. Children who were enrolled in observational studies received HIV-related and general medical care from their physicians and could also enroll in medication trials.[596]

Children in the Vera review participated in approximately 20 different observational studies. For some children Vera reviewers were unable to determine the exact name of the observational study, but determined from the trial description that it was observational. For a description of each observational study, please see Appendix 10.

The earliest studies focused on learning about transmission from mother to infant and on distinguishing between children infected with HIV and those who were carrying maternal antibody but not infected.[597] Later observational studies sought to learn more about the impact of treatment with antiretroviral drugs on children and young adults with HIV infection.

Two of the earliest studies, the Maternal Infant Transmission Study (MITS), sponsored by the Centers for Disease Control, and the Women to Infants Transmission Study (WITS), funded by the NIH, enrolled HIV-positive women who were pregnant or new mothers and their newborn

[595] This includes expanded access programs, all of which are pharmaceutical-company sponsored. The NIH-NIAID was a co-sponsor of the Burroughs Wellcome AZT Treatment IND along with the company Burroughs Wellcome.
[596] As described in Chapter 7. Children's Services required that all children with HIV in foster care be under the care of a specialized HIV physician or medical facility. The percentage of HIV-positive children enrolled in observational studies who received antiretroviral treatment from their physician is described in Chapter 5.
[597] Several mother-to-child observational research studies are grouped together as "transmission studies" because very little information was available about individual studies. Studies for which more information was available, such as MITS and WITS, are described separately.

children.[598] These studies, initiated early in the pediatric HIV epidemic, sought to answer basic questions about HIV, such as which mothers were more likely to transmit the virus to their infants and how infants with HIV infection could be distinguished from uninfected infants with maternal antibody. Infants were enrolled in these studies by their mothers during pregnancy or shortly after birth. The mothers and infants then returned periodically for physical examinations and laboratory evaluations.[599]

The Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV-Infection (P2C2) study was funded by the National Heart, Lung, and Blood Institute (part of NIH) in 1989 to study cardiac and pulmonary problems that were significant causes of illness and death among children with HIV. Specifically, this study aimed to describe lung and circulatory problems in infants born to mothers with HIV. P2C2 was carried out at five centers, including two in New York City—Mount Sinai School of Medicine and Presbyterian Hospital/Columbia University College of Physicians and Surgeons.[600] The study did not include treatment, but collected information on the children when they were treated for heart and lung problems. Approximately 800 children participated in this study nationally, including 26 children in foster care on the Vera review list.[601]

The Pediatric Late Outcomes Protocol (PACTG 219) was initiated in 1993 to determine the long-term consequences, both negative and positive, of exposure to antiretroviral drugs during pregnancy, infancy, and childhood. The late outcomes studies enrolled children (both HIV positive and HIV negative) whose mothers had been treated with antiretroviral therapy during pregnancy, children who had received antiretroviral therapy at birth, and children who were HIV positive and had been treated with antiretroviral and other therapy in clinical trials. The study was later expanded into PACTG 219C, which included any HIV-positive child, whether or not the child had been enrolled in another clinical trial. Children enrolled in PACTG 219 and

[598] Interviews with principal investigators conducted by Vera staff.

[599] MITS continued under the name PACTS (Perinatal AIDS Collaborative Transmission Study) through 2004. PACTS was conducted in four cities—New York, Atlanta (Emory University), Newark (University of Medicine and Dentistry of New Jersey), and Baltimore (University of Maryland). The New York sites were Harlem Hospital Center, Bronx-Lebanon Hospital Center, Bronx Municipal Hospital Center (Jacobi Hospital), Montefiore Hospital, and Metropolitan Hospital. The studies resulted in a number of published articles, including D. Thea, G. Lambert, J. Weedon, P. Matheson, E. Abrams, M. Bamji et al., "Benefit of Primary Prophylaxis Before 18 Months of Age in Reducing the Incidence of Pneumocystis Carinii Pneumonia and Early Death in a Cohort of 112 Human Immunodeficiency Virus-Infected Infants," *Pediatrics* 97, no. 1 (January 1996); E. Abrams, P. Matheson, P. Thomas, D. Thea, K. Krasinski, G. Lambert et al., "Neonatal predictors of Infection Status and early Death Among 332 Infants at Risk of HIV-1 Infection Monitored Prospectively from Birth," *Pediatrics*, 96, no. 3 (September 1995); P. Stratton, R. Tuomala, R. Abboud, E. Rodriquez, K. Rich, and J. Pitt, "Obstetric and Newborn Outcomes in a Cohort of HIV-Infected Pregnant Women: A Report of the Women and Infants Transmission Study," *Journal of Acquired Immune Deficiency Syndrome & Human Retroviruses*, 20, no. 2 (February 1, 1999): 179-86; and M. MacMillan, L. Magder, P. Brouwers, C. Chase., J. Hittleman, T. Lasky, et al., "Head Growth and neurodevelopment of infants born to HIV-1 Infected Drug Using Women," *Neurology* 57 (2001): 1402-11.

[600] NIH/NHLBI, Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted Human Immunodeficiency Virus (HIV) Infection-P2C2 Protocol, July 3, 1990.

[601] W. Shearer, S. Lipshultz, K. Easley, K. McIntosh, J. Pitt, T. Quinn et al., "Alterations in Cardiac and Pulmonary Function in Pediatric Rapid Human Immunodeficiency Virus Type I Disease Progressors," *Pediatrics* 105 (2000): e9.

PACTG 219C were seen periodically until age 24 and evaluated with physical examinations, laboratory tests, and questionnaires.[602]

Experimental Therapy Outside of a Clinical Trial

Vera staff reviewed one case where, at the request of the birth mother and the foster parent, the city child welfare agency permitted a child to be treated by a private physician with an unapproved medication called Kemron.[603] Notes in the child's file indicate that the child welfare agency researched the issue carefully and made a plan that included close monitoring of the child by Children's Services and a pediatric HIV physician who had cared for the child previously. In this case, a medical treatment plan was drawn up between the Human Resource Administration's Office of Legal Affairs, the mother, and the foster mother that acknowledged that the treatment was experimental and made outside of FDA guidelines and provided for ongoing collaboration between the physician administering the medication and the HIV specialist. The treatment plan called for a discussion of the use of an FDA-approved treatment if the child's condition was to deteriorate.

This child is mentioned here because Kemron was an unapproved treatment. Because the child was not enrolled in a clinical trial, this case is not included in Vera staff's analysis of enrollments.

Where Clinical Trials Were Conducted and Where the Children were Enrolled

As mentioned earlier in this chapter, both the NIAID and the NICHD funded clinical trials sites in New York City. Figure 8.8 lists the sites in New York City in which children in the Vera review were enrolled in both observational and interventional trials. More than half of all clinical trials enrollments took place at five medical centers.

[602] National Institute of Allergy and Infectious Diseases, PACTG 219: Pediatric Late Outcomes Protocol: A Multicenter Trial of the Pediatric AIDS Clinical Trials Group, Version 3.0, 9 March 2000.

[603] Kemron is low-dose oral alpha interferon. It was studied first at the Kenya Medical Research Institute in Africa which reported that Kemron was effective in relieving the symptoms of AIDS. The Kenya Medical Research Institute also reported an increase in CD+4 cells and a conversion from HIV-antibody positive to HIV-antibody negative. In response to the results of this report, as well as anecdotal reports from physicians in the US who treated patients with Kemron, the NIH sponsored a double-blinded randomized controlled study of low-dose oral alpha interferon. Two other placebo-controlled trials were conducted at Mt. Sinai Medical Center in Manhattan as well. The child in the Vera review was not in that study, but was treated at a private physician's office. National Institute of Allergy and Infectious Disease (NIAID), NIAID Will Pursue Clinical Trials of Low-Dose Alpha Interferon, Update, October 27, 1992 and National Institutes of Health, Interim Report: Low-Dose Oral Interferon Alpha as a Therapy for Human Immunodeficiency Virus Infection (HIV-1): Completed and On-Going Clinical Trials, Backgrounder, April 1992.

Figure 8.8: Clinical Trials Enrollment Sites

	All trial enrollments		Treatment trials		Observation trials	
Trial site	**Enrollments**	**% Enrollments**	**Enrollments**	**% Enrollments**	**Enrollments**	**% Enrollments**
Harlem Hospital Center	155	18.3	88	15.5	67	24.5
Bronx Lebanon Hospital Center	83	9.8	66	11.6	17	6.2
Columbia Pres. Hosp. Center	83	9.8	49	8.6	34	12.4
Children's Hospital of Brooklyn (SUNY Downstate) *	70	8.3	44	7.7	25	9.1
Kings County Hospital	61	7.2	39	6.9	22	8.0
Bellevue Hospital Center *	50	5.9	38	6.7	10	3.6
Incarnation Children's Center[604]	46	5.4	34	6.0	12	4.4
SUNY Stony Brook	42	5.0	28	4.9	14	5.1
Albert Einstein College of Medicine	34	4.0	27	4.8	7	2.6
Mt. Sinai Medical Center	33	3.9	19	3.3	13	4.7
North Shore University Hospital	26	3.1	17	3.0	9	3.3
Cornell-NY Hospital *	24	2.8	21	3.7	3	1.1
Schneider Children's Hospital/Long Island Jewish Medical Center	15	1.8	14	2.5	1	0.4
Metropolitan Hospital Center	12	1.4	8	1.4	4	1.5
New York Medical College/Westchester County Medical Center	11	1.3	9	1.6	2	0.7
St. Luke's-Roosevelt Hospital	11	1.3	9	1.6	2	0.7
Bronx Municipal Hospital Center/Jacobi Medical Center	10	1.2	6	1.1	4	1.5
Beth Israel Hospital	10	1.2	10	1.8	0	0.0
Other in NY	18	2.1	11	1.9	7	2.6
Other out of NY	18	2.1	14	2.5	4	1.5
UTD	34	4.0	17	3.0	17	6.2
Total enrollments*	**846**	100.1	**568**	100.1	**274**	99.9

* Total number of enrollments in observational studies and in treatment trials does not add up to total enrollments because there were four enrollments in trials or studies that could not be classified as observational or medication based on available information. Percentages do not total 100 percent because of rounding.

[604] Incarnation Children's Center was a sub-site of Columbia Presbyterian.

The Impact of Clinical Trials on Pediatric HIV Treatment

The FDA approved the first drug for treating children with HIV, Zidovudine (AZT), for pediatric use in 1990. Since then it has approved 14 additional medications for use in children younger than 12, based on clinical trials that found them to be both safe and effective.[605] The approved medications include several classes of drugs: Fusion Inhibitors, Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTI), Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI) and Protease Inhibitors. For five medications and three HIV vaccines tested in clinical trials in which children in the Vera review participated, the sponsors have not submitted data to support pediatric labeling.[606]

Among the reasons that a drug that has been found to be safe and effective in treating adults with HIV but not useful for children include the need for frequent dosing, the availability of less toxic alternatives, lack of proven efficacy, and the lack of a formulation such as a syrup or powder that is acceptable for use in children.[607] These medications include Indinavir, Atazanavir, ddC, and Maraviroc. There were ten clinical trials in which these treatments were tested. Fifty-eight children from Vera's review were enrolled in these trials (see Figure 8.9).

Figure 8.9 Enrollments in Trials of Drugs That Do Not Have Pediatric Labeling

Drug	Trial number	Enrollments of children on Vera list
ddC	PACTG 190	19
ddC	PACTG 138	11
ddC	PACTG 366	1
Indinavir	PACTG 338	19
Indinavir	Merck IDV + 2 NRTIs-01†*	1*
Indinavir	Merck IDV + 2 NRTIs-10*	1*
Indinavir	Merck IDV + 2 NRTIs-20*	1*
Atazanavir	PACTG 1020A	3
Maraviroc	Pfizer Maraviroc‡	1
Vaccine: rgp120/HIV-1 MN (Genentech) Vaccine rgp 120/HIV-1 SF-2 (Chiron/Biocine) Vaccine: gp160 Vaccine (MicroGeneSys)	PACTG 218	3
Total		60

† The full name of this trial is Merck Indinavir-Stavudine-Lamivudine 068-01. The subsequent extensions are likewise Merck Indinavir-Stavudine-Lamivudine 068-10 and Merck Indinavir-Stavudine-Lamivudine 068-20, respectively. (For details see Appendix 10).
‡ The full name of this trial is Pfizer Maraviroc A4001029 (Phase II). (For details see Appendix 10.)
* These enrollments are the same child. Two of these trials are extensions of the original trial Merck 068-801.

[605] Drugs Used in the Treatment of Pediatric HIV Infection, from http://www.fda.gov/oashi/aids/pedlbl.html, accessed October 3, 2008.
[606] Information on medications that do not have pediatric labeling as of December 2007 can be found at: http://www.fda.gov/oashi/aids/pedlbl.html. Information on the results of testing HIV vaccines in PACTG 218 can be found in J. Lambert, J. McNamara, S. Katz, T. Fenton, M. Kang, T. Van Cott, et al., "Safety and Immunogenicity of HIV Recombinant Envelope Vaccines in HIV-Infected Infants and Children," *Journal of Acquired Immune Deficiency Syndromes and Human Retroviruses*, 19, no. 5 (December 15, 1998): 451-61.
[607] Formulation refers to the form in which a drug is given. Children-acceptable formulations include liquids and dissolvable powders or pills that contain the dose of medication required by a child.

The recommended guidelines for treating children with HIV/AIDS today call for the use of combination drug treatments known as Highly Active Anti-Retroviral Therapy (HAART), which usually includes three drugs from at least two drug classes, one of which can be a protease inhibitor. The most recent guidelines recommend treatment with HAART for all children with HIV who are less than one year old and for children older than one year based on the development of symptoms, CD-4 counts, and viral loads.[608]

Conclusion

The Vera review found documentation of 846 enrollments of children in New York City foster care in 88 clinical trials. Enrollment in clinical trials sponsored by the National Institutes of Health accounted for 81.3 percent of all of the enrollments, and clinical trials sponsored by pharmaceutical companies made up 16.4 percent. Foster children were enrolled in all three phases of pre-marketing drug testing, with the smallest number of enrollments (3) in Phase I trials and the largest number of enrollments (189) in Phase III trials. There were 103 children who were enrolled only in observational research studies.

The clinical trials in which the foster children in the Vera review were enrolled took place at multiple sites across the United States and Puerto Rico. More than 20 New York City area hospitals conducted clinical trials related to pediatric HIV. Half of all the enrollments identified by Vera reviewers took place at five hospitals in New York. Foster children in the Vera review made up less than one fifth of all New York City enrollments in 19 NIH-sponsored clinical trials conducted in New York City.

Since the testing of treatments for pediatric HIV/AIDS began, the FDA has found 15 drugs to be safe and effective and has approved their use in children under the age of 12.

This chapter has described the observational research studies and medication clinical trials. The following chapter will describe the experience of the children who participated in the trials.

[608] The Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, "Guidelines for the Use of Antiretroviral Agents in pediatric HIV Infection, July 29, 2008," available at http://aidsinfo.nih.gov/contentfiles/PediatricGuidelines_PDA.pdf. The Guidelines contain the latest recommendations for diagnosing, treating, and monitoring children with HIV as well as comprehensive information about the antiretroviral medications—recommended use, efficacy, and toxicity.

Chapter 9: Description of Children's Medical Experience in Clinical Trials and Observational Research Studies

Chapter Summary

Vera's analysis divides children's experiences into three time periods. Each period is characterized by different types of trials, varying stages of HIV disease among participating children, and alternative treatments available outside of clinical trials. In the first period, 1986 to 1990, a small number of trials tested single drugs already approved for adults use, there were no existing approved treatments outside of clinical trials for HIV-infected children, and many of the children who participated suffered from multiple AIDS-related complications. The second period, 1991 to 1995, involved the testing of several new drugs and some combinations of approved drugs. Foster children in this period were often symptomatic for HIV disease but less sick than those in the first period, and many accessed approved drug treatment options outside of clinical trials. In the third period, 1996 to 2005, trials often tested combinations of three or four drugs, most of which had already been approved for pediatric use. Many participants were only mildly symptomatic when they entered a trial, but showed laboratory signs of disease progression. Most had accessed several treatment options outside of trials.

Although limited to the medical information contained in child welfare files, Vera's analysis found that children met the trials' eligibility criteria for age, HIV status, and disease stage. However, of 568 medication trial enrollments that were reviewed, Vera staff found two children who met exclusion criteria for a trial in which they were enrolled, meaning they should not have been enrolled in that trial. Also, of the 429 children who were enrolled in medication trials, reviewers found two children who were thought to be HIV infected when they entered a trial but who seroreverted while on the trial and two children for whom reviewers found conflicting information about their HIV status.[609] The latter two files were referred to Children's Services, who confirmed that one child had been enrolled appropriately.

Vera staff examined several aspects of the medical monitoring of foster children in clinical trials. These include documentation of toxicities and adverse events, responses by trial physicians to adverse events, and interventions by the Data Safety Monitoring Boards, as described in Chapter 8. As Vera researchers did not have access to clinical trial research or hospital medical records, a systematic quantitative analysis was not possible. When child welfare files did include medical information, adverse events were recorded and responses to those events conformed to the trial protocols. Though Vera staff could not compare the frequency of adverse events among foster children to that experienced in trials generally, the types of toxicities seen, some of which were severe, were consistent with those reported in published articles of trial results. In several instances, reviewers saw the Data Safety Monitoring Boards intervening and closing trial arms after interim study results suggested one type of treatment was more effective or had fewer toxicities than another.

[609] The number of medication trial enrollments and the number of children enrolled in medication trials is different because some children were enrolled in more than one trial.

Vera staff analyzed in detail each of the 25 deaths that occurred while foster children were participating in a medication clinical trial. All but two of these deaths took place prior to 1996. Most of these children were experiencing severe AIDS related complications at the time they entered the clinical trial. None of these deaths appeared attributable to trial medications.

Introduction

This chapter describes the medical experiences of the 532 children who, while in foster care, participated in the 65 medication trials and the approximately 20 observational studies discussed in Chapter 8.[610] It describes the types of trials, how children became candidates for trials, their eligibility for the trials, and the monitoring of their progress in the trials by the clinical trial team and by the foster care agency. The chapter ends with a discussion of the foster children who died while in an observational research study or a medication clinical trial.

How Vera Produced this Information

Chapters 2 and 8 describe the methodology for the medical review. The medical review sought to answer the following questions about each child enrolled in clinical trials (particular attention was given to looking for changes in trends in enrollment over the years):

- How was the child selected for entry into a clinical trial?
- Was consent obtained for the child's entry into a trial?[611]
- Was the child eligible for the trial based on the trial eligibility criteria as written in the trial protocol or described in published reports?
- Did the child meet the age criteria for the trial?
- What was the child's HIV status when entered into the clinical trial and what was the child's final HIV status?
- What was the child's state of health at entry into the trial and over the course of the trial?
- Who monitored the child's medical course in the trial, and how?
- Were there benefits or ill effects from a child's participation in a trial and how were any ill effects addressed?
- Did the child complete the trial and if not, why not?

Overall, Vera reviewers were able to see child welfare case management files for 96 percent (764 out of 796) of children, and foster care agency case planning files for 73 percent (656 out of

[610] There were three trials for which reviewers were not able to determine the identity of the trial, or its purpose. These were excluded from the analysis in this chapter. As discussed in Chapter 8, several observational studies of mother-to-infant transmission are grouped together.

[611] The topic of consent for a foster child to enter a clinical trial, and how it was addressed during the years of the review is discussed in Chapter 10.

902) of children on the review list. Reviewers also examined available documents from the Pediatric AIDS Unit (PAU).[612]

The quality of the medical information in the child welfare files varied. Some contained useful and consistent information from which the reviewer could synthesize a clear picture of a child's medical experience in a clinical trial. This was particularly true for children who spent time at foster care agencies with specialized units for HIV-exposed and HIV-positive foster children. Other files, however, had missing or incomplete information and reviewers were unable to determine the full medical experience of the child. These files gave a fragmented picture of a child's medical care. For example, an agency file might show clear evidence of a child's participation in a specific clinical trial, such as a signed and dated informed consent form, but little supporting documentation of clinic trial visits or of laboratory results documenting the monitoring process. Or, an agency might have strong documentation of a child's being monitored in a clinical trial, such as case manager or nurse's notes about trial-related clinic visits or laboratory results, but not enough information to determine who gave permission for the enrollment.[613]

Vera reviewers combined information from these sources to create as complete a picture as possible of each foster child's medical experience while in a trial. As described in Chapter 2, the data from the files were used both to complete a medical instrument and to create a medical narrative. The data recorded in the medical instrument and the narrative were used to answer the questions posed above, as well as to document the number of children for whom reviewers were unable to determine the answer to specific items on the medical instrument because the data was not available in the child's files. The unit of analysis used varies with the topic being discussed. There were 532 children in Vera's review who participated in clinical trials. Of these, 429 were enrolled in at least one medication trial; 103 were enrolled only in observational research studies. There were a total of 846 enrollments in trials, of which 568 were in medication trials. More explanation of the numbers can be found in Chapter 8 and later in this chapter.

Clinical Trial Enrollments

There were a total of 846 trial enrollments for the 532 children in Vera's review. Of those 532 children, 103 were enrolled *only* in observational research studies related to HIV disease. Eighty-nine children were enrolled in just one observational research study; 14 were enrolled in more than one observational research study. There were 429 children who were enrolled in at least one HIV medication/treatment trial. Looking at enrollment in all clinical trials (observational research studies and medication trials), 61 percent of children were enrolled in one trial, 25 percent were enrolled in two trials, and 14 percent were enrolled in three or more trials. Of those children enrolled in medication trials, 59 percent were enrolled in one medication trial, 18

[612] Some of the foster children in Vera's review were cared for by more than one agency; thus, a child could have more than one case planning file. For a detailed discussion of file review and methodology, see Chapter 2.
[613] In the PACTG trials, a centralized laboratory conducted many specialized tests such as CD-4 cell studies or viral loads. The laboratory reports are titled "PACTG Flow Cytometry," but do not specify the trial that requested the test.

percent were enrolled in two medication trials, and almost 4 percent were enrolled in three or more medication trials. Enrollment in multiple trials was more common in the earlier years of the review, when children with HIV were sicker and treatment options outside of trials were limited. Children were not enrolled in more than one antiretroviral medication trial at one time, though they may have been enrolled in a trial that sought to prevent or treat complications of HIV/AIDS at the same time that they were enrolled in an antiretroviral trial.

Figure 9.1: Children Enrolled in Clinical Trials by Trial Type and Number of Trials

	No. of Children	**Percentage of children enrolled in any type of research**
Total children enrolled in clinical trials*	**532**	100.0
In only one trial	322	60.5
In two trials	137	25.8
In three or more trials	73	13.7
In at least one medication trial**	**429**	80.6
In only one medication trial	316	59.4
In two medication trials	93	17.5
In three or more medication trials	20	3.8
In observational research studies only	**103**	13.7%

* Includes both medication trials and observational research studies.
** Children enrolled in medication trials might also be enrolled in observational research studies.

As discussed in Chapter 8 and illustrated in Figure 8.4, the large majority (79 percent) of the 568 enrollments in medication trials were in one of 15 trials. Most (71 percent) of these 15 trials began before 1995, and more than half took place between 1988 and 1991, the earliest years of the pediatric HIV epidemic. During these years, large numbers of HIV-infected children entered the foster care system, often with multiple medical problems related to drug exposure before birth, lack of prenatal care, and prematurity. In addition, they had either exposure to or infection from HIV at a time when standard treatment options did not exist.[614]

Chronology of the Clinical Trials. The number of enrollments and the types of clinical trials in which children in the review participated changed over the course of the 14-year period reviewed. Three periods can be distinguished and are described in Figure 9.2.

[614] See Appendix 5 for a list of when antiretroviral medications became available for children and adults. This information can also be found http://www.fda.gov/oashi/aids/pedlbl.html. The development of treatment for children with HIV/AIDS is also discussed in Chapter 4.

Figure 9.2: Characteristics of the Three Periods Covered by the Review

Time period	Clinical trials **	Trial enrollments **	Characterization
1986-1990*	10	263	• No medication available for use in pediatric HIV disease outside clinical trials except IVIG • Trials involved single drugs (monotherapy) that had been tested in adults with HIV disease
1991-1995	30	395	• Increased availability of FDA-approved monotherapy outside of trials • Trials of new antiretroviral medications and combination therapies.
1996-2005	38	136	• Protease inhibitors become available. • HAART is the standard of care[615] • Trials of new combinations and new protease inhibitors • Trials examine "immune reconstitution" and whether treatment with HAART restores immune system function.[616]

* The first enrollments in trials found occurred in 1986 and 1987, before the years covered by Vera's review.

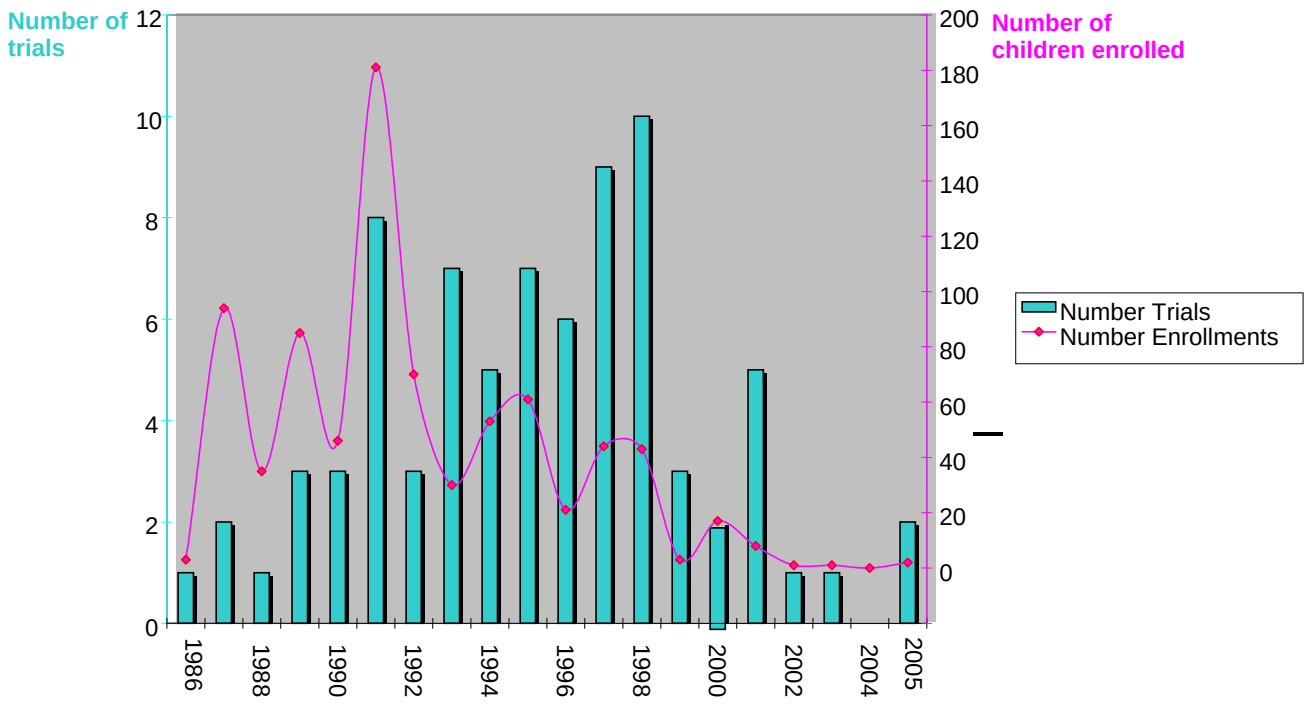
** The years of 10 trials and the dates of some enrollments could not be determined.

The number of enrollments in clinical trials during the three periods is illustrated in Figure 9.2. In the early years under review, there were few clinical trials for children with HIV disease and these trials had many enrollments. In later years, as more treatments became available, fewer children were enrolled in trials even though many trials were being conducted.

[615] HAART stands for Highly Active Antiretroviral Therapy. This is discussed in detail in Chapter 4.

[616] One of the ways that this was measured was to give doses of routinely used childhood immunizations and measure, with blood tests, whether the child developed the same level of response that is seen in children who do not have HIV.

Figure 9.3: Number of Trials vs. Number of Enrollments, by Year



FOSTER CHILDREN IN CLINICAL TRIALS 1986-1990: Many (40.2 percent) of the children in the Vera review entered foster care by 1990. Many children who participated in clinical trials between 1986 and 1990 entered foster care already experiencing manifestations of HIV disease. Many fit the "fast progressor" profile described in Chapter 4, experiencing multiple medical complications related to AIDS. Some of these children were not diagnosed with HIV until they entered care. Vera reviewers saw evidence of the challenges in diagnosing HIV disease in infants and children, and in treating children who were HIV positive—particularly making a definitive diagnosis of HIV infection before a child was 18 months old.

The decision of whether or not to allow foster children to participate in clinical trials of new treatments for HIV was an additional challenge. The following case from a Vera reviewer narrative illustrates these challenges:

> *This baby was born in 1989, with cocaine and methadone in his urine. He had severe withdrawal symptoms. He also had congenital syphilis. A combination of medical and social factors kept him hospitalized for five months as a "boarder baby," during which time he had multiple severe medical problems. He was tested for HIV during this period and found to be HIV antibody positive and severely immunosuppressed. He was placed on prophylaxis for Pneumocystis carinii Pneumonia (PCP).*

The child welfare files contain documentation that the social worker at the hospital called at least seven foster care agencies in New York City, seeking foster home placement for the baby, but without success. Most agencies felt the baby was too sick and there were few homes willing to take an HIV-exposed, and possibly HIV-infected, child. The child was transferred to Incarnation Children's Center (ICC), where he continued to be severely symptomatic, and had many hospitalizations. When he was one year old, consent was obtained from the PAU (as the parents could not be located) for the child to enter the Burroughs Wellcome AZT Treatment IND.[617] *There were only two trials approved for foster children at this time, and there was no drug treatment outside of trials except for IVIG.*[618]

The child showed some medical and developmental improvement on this trial, and an agency succeeded in placing the child in a foster home trained to care for HIV-infected children. Further HIV testing had definitively shown the child to be HIV infected. When he was 20 months old, he was hospitalized for pneumonia and bleeding. His doctors tried several treatments, but the child's health continued to deteriorate, and he died a month later.

Pediatric clinical trials in this early period tested antiretroviral drugs that had already been used with some success in HIV-positive adults. Reviewers noted only a few trials, but each trial enrolled many of the children who were part of Vera's review, and these children were often experiencing multiple HIV-related medical problems at the time of enrollment.[619] These trials tested the safety and effectiveness of single antiretrovirals (*monotherapy*). There were few treatment options outside of clinical trials for children with HIV disease at this time, and many HIV-infected foster children experienced illnesses and death regardless of whether they were in clinical trials.[620]

FOSTER CHILDREN IN CLINICAL TRIALS, 1991 TO 1995: From 1991 to 1995, an additional 245 children (46.1 percent, out of 532) in Vera's review entered foster care. New diagnostic methods allowed for an earlier definitive diagnosis in babies and children. Earlier diagnosis often led to earlier treatment for children who were symptomatic for HIV.[621] Some trials conducted during this period included children who had fewer symptoms and sought to define the optimal time to begin treatment with antiretroviral therapy.[622] There were a larger number of clinical trials, and some trials included hundreds of children across the nation as well as many of the foster children in this review. These trials used *combinations* of antiretroviral

[617] This trial will be referred to as "B-W AZT IND" in figures throughout this chapter. (For details see Appendix 10.)
[618] Intravenous Immunoglobulin (IVIG) was given to children with HIV with the hope that it would decrease the number of serious bacterial infections. It has no effect on the HIV virus.
[619] These six clinical trials were the earliest ones for children, and used IVIG, AZT, and ddC.
[620] See Chapter 4, Figure 4.4 for changes in the death rate of children with HIV over time.
[621] See Chapter 4 for a discussion of HIV testing advances.
[622] For example, PACTG 182 was a Phase III trial which looked at early versus late treatment of asymptomatic infants with AZT. Additional information can be seen in Appendix 10.

drugs, and children in general were not as sick (compared to children in early years of the review) when they entered a trial.[623]

During these years of the review period, children with HIV were enrolled in several types of trials. These included studies for treatment and prevention of common opportunistic infections seen with HIV infection, trials to evaluate the effectiveness of routine childhood vaccines for children with HIV and develop vaccination schedules and doses to meet their needs, clinical trials to prevent transmission of HIV from mother to baby, and treatment protocols for children with multiple AIDS-related complications who had failed all other drug treatments (referred to as salvage protocols). Reviewers noted that many children in foster care were treated for their HIV disease with antiretrovirals, which were now available *outside* of trials, as illustrated in the case below from a Vera review narrative:[624]

> *She was initially started on Bactrim for PCP prophylaxis, but developed an allergy and was switched to Dapsone (a medication to help prevent pneumonia). She started AZT therapy and Dapsone. She did well on her medications for a while, steadily growing and gaining weight…Six months later she had caught up considerably, approximately two years after starting treatment she was described in a neurological/developmental assessment as in the normal range.*

During this period, children with and without symptoms related to HIV and AIDS were enrolled in clinical trials. For many children in foster care, more effective treatments both in and outside of clinical trials improved the quality and length of their lives.

> *An agency medical record in 1994 indicated that the child had thrush and LIP (a lung inflammation common in HIV-infected children), and was receiving AZT and Bactrim. Thirteen months later, an ICC Medical Summary stated that "ddI [didanosine, an antiretroviral drug] was recently added to her regimen. She has had declining CD4 over the past year. If she does not show some improvement on combination therapy we will consider trying D4T through Bristol Meyers Open Label.[625]" Her health seemed to improve after the addition of D4T (Stavudine), with a December 1996 ICC note stating that she'd had no major illnesses or hospitalizations in the past 18 months.*

FOSTER CHILDREN IN CLINICAL TRIALS 1996-2005: The later years of the review, 1996 to 2005, involved many more clinical trials but fewer enrollments both nationally and among foster children in New York City.[626] Seventy children in Vera's review entered foster care during these years. These trials tested combinations of medications (highly-active antiretroviral

[623] There were 30 trials found by the review for this period.
[624] Antiretroviral treatment and prophylaxis against Pneumocystis carinii Pneumonia (PCP) outside of clinical trials for children in the Vera Institute review is described in Chapter 5.
[625] This refers to the Bristol Meyers Squibb Stavudine Parallel Track. This trial will be referred to as "BMS d4t Parallel Track" in figures throughout this chapter. (For details see Appendix 10.)
[626] Children in Vera's review participated in 38 clinical trials which took place during the years of 1996 to 2001. Some children in Vera's review were enrolled in them after 2001.

treatment, or HAART) that included protease inhibitors, a class of particularly effective anti-HIV drugs. Testing for HIV had improved and children were being diagnosed in their first months of life and treated early, with HAART and following guidelines developed by the NIH or the New York State AIDS Institute. Many children had fewer medical complications when they entered trials and many had few HIV/AIDS related health problems. If a child was enrolled into a trial, it was often because the trial addressed the specific HIV medical needs of that child. The following summary of a case from this period illustrates the differences between earlier and later clinical trial enrollments.

> *This child was born in 1997 to an HIV-positive mother who took antiretroviral medications for at least part of her pregnancy. The baby's urine tested positive for cocaine and heroin, and the baby had mild withdrawal symptoms. She received AZT for the first six weeks of life, and pneumonia prophylaxis. Within a few months after birth, viral tests confirmed that the child was HIV infected.*
>
> *The baby was released within days from the birth hospital and placed into a foster home. At 10 months of age, when the child's viral load began to rise and her CD4 count began to drop, the child was enrolled into PACTG 356 [triple antiretroviral therapy] and PACTG 219 [an observational research study for children enrolled in medication trials]. The birth mother signed the consents for both trials. While on this medication trial for 18 months, the child had mild-to-moderate nausea and vomiting, persistent diarrhea, and an episode of low platelets. She was continued on the trial medications after finishing the trial, continued to do well with good immune function and few illnesses.*
>
> *There were no developmental delays, but there were significant behavior problems for which the child entered therapy early on. She was adopted by her foster parents in her third placement just before turning five years old.*

Reviewers also saw that most children in foster care were treated for their HIV infection with options now available outside of trials, including approved combination antiretroviral therapy.

How Children Were Selected for Enrollment in Clinical Trials

The reasons children were considered for and enrolled in clinical trials varied over time as earlier diagnosis of HIV infection and more treatment options outside of clinical trials became available.

The Vera Institute review found that many HIV-exposed children who ultimately seroreverted were enrolled in observational research studies of mothers and infants. The average age at entry into foster care for the review years before 1996 was just over one year old. Many of these infants entered care directly from the hospital at birth, but because of limitations in testing techniques, they often could not be definitively diagnosed for 18 months.[627] Being followed in such an observational study seemed to bring with it close medical and developmental follow-up and intervention if necessary, and assured timely diagnosis of either seroreversion or HIV infection.

[627] An explanation of the limitations in HIV testing in infants can be found in Chapter 4.

Reasons for Clinical Trial Entry, 1986 to 1990. Vera reviewers found that in the early period of this study, many children in foster care who entered clinical trials were sick and showing physical or laboratory evidence of HIV infection or AIDS. The reviewers found many instances where the child's physician, birth parent, or foster parent requested that the child be considered for entry into a clinical trial while experiencing multiple medical challenges. Frequently, evidence of a child's deteriorating health from HIV disease would be the reason for consideration of entry to a trial. The following two examples from Vera reviewer narratives are typical of the children enrolled in the early clinical trials.

> *The child's health started declining in April 1990, at age four and a half. She was hospitalized several times and she experienced frequent infections. Her doctor prescribed AZT. In January 1991, her doctor wrote to the foster care agency saying that she is no longer responding well to AZT and that her T-cell count had dropped by half since starting treatment. The doctor requested that the child be enrolled in Bristol Meyers Squibb ddI Treatment IND.*[628] *Her health stabilized after starting on ddI, but she still experienced hospitalizations for illnesses such as PCP, sepsis, and whooping cough.*

> *In January 1990, the child's doctor stated that he was eligible for the Burroughs Wellcome AZT Treatment IND because he was HIV antibody- and p24 antigen-positive. The child also had abnormal immunoglobulin levels, progressive neurologic disease, persistent oral candidiasis, and unexplained fever for greater than two months.*

Reviewers also found situations where a parent or foster parent was opposed to a child's participation in trials. Reasons for caregiver opposition to clinical trial enrollment included fear that the clinical trials medications were toxic, concern about the amount of time and number of clinic visits involved, and concern that clinical trial enrollment would hamper the willingness of the physician to change doses or alter treatment for an individual child. Reviewers also saw a few examples where there was concern about a child being stigmatized by entering a trial. As the narratives below illustrate, these concerns were handled in different ways; in some situations the children were not enrolled, enrollment was deferred, or alternative permission was sought for enrollment. Vera reviewers wrote:

> *The foster mother told the case worker at the agency that someone at the hospital had recently asked her if she wanted her foster son to become part of an experimental AZT program. Notes state that "foster mother discussed it with the agency nurse and decided not to have her foster child participate at this time as his health has been improving for months without it." An agency progress note from the next month states, "Foster mother and nurse feel that the child should not have AZT treatment at present time, but the offer to become part of the research project remains open."*

[628] This trial will be referred to as "BMS ddI IND" in figures throughout this chapter. (For details about the trial, see Appendix 10.)

> *In late 1988, the child's doctor requested that he be entered in the IVIG protocol. His mother and his grandmother refused to consent and the child was not enrolled. The child received AZT in 2/90. Case notes indicate mother consented, but no written consent was found.*

Reasons for Clinical Trial Entry, 1991 to 1995. By the mid-1990s, the diagnosis of HIV infection could be made at an early age. When children in the review became symptomatic, or their blood tests showed increasing damage to their immune function, they were often treated *outside* trials with approved HIV drugs. If their disease continued to progress despite these HIV medications, clinical trial enrollment became an option. Children were generally a little older at entry to trials and some had few previous complications related to HIV:

> *When the foster child was about six years old and was living with his first foster mother, his health started to decline. He was reclassified by his infectious disease doctor as symptomatic. It was noted that he might be put on a treatment trial if his health got still worse, but for right now he would continue to just be followed closely. A few months later his doctor wrote a letter to the agency director saying that with the continued decline of the child's T-cells he was worried that the virus was becoming more active. Therefore, he suggested enrolling the child in PACTG 152. This was discussed with the foster mother, who apparently was willing "and even eager" for her foster child to begin treatment. As the parents were both deceased, the doctor requested consent from Children's Services.*

Reasons for Clinical Trial Entry, 1996-2005. By the late 1990s, the availability of sophisticated analysis to determine sensitivity or resistance of a child's HIV virus to specific drugs, called genotyping, meant that doctors could choose which antiretrovirals would be most effective for that specific patient.[629] For children whose disease became resistant to approved antiretroviral drugs, newer antiretrovirals were available through clinical trials. The following narrative describes the experience of one foster child.

> *In 1998, an HIV genotype test was done which identified the medications to which her virus was resistant. A week later, a letter from her doctor to the foster care agency recommends that the child begin Abacavir (1592U89). The letter states that "the child has received most of the currently available antiretroviral drugs in the past and is presently on combination therapy with three drugs to treat her HIV infection. The child now has a rising viral load, which is portent of worsening prognosis and also an indicator of the virus developing resistance to most of the currently approved drugs. I strongly recommend adding a new anti retro-viral drug named Abacavir (1592U89) made by Glaxo Wellcome Co. The drug is currently available for use in children under an expanded access study program for which approval has been granted by the institutional review board of the hospital. The drug would be used in combination with other anti-HIV drugs to which this child has not been exposed before so as to maximize*

[629] Genotyping assays are tests on the patient's plasma which can determine resistance of the patient's HIV virus to different antiretrovirals.

chances of therapeutic success." The maternal grandmother agreed but she was not the child's legal guardian. The doctor requested approval and consent was obtained from both the foster care agency and ACS.

Selection for Entry into "Salvage Protocols"

Particularly in the early years covered by the review, medical reviewers found that children were sometimes selected for trials referred to as "salvage protocols." These were trials for which children were eligible for entry specifically because of the failure of other available antiretrovirals to control their HIV disease. The review identified 10 salvage protocols. There were 73 enrollments in these ten trials which, with the exception of two trials, all began before 1995. Enrollment in the 10 salvage protocols is described in Figure 9.4.

Figure 9.4: Enrollments in salvage protocols

Clinical trial	Year first review child enrolled	Enrollments
BMS ddI IND	1990	5
PACTG 138	1991	11
PACTG 144	1991	29
BMS d4t Parallel Track	1993	5
PACTG 103	1993	2
H-LR Open Label ddC*	1993	2
PACTG 245	1994	16
AG NFV Exp. Access**	1997	1
PACTG 366	1998	1
GSK Open Label APV***	1999	1
Total		**73**

* The full name of this trial is Hoffman-LaRoche Open Label ddC. This trial will be referred to as "H-LR Open Label ddC" in figures throughout this chapter. (For details see Appendix 10.)
** The full name of this trial is Agouron Nelfinavir Expanded Access. This trial will be referred to as "AG NFV Exp. Access" in figures throughout this chapter. (For details see Appendix 10.)
*** The full name of this trial is GlaxoSmithKline Open Label Amprenavir. This trial will be referred to as "GSK Open Label APV" in figures throughout this chapter. (For details see Appendix 10.)

The following two narratives illustrate the types of medical situations that sometimes led to a child's enrollment into a salvage study:

In 1995 there is a letter from the child's doctor to HRA requesting consent for enrollment in PACTG 245. The request states, "The foster child is an eight year old in kinship care. Her mother is deceased and she has been with her grandmother since the age of two. She has been on AZT for several years. Recently she has dropped her t-cell count to less than

200 and has had several bacterial infections as well as loss of appetite.[630] *She is eligible for PACTG 245. This is a salvage protocol for children who have failed previous antiretroviral treatment. It offers different combinations of AZT, ddI and nevirapine. Her maternal grandmother is interested in enrolling the child. She is ready to sign an informed consent. Although the child has been with her for years I understand that CWA is the legal guardian. I am asking for consent."*

In 1990 she began receiving ddI on a compassionate use basis. She was AZT intolerant and her doctors at the hospital had "attempted to use AZT in the last 6 to 8 months and find that she becomes profoundly neutropenic." [631] *This letter further warns that her T-cells had dropped sharply, which indicates a profound immunodeficiency caused by HIV. She is "likely to acquire opportunistic or acute bacterial infections, and her prognosis is poor. In the hope to prevent further vital reproduction and clinical deterioration, ddI could be used as an anti-viral therapeutic agency to preserve life."*

Two of the earliest salvage protocols—the Bristol Meyers Squibb ddI Treatment IND and PACTG 144—were conducted in 1990 and 1991 and both involved the antiretroviral ddI. Enrollment in salvage protocols was seen as a last resort when the child had no other treatment options. The five children in Vera's review who were in the Bristol Meyers Squibb ddI Treatment IND had not tolerated treatment with the only other available drug at the time, AZT, and their disease had continued to progress. All were categorized as having moderately severe to severe HIV disease. There were 29 children in Vera's review who were enrolled in PACTG 144, a trial which compared two dosages of ddI. Vera's reviewers found that for those children for whom it could be determined, each had failed AZT (Zidovudine) treatment and was moderately to severely ill with HIV disease.

PACTG 138 was another early salvage protocol that used the antiretroviral drug ddC. Eleven children in Vera's review were enrolled. To be eligible for this protocol in 1990, a child had to have "AIDS or ARC and evidence of zidovudine intolerance and/or documented history of disease progression after six months of zidovudine therapy."[632] Disease progression meant that the child was exhibiting growth failure, neurodevelopmental regression (a loss of developmental milestones or increasing nervous system deficits), opportunistic infections, and laboratory evidence of HIV-related problems such as liver or blood abnormalities. [633] These criteria meant that only very sick children were eligible for this trial.

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[630] T-cells, a type of white blood cell involved in immune function, are affected by HIV-infection. The level of a child's T-cells are routinely followed by physicians monitoring the child, and sometimes when these cells decrease in number, different treatment options are sought. T-cells are also referred to as CD-4 cells

[631] Neutropenia, or low white blood cells, is a known potential side effect of AZT treatment. Sometimes this neutropenia resolves with reducing the dose or stopping the drug temporarily.

[632] ARC (AIDS Related Complex) is a term used during the early years of the AIDS epidemic to refer to patients with HIV infection who had some signs and symptoms of HIV but had not had opportunistic infections and did not have AIDS.

[633] NIAID, ACTG 138: A trial of two doses of 2'3'-dideoxycytidine (ddC) in the treatment of children with symptomatic HIV infection who are intolerant of ZDV[AZT] and/or show progressive disease while on ZDV [AZT], Version 7.0 Final, 9/17/93

PACTG 103, another salvage protocol, had two children in Vera's review enrolled in 1993. This study used AZT as a continuous intravenous infusion, rather than in syrup or pills, for children who had severe HIV-related encephalopathy.

In 1994, 16 children in Vera's review were enrolled in PACTG 245, all with advanced disease and progression of their HIV infection despite either AZT or combination antiretroviral treatment. This trial compared different combinations of three antiretrovirals: nevirapine, zidovudine, didanosine (ddI).[634] In the late 1990s, two children were enrolled in salvage protocols involving protease inhibitors in combination with other antiretrovirals. At this time, there were many options for HIV treatment, and these children had less severely symptomatic HIV disease but other antiretroviral treatments were not working. One child, having been treated for her severe HIV disease unsuccessfully with many antiretrovirals (including protease inhibitors), was to receive Amprenavir through a compassionate use protocol but died before the medication was received.[635]

Clinical Trial Eligibility

Vera's review looked at whether children met the enrollment criteria, as defined by each trial protocol, for the trials in which they participated. Eligibility criteria for the trials seen in the review are described in Chapter 8 and Appendix 10. Each medication trial typically had detailed and lengthy criteria that specified the ages of children who would be enrolled, requirements for documenting participants' HIV status, and a required stage of HIV disease based on symptoms, illnesses, and immune function.

Vera's medical reviewers determined, based on available information about the trial and about the child, whether the children who were enrolled met these eligibility requirements. In addition to inclusion criteria, reviewers looked for the exclusion criteria—a characteristic that means the child is ineligible for the trial—listed by each trial. Exclusion criteria varied by trial; many trials excluded children with liver disease or other conditions that would make the child more susceptible to toxicity from the trial medication and children with an active opportunistic infection.

For each enrollment, medical reviewers sought to answer the following questions:

1. Was the child in the age group specified in the trial protocol?
2. Was the child's HIV status (either HIV exposed or HIV infected) documented as required by the trial protocol?
3. Did the child's level of illness or symptoms meet the requirements for entry into the trial as specified by the protocol?
4. Did the child have any of the exclusion criteria specified in the trial protocol?

[634] For a full description of PACTG 245, see Appendix 10.

[635] The Amprenavir Compassionate Use protocol allowed physicians to obtain this antiretroviral medication from the pharmaceutical company when a child had failed to improve with other treatments. This protocol is GlaxoSmithKline Open Label Amprenavir. See Appendix 10 for details

Clinical trial sites are mandated by a trial's protocol to document the eligibility status of a child for a trial, document that the child did not meet any exclusion criteria, and maintain records on all participants in a clinical trial. NIH regulations called for these records to be reviewed at regular intervals by the contractor, Westat, at National Institute of Child Health and Human Development (NICHD) sites, and by monitors contracted by the PACTG at sites funded by the National Institute for Allergy and Infectious Diseases (NIAID).[636] These research records were not available for this review.[637] The medical information in the child welfare files allowed Vera reviewers to determine age eligibility status in 77 percent of the treatment trial enrollments.[638] In about 43 percent of the enrollments, Vera reviewers found documentation that showed that at the time of enrollment the child met all three criteria on which this review focused: age, HIV status, and stage of illness (see Figure 9.5).

Figure 9.5: Documentation of Eligibility Criteria Met at Entry into Medication Trial

Criteria	**Number**	**Percent of all enrollments in medication trials**
Met age criteria	433	76.2
Met HIV documentation criteria	288	50.7
Met stage of illness criteria	322	56.7
Met all three criteria above	243	42.8
Unable to determine if child met any of the criteria	136	23.9
Total enrollments in medication trials	68	100

Monitoring agencies such as Westat were charged with documenting that clinical trial protocols (including eligibility to enter a trial) were being followed. Review of correspondence between the NIH and Children's Services, and between principal investigators (the lead clinical trial researcher at a site) and Children's Services, as well as minutes and reports from the medical advisory panel (MAP), document that the PAU and those conducting the trials were aware that each clinical trial had specific eligibility requirements.[639] A few examples are cited below.

> *The doctor contacted the agency nurse and informed her that the child's T-cells had dropped from 632 to the 300s and that the child could either go on AZT and Bactrim or could participate in PACTG 240. The child was started on an AZT regimen as a precaution, while his medical eligibility for the trial was determined and the necessary consents were obtained.*

[636] For more on the monitoring process see Chapter 8. Standards for maintaining clinical trials research records are found in: DIAIDS, No.: DWD-POL-CL-04.00A1, Appendix 1.
[637] For information on Children's Services' efforts to obtain access to hospital and clinical research records see Chapter 2.
[638] Vera reviewers could not determine eligibility in some cases because of a lack of information in child welfare files; in other cases this was because the child enrolled in a trial before entering foster care (eligibility criteria pertain to the child's characteristics on the date of enrollment) or because the enrollment date could not be determined.
[639] See Chapter 8 and Appendix 10 for criteria for specific protocols.

The child's doctor writes that the child is failing AZT therapy and "is eligible for ACTG Protocol 138 for ddC because of his disease progression despite AZT therapy."

Age Eligibility. For the 65 *medication trials* identified in Vera's review, each of the trial protocols specified the ages that were eligible for that trial. This ranged from birth to 24 years.[640] Trials such as PACTG 247 or PACTG 345 which entered very young infants acknowledged that some of these children would likely serorevert. Among those children for whom the file material was sufficiently complete (92 percent) and protocols were available, there was compliance with age eligibility requirements in all of the enrollments.

HIV Status Eligibility. For all enrollments in observational or medication trials, Vera's review sought to answer the following questions:

- Did the child meet the criteria for HIV infection as required by the protocol inclusion criteria?
- Did any children who seroreverted participate in medication trials? How was this handled?
- Were there any children who were HIV negative who were enrolled in trials?[641]

To determine children's HIV status at entry into a trial, reviewers noted all HIV test results or references to test results found in available files. Medical reviewers noted the date of test, type of test, test result, and source of information. Copies of actual laboratory reports were considered the strongest source, but references to HIV testing results or the child's HIV status in documents signed by physicians or nurses, such as correspondence, clinical progress notes, and referral forms, were noted as well. The PAU developed and used various forms over the course of the review for recording and tracking HIV test results. The results noted on these forms were also used to establish the children's HIV status.

Vera's review used guidelines published by the Centers for Disease Control for establishing both HIV infection and seroreversion in infants and children. The guidelines were first published in 1987; they were revised in 1993 and again in 1999.[642]

In addition to HIV status at enrollment, Vera reviewers sought to determine what each child's eventual (final) HIV status was after the required testing had been completed By

[640] The exceptions to this were the two trials of prevention of maternal-infant transmission—PACTG 076 and PACTG 316—in which women enrolled during pregnancy and their infants were enrolled at birth.

[641] The files of a foster child who was never exposed to or infected by HIV were examined because the child was on a clinical trial for the treatment of chronic Hepatitis C. This trial used a drug (3TC) that was also used for treating HIV disease. This child is not included in the review's 532 children.

[642] The CDC Surveillance case definitions were used across the country and evolved over time as more accurate tests became available for diagnosing HIV infection in children. The case definitions define the criteria used by physicians to report a case of HIV infection to local and state health departments and the CDC. The case definition can be found in Centers for Disease Control and Prevention, Revised Surveillance case Definition for HIV Infection,; *Morbidity and Mortality Weekly Reports* 48 (December 10, 1999) (RR13): 29-31. See Appendix 7.

examining all records for the child throughout their stay in foster care, reviewers categorized each child as HIV infected, a seroreverter, or unable to determine.

HIV Status at Entry to Medication Trials and Final HIV Status. Figure 9.6 shows the HIV status of children when they entered medication trials. Reviewers found documentation that 83.6 percent of children entering medication trials were infected with HIV at the time they entered the trial. Complete testing results for HIV status were not available for 10.4 percent of children in medication trials, so Vera reviewers could verify only that these children had been HIV exposed. For the remaining 6.0 percent of children in medication trials, the available information did not allow Vera reviewers to determine the child's HIV status at time of enrollment in a trial.

Figure 9.6: HIV Status for All Enrollments at Time of Entry to Medication Trial

HIV Status	**Documentation at time of enrollment**	
	Enrollments	**% Enrollments**
HIV infected	475	83.6
HIV exposed	59	10.4
Unable to determine	34	6.0
Total enrollments	**568**	100.0

In some cases, although the reviewer could not determine the child's HIV status at entry to a clinical trial, additional test results or other information dated after the trial enrollment confirmed the child's HIV status. As Figure 9.7 shows, Vera reviewers found evidence that more than 92 percent of children who participated in medication trials were HIV infected.[643] None of the children whose HIV status was documented by Vera reviewers after their enrollment were HIV negative and placed in an HIV-related clinical trial.[644]

Figure 9.7: Final HIV Status for New York City Foster Children Enrolled in Medication Trials

HIV Status	**Documentation of final HIV status based on all available case information**	
	No.	**%**
HIV infected	397	92.5
Seroreverted	10	2.3
Unable to determine	22	5.1
Children enrolled in at least one medication trial	**429**	99.9*

*Percentages do not total 100 because of rounding.

[643] The total numbers in Figures 9.6 and 9.7 differ because the two tables use different units of analysis. Figure 9.6 refers to enrollments in clinical trials while Figure 9.7 refers to children enrolled in medication trials.

[644] The files of a foster child who was never exposed to or infected by HIV were examined because the child was on a clinical trial for the treatment of chronic Hepatitis C. This trial used a drug (3TC) that was also used for treating HIV disease. This child is not included in the review's 532 children.

Of the 532 children whose files Vera reviewed, there were two infants who were HIV exposed but whose files contained conflicting information about their final HIV status. One child was enrolled with the birth mother's consent in both a medication trial and an observational research study in 1994. Vera reviewers found a positive antibody test and conflicting results of a direct viral HIV test. The review could only conclude that although the child was exposed to HIV at birth, his final HIV status was unclear.[645] A second case involved an infant born HIV antibody-positive who had an extremely high viral load soon after birth. The child was entered into a medication trial involving a new protease inhibitor. Soon after starting the medication, the child's viral load dropped to less than 50 copies/ml. Vera medical reviewers found a subsequent HIV antibody test for the child which was negative. There were no further HIV antibody tests in the files. Vera reviewers found multiple positive but low viral loads consistent with HIV-infection.[646] Vera staff referred these two files to Children's Services for review, and Children's Services was able to confirm that the second child was enrolled appropriately. Children's Services had not yet responded with information about the first child when this report was completed.

The review identified 10 children who were HIV antibody-positive at birth and at time of trial entry and who ultimately seroreverted. The trials in which they were enrolled did *not* involve the use of antiretroviral medication. Seven of them were newborn infants enrolled in PACTG 247, a study which gave a calorie-dense infant formula to HIV-exposed babies for six weeks following birth. The HIV-related eligibility criteria for this trial stated that the infant "must be born to an HIV-positive mother," and the study anticipated that many babies would serorevert.

Another child who was born HIV antibody-positive but seroreverted while in a medication trial, was enrolled in PACTG 225 in 1996, which examined the efficacy of a routine childhood vaccine (MMR: measles, mumps, rubella) in both HIV-positive and seroreverted children. This child entered the seroreverter arm of the trial. The child had no adverse effects from the vaccine.

The two remaining children of the 10 who seroreverted were placed in medication trials because their symptoms at the time of enrollment suggested they were HIV infected. Both children were in the early period of this review, when definitive testing for HIV infection at birth was not available, so presumptive diagnoses based on their symptoms and laboratory tests were made in both cases. Vera reviewers found evidence that both children's medical providers had followed and documented their HIV status throughout their trial participation. One of these children was enrolled in PACTG 051 in 1990 at seven months of age. The child was HIV antibody-positive, and had increasing severe lymph node enlargement, as well as failure to

[645] This child is deceased.

[646] This phenomenon is reported in the medical literature; infants treated early with HAART for their acute HIV infection and who have suppression of their HIV virus, can lose their antibody response to the HIV virus and thus test HIV antibody-negative. This does not mean the child has been "cured", and it is not clear what the long-term significance is of this reversion. S. Kassutto et al., "Incomplete HIV Type I Antibody Evolution and Seroreversion in Acutely Infected Individuals Treated with Early Antiretroviral Therapy," *Clinical Infectious Diseases* 40 (2005): 868-873.

thrive. Her infectious disease doctors ultimately diagnosed her with congenital tuberculosis.[647] She seroreverted while on the antiretroviral trial and was removed from the trial. The files indicate she had some mild anemia and mild elevation of her liver function laboratory studies while on the trial, which disappeared with discontinuation of the trial medication. She was returned to her father at age six.

The second child, born in 1989, was HIV antibody-positive, and could not be placed in a foster home because of documented multiple medical complications: lymphadenopathy, repeated sepsis, failure to thrive, and recurrent diarrhea and dehydration. He was transferred from the birth hospital to ICC. His mother consented to his enrollment in PACTG 051 when he was three months old. He received AZT and IVIG, and was followed weekly at the clinical trial site. His health improved over several months, and he was transferred to a foster home. At age 16 months, testing at the trial site showed he had seroreverted. The doctors conducting the trial held several conferences to discuss this case after his seroreversion, trying to reach a consensus on what to do. The child remained on the trial medications for a few more months to "ensure that he stayed negative." In early 1991, he was transferred from the infectious disease clinic to the regular pediatrics clinic for his routine pediatric care. He was returned to his father in 1992, as his mother had died from AIDS.

HIV Status of Children in Observational Research Studies. As described in Chapter 8, there were several types of observational research studies. This review identified 274 foster children who were enrolled in observational studies. Of these 274 children, 103 were enrolled only in observational studies, while 171 were also enrolled in at least one medication trial. Reviewers also found that many children who were enrolled only in observational studies were on antiretrovirals for treatment of their HIV disease.

Vera's review found that 57 (55.3 percent) of the 103 children who were enrolled *only* in observational studies ultimately seroreverted. Several studies—Pediatric Pulmonary & Cardiovascular Complications (P2C2), Women and Infants Transmission Study (WITS), Maternal Infant Transmission Study (MITS), Early Diagnosis and other transmission studies—enrolled children before or at the time of birth. [648] These study protocols anticipated that many of the enrollees would ultimately serorevert. Of the 96 children enrolled in these studies, 35 (36.5 percent) were ultimately found to be HIV positive, 56 (58.3 percent) seroreverted, and for 5 (5.2 percent) their final HIV status could not be determined. [649]

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[647] Congenital tuberculosis, in which the disease is transmitted from the mother to the infant either before or at birth, is rare in the United States, but increased with the appearance of HIV infection in pregnant women during the time period this review covered. Infants with congenital tuberculosis can present with respiratory symptoms, enlarged liver and spleen, enlarged lymph nodes, and failure to thrive, symptoms similar to those in HIV infection. M.F. Cantwell, Z.M. Shehab, A.M. Costell, L. Sands, W.F. Green, E.P. Ewing, S.E. Valway, and I.M. Onorato, "Congenital Tuberculosis" *New England Journal of Medicine* 30 no. 15 (April 14, 1994):1051-1054.

[648] See Chapter 8 and Appendix 10 for a more detailed description of these observational trials.

[649] This is a higher infection rate than would be expected and most likely represent selection bias in the sample. This bias is to be expected: Vera was asked to review children enrolled in clinical trials and therefore the expectation is that most children would be HIV positive.

Many of the children continued to be followed in the observational study after seroreversion, often at the same medical center where they continued to get their routine pediatric medical care. Children were regularly retested as required by the protocol, and a definitive HIV diagnosis was made. Vera's medical reviewers found evidence that this close monitoring also encouraged early intervention for medical issues, as well as developmental delays, educational issues, and psychological problems, consistent with this statement by a pediatrician and principal investigator interviewed by Vera staff:

> *One of the other things we offered them, which could have been an incentive, is …whether your kid's infected or not, is irrelevant to us. We will take care of them for as long as you want us to take care of them, outside of the study. Bring them back to our clinic, yes they're normal … this is what we're offering to you.*

Observational research studies did, however, require children, even if they had seroreverted, to have blood samples drawn or other studies done on a regular basis to evaluate developmental progress. Reviewers noted that some foster families had trouble keeping up with the required study visits and medical visits sometimes interfered with schooling. Vera reviewers noted that this was particularly true for foster parents who were caring for more than one HIV-positive foster child.

Some observational research studies were longer-term studies that were attached to medication clinical trials or required the child to be enrolled in an antiretroviral medication trial.[650] Thus, many children in Vera's review who were enrolled in these trials were already known to be infected with HIV. However, the design of some of these trials also included children who had seroreverted before entering the observational study.[651] The Pediatric Pulmonary & Cardiovascular Complications (P2C2) Study enrolled 26 New York City foster children and followed them for several years for cardiac and pulmonary complications. Children were enrolled by their mothers during pregnancy or just after birth. The study compared the cardiac and pulmonary status of those children who were HIV infected to those who were exposed and seroreverted.

Disease Stage Eligibility. As described in Chapter 8, to be enrolled in a particular clinical trial, a child needed to meet that trial's criteria for the severity of illness. Some clinical trials, such as PACTG 152, were designed to enroll children who were symptomatic from HIV. The salvage protocols described previously enrolled very ill children whose disease had progressed in spite of treatment. Other trials, such as PACTG 128, enrolled children who were not symptomatic to determine whether early treatment of HIV delayed the onset of HIV symptoms. Many children entering trials in the later years of the review were not severely symptomatic but were failing

[650] PACTG 219 or PACTG 188, for example, which were designed for children who were concurrently enrolled in a medication trial.
[651] These trials are described in more detail in Chapter 8.

available drug therapy, as indicated by deteriorating immune function or by analysis of the drug resistance, or sensitivity, of a child's HIV virus.

For each child enrolled in a clinical trial, medical reviewers sought to answer two questions:

1. How ill were the children when they were enrolled in clinical trials?
2. Did each child meet the stage of illness criteria for the trials in which he or she was enrolled?

For each child enrolled in a clinical trial, Vera medical reviewers recorded all information in the child welfare files about the child's clinical status (symptoms and signs of HIV disease such as opportunistic infections and other AIDS-defining illnesses, hospitalizations, growth parameters); immunologic status (T-cell counts, viral loads) and other laboratory values (blood counts, liver and kidney function, etc.), and the dates when these signs and symptoms occurred.[652] Using the medical information described above, medical reviewers classified the severity of a child's HIV illness at the time of clinical trial enrollment using the Centers for Disease Control classification systems.[653] The classifications were N (no symptoms), A (mild symptoms), B (moderate symptoms), or C (severe symptoms).

For about 69 percent of the children, reviewers were able to determine the severity of illness at the time a child entered a medication clinical trial. The severity of illness of children enrolled in trials changed over time, with children enrolled in earlier trials falling into a higher category of illness than children in later trials. In the early period (1986 to 1990), 21.3 percent of the children were moderately ill with HIV disease, and 52.5 percent were severely ill. As the diagnosis of HIV infection in babies and children was made earlier and the treatment options began to expand, the severity of illness is spread more evenly across the A, B, and C categories. From 1991 to 1995, 31.2 percent of the children were in Category C. That percentage dropped again in the 1996 to 2005 period, to about 24 percent (see Figure 9.8).

[652] In the medical context, a symptom refers to what a person feels—such as shortness of breath or nausea. In contrast, a sign is an objective finding, such as a rash, an enlarged liver or an abnormal x-ray.

[653] The early CDC classification system, developed in 1987, was based on clusters of symptoms that were found in stages of HIV infection. It placed children in categories from Class P-O (perinatally-exposed with the HIV antibody but an undetermined final diagnosis), to Class P-1 (HIV-infected but asymptomatic) to Class P-2 (symptomatic HIV infection with multiple categories for all possible signs and symptoms of HIV disease). The revised system, published in 1994, reflected the development of increasingly accurate methods of laboratory testing for immune function. The severity of HIV disease was determined by a combination of laboratory values of immune function and clusters of symptoms and illnesses. The two CDC classification systems can be found in Appendix 7.

Figure 9.8: Severity of Illness at Entry to Intervention Clinical Trials

	All enrollments		Enrollments 1986-1990		Enrollments 1991-1995		Enrollments 1996-2005	
Symptoms (CDC Category)	**N**	**Percent**	**N**	**Percent**	**N**	**Percent**	**N**	**Percent**
No symptoms (Category N)*	20	3.5	2	1.6	6	2.8	12	8.1
Mild (Category A)	91	16.0	8	6.6	46	21.4	37	25.0
Moderate (Category B)	114	20.1	26	21.3	50	23.3	38	25.7
Severe (Category C)	166	29.2	64	52.5	67	31.2	35	23.6
Unable to determine**	177	31.2	22	18.0	46	21.4	26	17.6
Total enrollments	**568**	100.0	**122**	100.0	**21**5	100.1***	**148**	100.0

* There were a small number of children who were in the "E" category, indicating they were HIV-exposed at birth but not symptomatic for HIV disease. These were included with the N category on this table.

** The severity of the child's disease could not be established by reviewers for 177 of the enrollments. For 83 of these enrollments disease severity could not be established because of missing trial enrollment dates. The total enrollments by year do not add up to 568 because of these 83 enrollments. For the remainder, the reviewer could not find documentation in the files to establish disease severity.

*** Percentages to do not total 100 due to rounding.

Exclusion Criteria. Each clinical trial also had exclusion criteria. Trial protocols mandated that children with any of the exclusion criteria should not be enrolled in that clinical trial.[654] Reviewers found two children who appeared to meet exclusion criteria for the medication trials in which they were enrolled.

One of these two children participated in PACTG 338, even though the child's blood tests for liver and pancreas problems exceeded the limits for entry into that trial. These problems were documented in the file and known to the child's physician, who had ordered several tests in the previous year to look for a cause. Upon entry into PACTG 338, the child began to have nausea and vomiting, which resulted in her removal from the trial in less than two weeks. She was placed on different HIV medications outside of a trial, did well medically, and was adopted.[655]

The other child was enrolled in two trials in 1996 when she was two months old.[656] Children with a birth weight below 1800 grams were excluded from participating in PACTG 292, a pneumococcal vaccine trial for HIV-infected children. This child, who was a very sick,

[654] Exclusion criteria usually included being treated with a medication known to be contraindicated if taken at the same time as the medications used in the clinical trial, being treated with other experimental medications, having had an allergic reaction to any of the drugs being used in the trial, or having a condition that could be made worse by any of the clinical trial medications.

[655] Nausea and vomiting are often seen with liver and pancreas problems.

[656] PACTG 292 is described in Appendix 10. This clinical trial tested the safety and effectiveness of a new vaccine against the pneumococcal bacteria, a common cause of serious bacterial infections in children with HIV.

premature, low birth-weight baby diagnosed as HIV infected within the first months of life, did not appear to meet the minimum birth weight criteria for the trial. She was also enrolled in PACTG 300, a medication trial for HIV treatment. At age six months, she died of severe HIV disease.

Monitoring, Adverse Events, and Toxicities

Medical reviewers sought to answer the following questions for each child enrolled in a medication trial:

- Who monitored the child's medical course in the trial, and how?
- Were there benefits or ill effects from a child's participation and how were ill effects addressed?
- Did the child complete the trial and if not, why not?

The medication trials in which children in Vera's review were enrolled had very specific monitoring requirements.[657] The goals of the monitoring were to identify any adverse reactions or toxicities to the medication and to track progression of HIV disease during the trial. Each clinical trial specified protocols for how often clinic study visits were to occur, how HIV disease progression was to be assessed, and the types and frequency of laboratory tests and other examinations. The protocols, and NIH policy, required clinical trials sites to address and report adverse events or toxicities.[658] The sites were to routinely evaluate compliance with the schedule and dosages for administering trial medication as well: medication bottles were collected at regular intervals and the amount of remaining medication was noted to check if the correct amount of medication had been given.

Medical reviewers relied on the case planning files to assess the extent to which children were monitored by both the medical facility conducting the clinical trial and the foster care agency. Case planning files frequently contained documentation that clinical trial sites were in compliance with the monitoring requirements stipulated in the protocols. This documentation included copies of clinic visits with physician notes, laboratory results, growth parameter flow charts, hospitalization records, and evaluations by specialists such as neurodevelopmental or psychological consultants. However, because files at agencies were sometimes missing or incomplete, Vera reviewers could not fully assess monitoring efforts. Overall, the review found that agencies had evidence of this monitoring in 51 percent of all trial enrollments; for the

[657] The monitoring requirements are also discussed in Chapter 8.

[658] Individual sites reported adverse events and toxicities to the PACTG Operations Center, which, in turn, reported them to the FDA, as required by FDA regulations for new drug testing. Each protocol addressed how adverse reactions, toxicity, and disease progression were to be addressed. Possible responses included modifications of the dose, holding the medication for a period of time and restarting at a lower dose, switching the child to a different arm of the trial, and taking the child off the trial medication. Children taken off medication continued to be seen at regular intervals until the end of the trial.

remainder of the enrollments, the available files did not confirm that monitoring had or had not occurred.

The amount and detail of monitoring varied greatly among agencies. Overall, agencies with specialized HIV placement programs were more likely than other agencies to gather detailed medical documentation. Often, a nurse from agencies with specialized programs accompanied the foster parent and the child to clinic visits. Reviewers noted that the nurses documented and helped ensure exchange of information and understanding of events such as changes in medication dosage, movement to a different arm of the trial, or withdrawal from a trial. Documentation practices also varied depending on the medical site. Some hospitals documented clinical trials visits using duplicate forms, and routinely sent one copy to the foster care agency. Other hospitals left it to the agency to request documentation of clinical trials visits through the hospital's medical records department.

Although sometimes reviewers found that documentation was scant, caseworkers' notes frequently indicated an understanding of a child's medical course while in a trial, and some caseworkers reliably documented the general course of events in these notes and in the quarterly Utilization Care Reviews (UCR), a document that agencies used to update Children's Services about all aspects of a child's care. Below are examples of comments from Vera medical reviewers about the agencies' monitoring of children:

> *There seems to have been good monitoring of the child while she was in the clinical trials. The agency nurse kept diligent track of the child's T-cell counts and her progress in the studies. Medical updates were sent to Children's Services and it was clearly communicated to the case manager that the child was participating in these trials as seen in several Children's Services-approved UCRs in the case management file.*[659]
>
> *While the child was under medical surveillance for all of his life in foster care, the documentation in the ACS and PAU files of his trial participation is very sparse. It is entirely unclear when he began taking AZT or when he entered the trial. There was one notation that FC [foster child] was on week 36 of protocol PACTG 051. As his health quickly deteriorated and he died there is hardly any mention of AZT and his involvement in a clinical trial.*
>
> *There seemed to be good monitoring of the foster child during both trials. There are monthly updates on his health and the agency nurse regularly checked in with the maternal grandmother/foster mother to see if he was having any adverse side effects to the trial medication. No side effects were reported. It also appears that the agency nurse accompanied the grandmother and child to many of the trial medical visits.*

[659] Foster care agencies were required to make reports at regular intervals, known as Uniform Case Reviews (UCRs). The UCRs were submitted to Children's Services case managers and provided a record of services provided to each child and decisions made for the child's future. Children's Services case managers needed to approve the UCR for the agency to move forward with its plans.

Reviewers also found evidence that the medical sites followed the clinical trials protocol requirements for reporting and addressing adverse events. Evidence of responsiveness to minor events took the form of, in the first example below, a physician waiting to see if mild nausea resolved on its own, a reduction in a trial medication dose for a moderate anemia, and a temporary suspension of trial medication for blood tests that showed abnormal liver function. The second example represents more significant events, such as severe liver toxicity or evidence of severe immune failure: Vera reviewers saw cases in which severe toxicity resulted in a child being transferred to an alternative arm of the trial that had a different medication regimen or removing the child from the trial altogether. Vera reviewers wrote:

> *The monitoring of this child was consistent and regularly done. There are almost monthly lab reports and other documentation detailing the foster child's progress in the clinical trial. When the older sister/ foster mother mentions that she thinks the child's medication is the source of the child's vomiting, the agency caseworker tells her to call the agency nurse and the child's doctor so they could talk about changing her medication. These types of conversations are documented as happening on a fairly consistent basis as the child's case planner and nurse made regular inquires into how well the child was feeling and whether there were any problems they needed to be made aware of regarding the child's health.*

> *He was placed on the Burroughs Wellcome AZT Treatment IND, but two episodes of pancytopenia requiring transfusions result in AZT being stopped four months later.*[660] *Bristol Meyers Squibb ddI Treatment IND is begun later the same year and continued through 1992, with occasional dose-reduction when blood tests indicate that liver toxicity is occurring. In 1992, the ddI is stopped because of the child's continued weight loss. The child's CD4 count is very low, and he is hospitalized three times for pneumonia and gastrointestinal problems. He is placed back on AZT, but there are notes saying he is being considered for 3TC at the NIH.*

To document adverse events that occurred for a child in a medication trial, Vera reviewers noted any mention of signs or symptoms reported by a child or foster parent, and any physical findings, laboratory examinations, or investigations for new or persistent problems noted during clinic visits. For example, in cases in which a child had the onset of new weakness in his or her arms or legs while in a trial, reviewers often found clinic notes or child welfare files that described the evaluation of the problem including results of a CT scan of the brain, an evaluation by a neurologist, and results of blood tests.[661]

[660] In pancytopenia, the red blood cell count, white blood cell count and platelet count are all low. This is a known side effect of AZT and other medications that affect the function of the bone marrow where all three types of blood cells are produced.

[661] Although Vera reviewers only had access to child welfare files, the foster care agency files often had copies of medical notes, including clinical trials visits.

Medical reviewers graded toxicities and adverse reactions using the same criteria used in the clinical trials protocols.[662] The protocols used a common grading system, based on a four point scale, in which each adverse reaction is assigned a grade of mild (grade 1), moderate (grade 2), severe (grade 3), or life threatening (grade 4). A simple, transient skin rash, for example, is considered grade 1; a severe blistering skin reaction, grade 4.[663] Vera reviewers collapsed the degree of toxicity into three categories on Vera's medical review instrument: grade 1/2, grade 3/4, and "unable to determine" (UTD).

The monitoring process also involves recording the presence or absence of symptoms and signs at regular intervals during a clinical trial. This includes conditions present before a child entered a clinical trial and conditions that began after entry. For example, at the time they entered a clinical trial many of the children in Vera's review had mild to moderate anemia, a recognized effect of HIV in children. This would still be recorded during trial monitoring as grade 1/2 toxicity. The following examples from a medical reviewer narrative describe the type of information about toxicity that was found in the child welfare files.

> *In case planning files, notes indicate that the child, on a few occasions, was taken off PACTG 152 clinical trial medications because of high liver function tests (LFT).* [664] *Notes indicate that the doctors waited for his LFTs to decline before placing him back on the trial medications. For example, a "placement medical history" sheet found in case planning files, states that the child's LFTs have increased and he is off of study medications as of today. A "placement medical history" sheet states that LFTs have improved and that study medications can be restarted.*
>
> *While on PACTG 152, he has several grade1 or 2 toxicities, and a grade 4 toxicity for anemia (hemoglobin = 5.4). However, this could also be attributed to his sickle cell disease and not the antiretroviral drugs from the clinical trial. He finishes the trial and is changed to other HAART.*

Figure 9.9 below describes the toxicities recorded by the medical reviewers for all children in Vera's review who participated in medication trials. This figure includes all 429 children who were in 568 enrollments in medication trials. Out of the 429 children for whom there was documentation concerning toxicities, most had no toxicities. Medical reviewers found that 103

[662] These criteria are created and published as the "Grading Table for Pediatric Adverse Experiences" by the Division of AIDS Toxicity at NIAID.

[663] Vera acknowledges the limitations in assigning a grade to a reaction based on a finding in the child welfare files as opposed to clinical research or hospital medical records. At best, the grading of toxicity in this report represents an estimate that is dependent on the information available for a particular child. Grading of toxicities based on objective data such as a laboratory result has a higher degree of accuracy than grading of a toxicity based on a reported symptom such as pain or nausea, about which the reviewer was relying on notes made by a physician, nurse, or caseworker based on a description by the child or foster parent. The UTD category was selected when there was not enough information in the child's files to determine whether a toxicity had or had not occurred.

[664] Liver function tests (LFTs) measure the level of specific chemicals in the blood that are found in higher than normal amounts when there has been an injury of any type to the liver.

children had *at most* grade 1 or 2 toxicity while in a trial, which are mild to moderate in nature. Sixty-one children had at least one grade 3 or 4 toxicity, which are severe.

Figure 9.9: Aggregate Toxicities Found for Review Children in Medication Trials

Level of toxicity	**Children**	**% Children**	**Enrollments**	**% Enrollments**
No toxicity found*	265	61.8	317	55.8
Grade 1 or 2 at most	103	24.0	155	27.3
Grade 3 or 4 at least	61	14.2	96	16.9
Total	**429**	100.0	**568**	100.0

* This includes children for whom there was adequate information and no toxicity was found and children for whom there was insufficient information to make a determination.

Figure 9.10 describes in more detail the types of toxicities reviewers found. Because there was inadequate information available to make a determination of toxicity for many of the children, this data cannot be used to determine the overall occurrence of toxicity among children in Vera's review or to compare them with the rates of toxicity reported for children around the country who were enrolled in the same clinical trial. The review can only report the absolute numbers for all toxicities found and the number of children for whom information was available.

The range of types of toxicities reflects the standardized toxicities for which NIAID requires monitoring.

Figure 9.10: Toxicity events by type for all medication trials

Adverse event:	**Hematology**	**Liver or pancreas**	**Kidney and electrolyte**	**Nausea, vomiting and diarrhea**	**Nervous system**	**Allergic or skin reactions**	**Other***
No toxicity	67	65	137	144	182	214	190
Grade 1 or 2	125	100	55	96	39	20	31
Grade 3 or 4	50	50	9	13	15	2	
UTD	326	353	367	315	332	332	347
Enrollments	568						

*The "other" category includes a group of toxicities such as fat redistribution syndrome and elevated cholesterol, which were not graded but noted as present or absent.

Responses to Adverse Events. Medical reviewers sought documentation indicating whether the physicians who were conducting the clinical trials followed the trials' protocols when toxicity occurred. Because the quality and quantity of medical information about the children in Vera's review varied, it is not possible to quantify with certainty either the frequency of adverse events or the actions taken in response. However, reviewers found evidence of adverse events which

resulted in changes in trial medication or other actions by the clinical trials investigator. The documented responses included reduction of medication dose, temporary discontinuation of medication, hospitalization, crossover to a different arm of the trial, and removal from the trial. For example:

> *Three months later, progress notes state that "Foster mother said that the child is doing very well. She said he had been taken off his study medications since some levels in his liver had been getting too high. She said he was off all medications except Bactrim." Progress notes indicate that the abnormalities had resolved and the child was back on the study medications by the end of the month.*

In addition, although not required by the trial protocol, trial physicians sometimes adjusted the timing or frequency of medications in response to problems a caregiver was having in administering medication. Sometimes the toxicity was severe enough that hospitalization was required. Examples reviewers found of responses that necessitated hospitalization included transfusions for anemia or low platelets, treatment for severe vomiting and diarrhea, or an intensive workup of a new neurologic problem.

Reviewers saw at least 24 examples of a child being moved to a different arm of a trial (but remaining in the trial) because he or she could not tolerate the drugs in that arm, the arm was shut down after review by the Data Safety and Monitoring Board, or because the child reached a clinical or immunologic endpoint for that arm.[665] During the course of PACTG 152, one treatment arm was discontinued because of significantly inferior results compared to the other two arms. Vera reviewers wrote:

> *The doctor explained that the child had entered PACTG 152 in 10/92 and remained in the trial until 2/95 when the AZT-only arm was unblinded at the recommendations of the Data Safety Monitoring Board of the trial, and it was discovered that he was in that arm. He was changed to the AZT and ddI.*

Not all children in Vera's review completed the clinical trials in which they were enrolled. It was often difficult to tell if children were withdrawn from a clinical trial because, even when their trial medications were stopped, they were still followed at regular intervals at clinical trials sites. In addition, many children were adopted while they were enrolled in a clinical trial and no further information about their trial course was available. However, the Vera review documented

[665] Each medication trial protocol defined what clinical findings (such as lack of expected weight gain) or laboratory findings (such as very high liver function tests) would result in a child being removed from an arm of a trial or the trial itself. The Data and Safety Monitoring Board is a group of independent scientists who review clinical trials data at regular intervals and recommend changes in trial protocol or discontinuation of the protocol if warranted by a review of the preliminary results. This is discussed in detail in Chapter 8.

113 instances (19.6 percent of all enrollments in medication trials) in which children did not complete the trial (see Figure 9.11).[666]

Figure 9.11: Children Who Did Not Complete Medication Trials

Reason for removal from medication trial	Frequency
Trial or trial arm was discontinued	22
Adverse event or toxicity*	20
Trial endpoint reached	10
Request of principal investigator	12
Seroreversion	2
Request of caregiver or family	3
Death**	25
Other	19
Total	**113**

*This number of adverse events is not the total number of adverse events found, just those which resulted in removal of the child from the trial.
**Deaths of children while enrolled in medication trials are discussed in detail later in this chapter.

Reviewers found 22 children who were removed from their trial because the trial or the study arm the child had been assigned to had been stopped. Although sometimes children were switched to a different arm of the trial, sometimes they were completely removed and either put on antiretrovirals outside of a trial or entered into another trial. Vera reviewers wrote:

> *When the Data Safety Monitoring Board reported that the AZT arm of PACTG 152 was less effective than the ddI or AZT/ddI arms, the child was removed from the trial and started on open label AZT and ddI with a noted increase in CD-4 cell count from 250 to 460 in a two month period.*

Twenty children were withdrawn from their trial because they had an adverse event or toxicity in response to the trial medication. Sometimes the removal was required as specified in the trial in response to a specific toxicity (such as severe liver toxicity which did not resolve with dose reduction or temporary stopping of the trial medication). However, reviewers also saw cases in which the principal investigator or trial physician elected to remove a child from the trial because although the child had not yet met a toxicity endpoint, he or she had had some lesser toxicity and the physician felt the child was not doing well on that trial. Vera reviewers wrote:

> *The child enrolled in PACTG 338 in 1997 and had immediate problems with severe nausea, vomiting and diarrhea from the Ritonovir. Physicians stopped the study medications and remove the child from the trial within two weeks. A nurse writes to the agency, "Until recently the child has done well with the study medication. However the*

[666] These 113 removals should be considered a minimum, since caseworkers might not have seen documentation of every removal and often there was no documentation of why or when a child left a trial. In addition, child welfare files were unavailable for some children and files would not contain removals that took place after a child left foster care.

> *last few visits she has shown a decline in CD4 count, inadequate weight gain and recurrent thrush. At this point in time, her doctor believes the study medication is no longer providing beneficial treatment for her and plans to stop the study medications and start her on AZT and 3TC combination therapy."*

Ten children in Vera's review were removed from a trial because they had met an endpoint as defined by the trial protocol; these endpoints were sometimes clinical ones (such as HIV disease progression) or immunologic ones (such as a dropping level of CD4 cells or a rising HIV viral load). Vera reviewers wrote:

> *The child was removed from PACTG 240 after six months, because of "disease progression" which was defined by the doctor as progressive neurological impairment, developmental delay and growth failure.*

The principal investigators of trials removed 12 children from trials. Reviewers found the exact reason for the removal was not clearly defined in many cases and could have been because of adverse events or meeting of an endpoint. However, as seen in the example below from a Vera reviewer narrative, there were also logistical or other reasons.

> *The child participated in PACTG 345 for ten days. The child was taken off the study because of the difficulty in obtaining blood after several attempts. The trial team who took care of the child stated that it was "too agonizing" to keep the child on the trial as it would require frequent blood draws for the pharmacokinetic part of the trial.*

As described earlier in the HIV status section of this chapter, two children seroreverted while they were on a medication trial. Upon testing which definitively showed that they had seroreverted, both children were removed from the trials.

Some children were withdrawn from a trial at the request of a caregiver such as a foster parent, a parent or legal guardian, or a request by the child. Vera reviewers wrote:

> *The foster child was enrolled in PACTG 254 and was removed from the trial eight months later because of parental "drug non-compliance." The doctor noted that despite long discussions with both the maternal aunt and the mother about the need for medications, both expressed great concern over giving any medications to the child… The mother reiterated that she does not believe in medicine and she felt it was experimental medication. The child's maternal aunt agreed.*

> *She was enrolled in PACTG 245 (ddI, NVP, AZT) which is referred to as a "salvage protocol." She was only on this trial about [two] months before the grandmother, who is her foster mother, asked that she be removed, as the child was miserable, with nausea, vomiting, diarrhea, and continued encephalopathy that had her essentially bedridden in the hospital.*

There were 19 children removed from a trial for a variety of other reasons, including such things as changes in the trial site or relocating caregivers. Vera reviewers wrote:

> *The child was enrolled in PACTG 152. She was withdrawn early from the trial because that trial site was discontinued and the foster parents wanted her to continue receiving her infectious disease medical care there.*

The circumstances of the 25 children who died while enrolled in a medication trial over the years the review covered are described in the last section of this chapter.

Trials in which Children Experienced Adverse Events. The review looked separately at toxicities and adverse events for the 14 medication trials with the highest enrollments in Vera's review, presented in Figure 9.12. The absolute numbers in the table cannot be compared to published toxicity data for each of these trials, as the Vera review did not have complete data on all foster children enrolled in each trial. However, the types of toxicities are similar to those seen in the published reports of these trials.[667] For example, trials which included AZT as a study medication showed the known toxicities of AZT such as anemia or thrombocytopenia, and those with ddI showed known toxicities such as liver function abnormalities or nausea and vomiting.

Not surprisingly, more than half of the moderate to severe (grade 3 or 4) toxicities found in all medication trials were found in the 14 trials with the highest enrollments in the review. Again, these are absolute numbers of toxicities found in each trial, and not percentages of total toxicities found. In general, as the number of enrollments in a trial decreased, the number of toxicities did as well.

[667] Appendix 11 includes articles that have been published in peer-reviewed journals, reporting the results for each of these 14 trials.

Figure 9.12: Toxicities in 14 Review Medication Trials with the Greatest Number of Enrollments

	Number of enrollments	Total number of episodes of toxicities*	Grade 1 or 2 toxicities	Grade 3 or 4 toxicities	Other toxicities**	Deaths of children in the trial
PACTG 152	123	62	29	25	8	7
B-W AZT IND	53	29	15	12	2	4
PACTG 300	46	25	19	5	1	1
PACTG 051	35	17	7	9	1	3
PACTG 240	32	17	11	5	1	1
PACTG 144* **	29	15	11	4	0	3
PACTG 045	21	8	8	0	0	0
PACTG 190	19	9	5	4	0	0
PACTG 338	19	6	2	3	1	0
PACTG 245* **	16	8	5	2	1	1
PACTG 128	15	9	3	5	1	0
PACTG 377	14	4	3	0	1	0
PACTG 138* **	11	5	2	3	0	2
PACTG 327	11	5	5	0	0	0

* A child on the trial could have more than one toxicity in a trial, and some children had none.
** In the guidelines to grading toxicities by the NIAID, some types of toxicities (such as development of glucose intolerance) were not graded but noted as present or absent.
*** These three trials are salvage protocols.

Besides the 14 trials in Figure 9.12 with the most enrollments, reviewers found 13 other trials in which children in Vera's review experienced grade 3 or 4 toxicities. These are shown in Figure 9.13. The number of enrollments in each trial ranges from one enrollment to nine. Descriptions of these trials can be found in Appendix 10. There were two deaths, which both occurred in the Bristol Meyers Squibb ddI Treatment IND salvage protocol; these deaths did not appear to be related to the trial drug.

Figure 9.13: Other Medication Trials in which Review Children had Grade 3 or 4 Toxicities

Clinical trial	Enrollments in trial	Number of grade 3 or 4 toxicities	Deaths while in the trial
BMS ddI IND	5	3	2*
PACTG 254	8	3	0
AG Nelfinavir**	5	2	0
PACTG 103	2	2	0
BMS d4t Parallel Track	5	1	0
PACTG P1006	1	1	0
PACTG 403	1	1	0
PACTG 179	1	1	0
PACTG 345	9	1	0
PACTG 356	4	1	0
PACTG 382	2	1	0
GCO pneumococcal vaccine***	4	1	0
Merck IDV+2 NRTIs-01****	1	1	0

* These two deaths are described in the sections of this chapter on salvage protocols and on deaths.
** The full name of this trial is Agouron Nelfinavir 1343-524. This trial will be referred to as "AG Nelfinavir" in figures through out the chapter. (For details see Appendix 10.)
*** The full name of this trial is GCO pneumococcal vaccine 92-587 PE. This trial will be referred to as "GCO pneumococcal vaccine" in figures through out the chapter. (For details see Appendix 10.)
**** The full name of this trial is Merck Indinavir-Stavudine-Lamivudine 068-01. This trial will be referred to as "Merck IDV+2NRTIs-01" in figures throughout this chapter. (For details see Appendix 10.)

The review also looked at documented toxicities by the phase of the trials. Vera's medical reviewers found no deaths of children while enrolled in the Phase I trial. The Phase III trials had the highest number of enrollments and the highest number of children experiencing toxicity (see Figure 9.14).

Figure 9.14: Presence of Toxicities in Medication Trials by Trial Phase

Phase of trial	Number of enrollments	Grade 1 or 2 toxicities	Grade 3 or 4 toxicities	Other toxicities	Deaths*
Phase I	3	1	0	0	0
Phase I/II	65	17	6	7	2
Phase II	100	25	18	4	3
Phase II/III	104	41	12	2	3
Phase III	189	43	39	10	10
Phase could not be determined	39	11	5	5	0
Expanded Access Programs	68	17	16	3	7
Total	568	155	96	31	25

* One child was enrolled in two trials at the time of death. She was in one trial that was a phase I/II, and in one trial that was a phase II/III. She is counted in the phase I/II category.

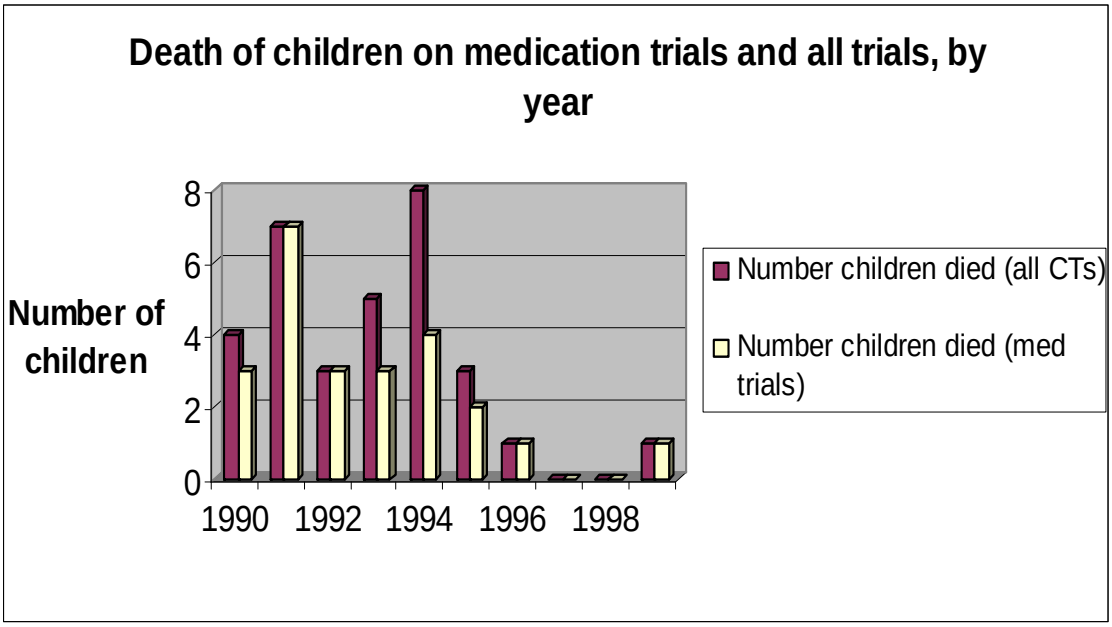
Deaths of Children while in Clinical Trials

Chapter 5 discusses children who died while in foster care but who were *not* enrolled in a medication clinical trial at the time of their death. This section discusses those children who were enrolled in a clinical trial when they died. There were 32 deaths among the foster children while they were enrolled in clinical trials during the years covered by this review. As noted in the previous section, 25 children died while enrolled in a medication trial.[668]

Figure 9.15 shows all deaths that occurred while a child was in either an observational or medication trial. Reviewers sometimes found it difficult to determine whether a child who was enrolled in a trial was still in that trial at the time of his or her death. This was often because the date the child might have left the trial was not documented in the files reviewed. Sometimes children in medication trials were taken off their trial medications (because of adverse events, disease progression despite the trial medication, or other reasons as discussed in the previous section), but were still followed by the trial site, so their clinic visits would continue to record the weeks of the trial. Reviewers also saw situations where children were so severely ill with AIDS that the child's doctors, the agency, and caregivers collaboratively decided to remove the child from the trial medications (but not necessarily from the trial itself) and give palliative or comfort care until the child's death.

[668] Seven children enrolled in observational research studies only also died while in foster care. Observational trials did not involve the testing of a new drug or treatment and participation was not connected to the cause of death. Each of these children were HIV infected. One child who died was enrolled in an observational research study (PACTG 188) and also in a medication trial PACTG 240. This child is counted among the 25 who died while participating in a clinical trial.

Figure 9.15



The pattern of deaths of children in clinical trials reflects the changes and advances in the treatment of pediatric AIDS. Fifty-two percent of the deaths of a child while enrolled in a trial and in foster care occurred before 1993. Only two children died while enrolled in a clinical trial after 1995.

Observational Research Study Deaths. Seven children died while enrolled only in observational research studies. These children were enrolled primarily in transmission studies such as MITS, WITS, and PACTG 219. Many children who died while on observational research studies were being treated with FDA-approved antiretroviral medications for their HIV disease *outside* of medication clinical trials. Two of the children died while enrolled in P2C2, an observational research study which followed both HIV-infected and seroreverted children for cardiac and pulmonary complications.

Medication Trial Deaths. As noted earlier, the review identified 25 children who died while they were enrolled in a *medication* trial. Vera researchers examined the circumstances of each death and the possible relationship between the death and the clinical trial in as much detail as the available files allowed.

As noted in Figure 9.16, deaths of children enrolled in clinical trials occurred in three expanded access programs and eight NIH-sponsored trials. Five of the trials were salvage protocols. One was a vaccine trial for infants for pneumococcal pneumonia; the child enrolled in this trial was also enrolled in an antiretroviral trial (PACTG 300).

The child who was enrolled into the Amprenavir Compassionate Use protocol died before she received the trial medication, but she is included in this discussion because she was still enrolled in a trial at the time of her death.

All NIH-sponsored PACTG trials in which deaths occurred had been recommended by the MAP and approved by the commissioner. The Burroughs Wellcome AZT Treatment IND was approved by the commissioner prior to the institution of the MAP. Child Welfare considered children for entry into Bristol Meyers Squibb ddI Treatment IND on a case-by-case basis.

Figure 9.16: Eleven Medication Trials in which Children Died

Trial	**Phase**	**Number of children who died while enrolled***	**Total enrollment in trial**
B-W AZT IND	Expanded Access	4	55
BMS ddI IND **	Expanded Access	2	5
GSK Open Label APV†**	Expanded Access	1	1
PACTG 051	III	3	35
PACTG 138**	II	2	11
PACTG 245**	I/II	1	16
PACTG 152	III	7	123
PACTG 144**	II/III	3	29
PACTG 240	II	1	32
PACTG300	II/III	1	46
PACTG 292	I/II	1	4

*One child was enrolled in two trials at the time of death; one trial was an antiretroviral medication trial and the other was a childhood vaccine trial.

** These are salvage protocols, described previously in this chapter.

† The full name of this trial is GlaxoSmithKline Open Label Amprenavir. This trial will be referred to as "GSK Open Label APV" in figures through out the chapter. (For details see Appendix 10.)

As discussed earlier, the ability to determine whether a child fulfilled a trial's criteria for age, HIV status, and disease stage was largely dependent upon the files available for review. Vera reviewers found documentation that nine of the 25 children who died while enrolled in a medication clinical trial met all three criteria and eight met two of the three criteria. For five children, only age eligibility was documented in the files. Two children had exclusion criteria; these are the *same* two cases discussed in this chapter in the eligibility section.

All but two of the 25 children met the CDC surveillance definition for HIV infection at the time of entry in the trial; these two were documented as HIV exposed when they entered the trial. For the child who died while enrolled in the pneumococcal vaccine trial, HIV exposure and seroreversion were both an acceptable status for entry. The other child had missing HIV testing documentation, so reviewers could not establish final HIV status.

Most of these 25 children were in the highest category of illness (CDC stage high-B or C) for HIV disease at the time they entered a clinical trial.[669] Vera reviewers noted that children who died while enrolled in salvage protocols were especially ill from AIDS- related complications at

[669] The CDC disease staging for pediatric HIV disease is discussed earlier in this chapter.

entry to the trials. Three children had mild symptoms of HIV at entry to a trial: two infants had the very early onset of progressive HIV symptoms and failure to thrive, and were enrolled respectively in PACTG 152 and PACTG 300 and one child was mildly symptomatic and enrolled in a trial that accepted children with mild HIV disease (PACTG 240).

More than half (65.2 percent) of the moderate to severe toxicities (grade 3 and 4) that occurred in this group of children who died were seen on the salvage protocols. These toxicities are similar to those seen in the larger group of all children in Vera's review who were in salvage protocols; this is discussed earlier in this chapter. Adverse events were also recorded for children who died while on medication trials. These included anemia requiring transfusion for two children, diarrhea requiring medication dose reduction or antibiotic treatment for two children, and three instances of temporary AZT dose reduction as required by the trial protocols because of hematologic (blood) toxicities.

Reviewers analyzed these 25 deaths, looking for trends in the trials, the medical history of the children, their clinical course while in the trial, and the cause of death. Four trends were identified and are summarized in Figure 9.17.

Figure 9.17: Categories of Deaths while Enrolled in Medication Trials

Category	**Trials involved**	**Total number of children**
Child enters foster care before1994 with advanced HIV disease, monitored on trial, disease progresses, dies of AIDS-related causes. Some trials were "salvage protocols."	BMS ddI IND, B-W AZT IND, PACTG 051, PACTG 138, PACTG 245, PACTG 152, PACTG 144	17
Child enters foster care before 1992, with advanced HIV disease, monitored on trial, disease progresses and child becomes terminally ill with AIDS, trial medication is stopped, palliative care given, child dies.	PACTG 051, PACTG 152	2
Child with advanced stage of AIDS who is enrolled in trial as a last option for treatment, medications probably never received.	B-W AZT IND GSK Open Label APV	3
Child with symptoms of mild to moderate HIV disease who is placed on a trial, monitored and doing well, then dies with non-trial related illness.	PACTG 152, PACTG 240, PACTG 300 PACTG 292	3*
Total number of children who died while enrolled in a medication clinical trial.		25

* One child was enrolled in both PACTG 292 and PACTG 300.

Among the 25 children who died while enrolled in a clinical trial, 17 entered foster care in the early years of the review, had advanced HIV disease, entered a medication trial, were followed by the trial site for toxicities, and died of AIDS-related causes. The following narrative is an example from this group:

> *This child was first tested for HIV at about one year of age because she had enlarged lymph nodes, an enlarged liver and spleen, and recurrent respiratory infections. She was diagnosed with LIP in late 1988. She had failure to thrive and was developmentally delayed especially in speech. Eight months later, her immunologic function was severely suppressed with CD-4 count of 11 (1 percent). Four months after that, she was started on AZT. AZT was discontinued two months later due to neutropenia. Nine months later her physicians requested consent for enrollment in the Bristol-Myers Squibb ddI Treatment IND.[670] The child was on this CT for 10 months, developed wasting syndrome and passed away.*

Two additional children had advanced disease and the decision was made to stop their trial medications and to give them only comfort care until their deaths.

> *This child was born in 1988, and was category C disease severity when he was enrolled in PACTG 051. He experienced anemia and hepatic toxicity which were managed by decreasing the dose of AZT. He was a severely disabled child with spastic quadriparesis, cerebral infarction, and a seizure disorder. He had a feeding tube. The child was terminally ill and the trial AZT was stopped (but child continued to be followed on the trial). One month later he was transferred to the hospital with fever and hepatitis and he died during the admission at the age of three and a half years.*

Three children were terminally ill with AIDS at the time they were enrolled in a trial as a last option for treatment. It appeared to reviewers that these children may have never received the trial medications before they died, but they had been enrolled in the trial.

> *The child had an extremely high viral load shortly after birth and at two months of age, she was begun on Bactrim prophylaxis, and triple antiretroviral treatment. Her doctors ordered pheno/genotyping studies which showed that her HIV virus was resistant to the HIV drugs she was on. She was admitted again for her final hospitalization. She had Candida esophagitis, jaundice, and bilateral Pneumocystis pneumonia. Genotyping showed that Amprenavir would be effective, but it was not approved for children less than four years old. There was an urgent letter written by her doctor to Glaxo-Wellcome asking to place the child on Amprenavir on a compassionate use basis. This was arranged, but the child died before the Amprenavir arrived.*

Three children were mildly to moderately symptomatic with HIV disease when they were enrolled in medication trials. They were monitored and seemed to be doing well, but died of non-trial related causes (pneumonia, meningitis, and a respiratory illness).

> *This child went into foster care from the birth hospital. By age three months, she was symptomatic for HIV disease. She was on AZT briefly, and then was enrolled in PACTG 152 at three months old. Her mother signed the consent. The baby was doing well, but developed pneumococcal meningitis and died.*

[670] This is the ddI Expanded Access Program.

From the available files for these 25 children, medical reviewers found no children who died of allergic reactions to trial medications or of factors which might be directly linked to the medication or clinical trial.

Conclusion

This chapter has described the experience of the children in Vera's review while they were enrolled in clinical trials and observational research studies. The emphasis in this chapter has been on three distinct periods of the review, noting that the ability to diagnose and treat pediatric HIV/AIDS differed significantly over time and that this impacted on both the number of enrollments and the types of clinical trials in which children enrolled. The chapter has discussed the degree to which eligibility and exclusion criteria were met, monitoring of the children while enrolled in the trial, toxicity that occurred and deaths of children enrolled in clinical trials. Chapter 10 will build on this information by describing the extent to which the enrollments described in this chapter followed Children's Services policies for enrollment and monitoring of foster children in clinical trials and observational studies.

Chapter 10: Following Child Welfare Policy and Federal Research Regulations

Chapter Summary

Many records were not available for review even though regulations required Children's Services to ensure their retention. In some situations, files were unavailable due to events beyond the agency's control; in others, file retention practices were at fault. Regulations required medical decisions, consents, and other information to be documented. Some files were meticulous in this respect, but many files that indicated children had participated in a clinical trial were missing information such as enrollment dates, a signed informed consent form, and, in some instances, the name of the trial. Some files had little or no documentation for years of a child's stay in foster care. The unavailability of some files and missing documentation in others violated state regulations and limited parts of Vera's analysis concerning policy compliance.

Human Resources Administration (HRA)/Children's Services followed its own written trial review policy for 15 medication trials in which foster children were enrolled. These 15 trials enrolled a majority of the children in foster care who entered medication clinical trials. The agency also rejected requests to enroll children in many trials, and no children in foster care enrolled in those trials. In 47 medication trials with 129 enrollments, however, the agency did not follow the policy outlined in the policy documents. Ninety-eight of these enrollments took place in foster care.

Similarly, Vera reviewers did not find informed consent materials for many children who participated in medication clinical trials. Where Vera reviewers identified an enrollment date indicating that trial participation started in foster care, Vera found no informed consent materials about 21 percent of the time—a proportion that rises when enrollments that took place out of care and when the date of enrollment is unknown are included. In a substantial proportion of enrollments, however, they found information indicating that some parts of the consent policy had not been followed. Problems included missing signatures on informed consent documents, enrollments of children in foster care prior to the commissioner's approval of a trial, unauthorized people signing consent documents, and problems with the process of searching for parents.

Vera's analysis found that hospital IRBs appointed independent advocates, as required by the federal research regulations for some clinical trials, for 152 children. Limitations on data collected by Children Services and the lack of access to hospital IRB records prevented Vera staff from determining if independent advocates were appointed in every instance in which they were required. The role of the independent advocate, moreover, was poorly understood.

Introduction

This chapter examines how closely child welfare agencies followed the policies set out by federal, state, and local regulations, and agency directives. Its primary focus is on compliance

with policy and regulations. The chapter discusses how well Children's Services followed regulations on record retention and documentation, its own policy for clinical trial review and approval, and its policy regarding informed consent and approval of individual enrollments. The chapter also addresses issues related to the quality of the informed consent process and compliance with the section of the federal regulations related to independent advocates.

Documentation and Record Keeping

Concerns about the quality of child welfare record keeping are longstanding in New York City and elsewhere.[671] When the city created the Administration for Children's Services in 1996 it was widely acknowledged that the child welfare system was overwhelmed and that record keeping often received a low priority.[672] Vera staff did not intend to study file retention and quality; however, the absence and quality of records for many of the children whose files Vera reviewed affected the findings of this report.

This section of the chapter examines two aspects of documentation: the presence or absence of a file, and the quality of documentation in the file.[673] New York Code of Rules and Regulations (NYCRR) title 18 section 428 lists the records that Children's Services and other child welfare agencies in New York State must collect and maintain about children in foster care, the intervals at which the information must be collected, and, in some instances, who must collect it. The regulations also make Children's Services responsible for ensuring that contract agencies comply with these regulations.

Compliance with Regulations on File Retention. Current regulations, instituted in 2005, mandate that foster care records be kept for 30 years following the discharge of a child from foster care.[674] This rule did not apply to the records of most of the children in Vera's review, however, because they had already left foster care when this new regulations came into effect. The pre-2005 regulation reads as follows:

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[671] Concerns about record keeping are expressed in many of the reports and studies cited in Chapter 3 of this report. Federal concern with the record keeping of child welfare agencies dates back to at least 1993, when the Omnibus Budget Reconciliation Act of 1993 Section 13711 provided states funding for developing standardized electronic record keeping, known as SACWIS (Statewide Automated Child Welfare Information Systems).

[672] See Administration for Children's Services, *Protecting the Children of New York: A Plan of Action for the Administration for Children's Services* (New York: Administration for Children's Services, 1996). Information from interviews conducted by Vera staff was consistent with this characterization.

[673] Vera staff did not follow a standard file audit approach that compares legally required elements with what is actually in the files—the aims of this report were focused on the experiences of children who participated in clinical trials. The volume of files and the sequence in which they were identified would have precluded this approach in any case. An August 2007 report by Children's Services and the Department of Investigation on child fatalities took 18 months to complete detailed examinations of 12 child protective investigations. See Children's Services and Department of Investigation, *A Department of Investigation Examination of Eleven Child Fatalities and One Near Fatality* (New York: Administration for Children's Services and Department of Investigation, August 2007). By contrast, Vera's file review for this report examined the files 796 children.

[674] NYCRR 18, 428.10.

> Such records, whether maintained by a district or provider agency shall be retained until the youngest child who received services becomes 21 years of age, or six years after the termination of services, whichever is later.[675]

To comply with this regulation, contract foster care agencies had to make a series of calculations. First, the agency needed to identify the youngest child to receive services in a family—even if another contract agency provided services to that child. Then the agency had to determine the last date of payment for that child and compare it to the date the child turned 21. After making these determinations, the agency could then calculate how long it was legally required to retain the record. For children who died while in foster care, the regulation is vague about whether agencies need to retain records for six years after the child's death or until the child *would* have turned 21 years old.

Vera staff analyzed Child Care Review Service (CCRS) data to determine which records agencies were required to maintain using different interpretations of the regulation. Of the 796 children whose records Children's Services asked Vera to review, the retention regulation called for the files of 741 children to be available.[676] Of the 532 children who Vera reviewers identified as participating in clinical trials, the regulation called for the files of 499 children to be available (see Figure 10.1).

Figure 10.1: Compliance with File Retention Regulations

	Files available for all 796 children referred to Vera for review		**Files available for 741 children for whom files were legally required to be retained**	
Children for which:	**N**	**%**	**N**	**%***
All files were available for review (both case management and case planning files)	557	70.0	525	70.9
Some files were not available for review (case management and/or some of the case planning files)	117	14.7	102	13.8
Only case management files were available for review, no case planning files available	111	13.9	103	13.9
No case management or case planning files were available for review	11	1.4	11	1.5
Total children	**796**	**100.0**	**741**	**100.1**

*Column does not add to 100.0 due to rounding.
Source: Vera file review.

At the request of the commissioner of Children's Services, Vera reviewers compiled a list of agencies, the number of files requested, and the number of files made available. Children's Services made several inquiries to its contract agencies asking why they could not locate all the

[675] Published as 18 NYCRR 428.15.
[676] The date used for this analysis was October 10, 2006, the most recent update of the CCRS data used to generate this information. On that date, a majority of the files had been requested for Vera's review.

requested files. In the fall of 2007, Children's Services sent a letter to contract agencies asking them to produce all remaining records for the review or to explain why the records were unavailable. Eleven agencies responded in writing to these inquiries. Some agencies responded but did not provide an explanation for why the files could not be located.[677] Two agencies cited water damage, and others acknowledged problems with record storage practices or the firm hired to warehouse the records. During the course of the Vera review, staff at several agencies told Vera staff that they store all records indefinitely. Those that did not store records permanently sometimes cited the cost of storage as a reason.

Compliance with Regulations on File Content. State regulations and New York City child welfare policies specify a wide range of information that is required to be present in child welfare files, including:

> all reports of medical or clinical examinations or consultations, including medical examinations and laboratory tests, psychiatric or psychological examinations or consultations (either court-ordered or voluntary), dental examinations; and medical consent forms signed by the parent or guardian, by the commissioner of the social services district, or by the child if the child has the capacity to consent, as applicable, regarding medical treatment for any child in foster care placement [678]

Various HRA/Children's Services policies also mandated that informed consent documents for medical treatment, results of HIV tests, and other types of medical information be maintained in case planning and case management files.[679] In addition, the Pediatric AIDS Unit (PAU) had responsibility for maintaining files that recorded HIV test results, participation in clinical trials, and clinical trials monitoring information.[680]

Vera reviewers found many instances where caseworkers documented consent for medical procedures outside of clinical trials. At some foster care agencies, especially those with specialized HIV programs, files contained detailed records of medical consents, clinic visits, lab results, and other required information. For example, a medical reviewer noted:

> *[Foster child's] monitoring was constant and well-documented throughout his life in the progress notes. Through these notes, which include copies of hospital notes, stacks of*

[677] One agency cited a retention policy inconsistent with the regulation: "Files are generally maintained in storage for a 10-year period, although oftentimes for longer periods of time" (letter, September 9, 2007, to Yelena Gladkova from Luz Liburd, Concord Family Services).
[678] 18 NYCRR 428.3 (2) ii.
[679] See, for example, Policy Bulletin 94-1 dated March 15, 1994, and Policy Bulletin 98-2 dated December 30, 1998, as well as a memo dated September 2, 1994, from Michael Dowling, OCFS commissioner, to Local District Commissioners, re: Emergency Order Revising Testing Regulations.
[680] Several policy bulletins mandate that HIV test results must be recorded by the PAU. See, for example, CWA Bulletin 89-5 dated August 7, 1989, from Stephen Joseph, commissioner of health, and Brooke Trent, executive deputy commissioner CWA, to Foster Care Agency Directors, re: HIV Antibody Testing of Children in Foster Care.

consent forms for transfusions, Broviac central venous catheter placement, etc., a fairly comprehensive understanding of his medical experience can be put together.

Other child welfare files, however, contained little or no information on medical consents, examinations, or lab results. In at least 76 situations, Children's Services produced a case management file but the file contained little or no information. In some instances, the missing information coincided with the period in the late 1980s and early 1990s when a child was in a kinship placement in "direct care" (where foster care services were provided by the city directly instead of contracted out; see Chapter 3).

The child's case management file was very small. The foster care agency said that there were two files for the child but said only one was located. Although the baby was born in 1986 with a positive toxicology for cocaine and placed in foster care with the maternal grandmother upon discharge from the hospital, there are no medical records in the files until 1990. The child was transferred to a non-kinship foster home in March 1991 at age four and a half.

The impact of unavailable files and information on the Vera review is discussed in Chapter 2.

Adherence to Trial Approval and Enrollment Policy

This section describes how Vera gathered information on compliance with policies on trial review and enrollment approval. It then summarizes compliance with the agency's trial review processes overall and describes compliance with review policy during different periods. Finally, the section describes enrollments in trials that were not approved by the commissioner. Because trial review and informed consent policies were intertwined, the analysis below contains information on both aspects of policy.

How Vera Gathered This Information. Vera staff relied on two sources of information to determine how closely Children's Services followed its trial review policy: documents contained in child welfare files and several boxes of documents provided by Children's Services for review. The boxes of documents came primarily from the Pediatric AIDS Unit and the files of lawyers who worked on clinical trials policy. The documents included:

1. letters from the commissioner approving the enrollment of foster children in specific clinical trials,
2. memos to the commissioner recommending approval or disapproval of a trial,
3. reviews of individual trials by members of the medical advisory panel (MAP),
4. handwritten notes from MAP meetings,
5. memos and e-mail among and between legal and PAU staff,
6. correspondence from the PAU and other child welfare agency staff to clinical trial researchers and contract foster care agency staff,

7. letters written by consultants to the PAU,
8. virtually all of the quarterly reports produced by the PAU from 1992 to date, many of which announced the approval of clinical trial or that a MAP was held, and
9. letters of agreement between HRA/Children's Services and medical centers for specific trials.[681]

Some documents contained inconsistent information. This was particularly true in documents produced between 2003 and 2005 that described events that took place many years earlier. In these situations, Vera staff placed greater weight on contemporaneously produced documents and documents produced by people who were directly involved in decision making. Vera staff gave greater weight to PAU quarterly reports produced before 1996 than to reports after that date because 1996 was the year in which the PAU computer malfunctioned and many PAU personnel changed. Vera staff also gave greater weight to documents produced as part of a decision-making process, such as the actual MAP reviews and doctors' and lawyers' memos to the commissioner, than to summaries of trials that were approved or disapproved.

Near the end of this project, project leaders asked Children's Services to review its determinations concerning trial reviews. Where Children's Services disagreed with Vera reviewers' determination, project leaders asked for documentation supporting Children's Services position.

Information on whether or not an informed consent document was present for a clinical trial enrollment came from individual child welfare files and from files in the PAU. Both child welfare and medical reviewers gathered information about the consent process. The information they collected included where the form was found, who signed the form, and the dates of the signatures. Vera staff gathered information from standard consent-related forms used by the PAU (including Notification of Enrollment of a Foster Child in a Clinical Trial and Notification of Enrollment of a Child in Joint Custody forms sent by clinical trials researchers to Children's Services) and 853C forms that foster care agencies sent to Children's Services requesting approvals of enrollments. Other consent-related documents included letters from clinical trial researchers requesting approval of enrollment, letters from Children's Services advising clinical trials researchers that approval had been granted or denied, notes in child welfare files, and medical progress notes. In a few instances reviewers found handwritten notes from parents or letters from clinical trials researchers to parents regarding clinical trials enrollment.

Compliance with Trial Review Policy Summary. Vera project staff analyzed whether enrollments in the trials identified in its review conformed to the written policy in place at the time child welfare officials considered the trial. As described in Chapter 7, New York City's child welfare agency had different policies in place during different periods. Figure 10.2 refers to those different periods.

[681] Appendix 9 contains an example of a letter of agreement.

Figure 10.2: Approval Policies for Enrollment of Foster Children in Clinical Trials

Period	Basis of Policy	Key Policy Points
1985 to June 1989	Internal memos	Children in foster care not allowed in clinical trials. Observational studies approved or disapproved upon request.
1989 to May 1991	Internal memos	Only HIV/AIDS trials permitted and only after commissioner approval. This policy applied only to research and clinical trials for HIV/AIDS. Commissioner or delegate must approve all enrollments of individual children, including those for whom a parent signed a consent form. After commissioner approves a trial, a delegate is permitted to approve enrollment of individual children. Parental consent sought first. No children allowed in Phase 1 trials. IRB approvals and letters of agreement with hospitals required.
May 1991 to April 1994	Letter dated May 28, 1991	Only HIV/AIDS trials permitted. Formal process for reviewing trials by the Medical Advisory Panel and recommending commissioner approval or disapproval. Approval for individual enrollments is assumed if commissioner approved the trial. Parent consent sought first and required if parental rights have not been terminated, unless parent could not be found. No children allowed in Phase 1 trials. IRB approvals and letters of agreement with hospitals required. Foster care agencies are permitted to sign consent forms for children in joint guardianship but only with prior PAU approval.
April 1994 to December 1998	Bulletin 94-1	Same as above, except that for foster children in joint guardianship, foster care agencies need to *notify* the PAU, but do not need *prior approval* to sign consent forms.
December 1998	Bulletin 98-2	Same as above, except that the policy establishes process of independent physician review for Phase I & II enrollments.

The Vera review identified 88 trials in which children participated while in foster care. Enough information was available to analyze the review processes for 85 of those 88 studies.[682] *This analysis includes only trials in which foster children participated.* Vera staff identified at least nine trials that HRA/Children's Services disapproved and in which no children in foster care participated. They also identified a small number of approved trials in which no children in foster care participated.

1986 TO 1991 TRIAL REVIEW SUMMARY: From 1986 to May 1991, foster children enrolled in 13 trials: seven medication trials and six observational studies.[683] The HRA commissioner approved three of the seven medication trials, all after 1988: PACTG 045, PACTG 051, and the Burroughs Wellcome AZT Treatment IND.[684] Children in foster care also participated in four medication trials that the commissioner did not approve: PACTG 052, PACTG 128, the Bristol Meyers Squibb ddI Treatment IND,[685] and an unidentified NIH AZT Protocol.[686] Of the 131

[682] The three studies not included in this analysis involved four enrollments.
[683] Vera divided medical research examined in this report into two types. The first type, medication and expanded access trials, involved some type of medical intervention aimed at developing treatment for HIV/AIDS or its symptoms ("medical trials"). The second type, observational studies, sought to learn more about the disease without developing treatment. For purposes of analysis, we have grouped expanded access programs with medical trials.
[684] This trial will be referred to as "B-W AZT IND" in tables throughout this chapter. (For details see Appendix 10.)
[685] This trial will be referred to as "BMS ddI IND" in tables throughout this chapter. (For details see Appendix 10.)

enrollments in medical intervention and expanded access trials during this period, 109 (83 percent) occurred in commissioner-approved trials. The number of enrollments cited throughout this section includes children enrolled prior to entering foster care who continued to participate while in foster care.

Vera reviewers identified 179 enrollments of foster children in observational studies. The commissioner approved three observational studies in which 68 of these 179 children participated. The three approved observational studies were the Women and Infants Transmission Study (WITS), the Pediatric Pulmonary and Cardiovascular Complications Study (P2C2), and the Early Diagnosis of HIV Infection study.[687] Three children in foster care participated in an observational study, the Incidence of Arrhythmias study, which was not approved by the commissioner.[688]

Vera staff could not determine conclusively if the commissioner approved or did not approve several other observational studies, all of which were focused on collecting information on the transmission of HIV from mothers to their newborn infants (see Chapter 8). The studies did not bar or require any medical treatment or participation in other clinical trials. In some transmission studies, informed consent for both the mother and the newborn could be obtained from the mother prior to birth of the child—and thus before entry into foster care. Records show that HRA approved some transmission studies at some hospitals. Vera staff found no evidence that HRA rejected requests for participation in any transmission study. The records did not allow Vera staff to make more detailed determinations.

The observational study in this group with the greatest number of children who participated while in foster care is the Mother to Infant Transmission Study (MITS),which involved 72 children in foster care. This number may not be conclusive, however, for a number of reasons. First, the study had different names in different time periods. Second, sometimes Vera reviewers found evidence that a child participated in a transmission study, but in 36 enrollments the reviewers could not identify the *specific* transmission study in which the child participated. Finally, in many of the transmission studies, Vera reviewers could not find an enrollment date that would have allowed them to determine if the child enrolled in the study prior to or while in foster care.[689]

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[686] One child participated in this last study. Information on the study and the enrollment were incomplete. The child who participated received IVIG and AZT, but the times at which these medications were provided do not correspond to periods when two large studies that included these medications, PACTG 045 and PACTG 051, took place. This trial will be referred to as "NIH AZT Protocol" in tables throughout this chapter. (For details see Appendix 10.)

[687] This trial will be referred to as "the Early Diagnosis Study" in tables throughout this chapter. (For details see Appendix 10.)

[688] This trial will be referred to as the "Arrhythmia Study" in tables throughout this chapter. (For details see Appendix 10.)

[689] For purposes of counting the number of trials and observational studies, 88, Vera counted these as two studies: MITS as one study and the unidentified transmission studies as one study. Many of the unidentified transmission study enrollments may have been in one of the known transmission studies (MITS or WITS).

1991-2005 TRIAL REVIEW SUMMARY: From the time that the MAP trial review policy was instituted in May 1991 through 2005, Vera reviewers found 533 enrollments of New York City foster children in 76 HIV/AIDS-related studies. This includes 437 enrollments in 58 medication trials and 95 enrollments in 14 observational studies.[690] There were also four enrollments in three trials in which Vera staff could not determine if the research was an observational study or a medication clinical trial. These three trials are excluded from the analysis below because of a lack of information—a lack that runs counter to the child welfare agency's policy requirements. As in the previous section, enrollment numbers here include children enrolled in trials outside of foster care but who participated in the trials at some point during a stay in foster care.

Figure 10.3 shows the medication trials by their review status and the number of enrollments for each review status category. Six of the 58 medication trials the MAP would *not* have been expected to review. PACTG 076 and PACTG 316 were trials that tested medications designed to stop the transmission of HIV from a mother to a child; therefore, the mother signed consent forms for her and her newborn's participation before birth. Two other studies, PACTG 725 and PACTG 727 were sub-studies of a trial that the MAP reviewed and recommended, PACTG 377. Finally, Children's Services approved two trials in 2005 using its draft policy that did not require a MAP review. Nine children participated in these six studies while in foster care.

Figure 10.3: Summary of Trials by MAP Review Category

Review category	**Trials**	**Enrollments**
Review by MAP not required	6	9
MAP reviewed and recommended	15	330
MAP reviewed and not recommended	3	21
MAP reviewed, but no recommendation forwarded to the commissioner	4	13
Not reviewed by MAP	30	64
Total	**58**	**437**

Fifteen of the 58 medication trials the MAP reviewed and recommended. The commissioner approved each of these trials. These 15 trials were 26 percent of the 58 medical intervention and expanded access *trials* and involved 330 (76 percent) of the 437 *enrollments* by children who participated while in foster care from 1991 to 2005.

Three medication trials the MAP reviewed and did *not* recommend. Twenty-one enrollments took place in these three trials. In one of the trials not recommended by the MAP, PACTG 247 (a trial that tested a calorie-dense infant formula in children born to HIV-positive mothers), the commissioner approved enrollment in the trial if the parent consented. Four trials the MAP

[690] To determine the policy that applied, Vera staff examined the policy documents. Where the policy documents did not provide enough information, Vera examined the first date of enrollment into the trial. If it was before June 1991, then Vera staff classified the trial as taking place before the institution of the MAP policy. Where no enrollment date existed, Vera staff examined the reviewer narrative and trial protocols to determine if the enrollment took place before or after June 1991.

reviewed but a recommendation was not made to the commissioner. These four medication trials were tabled or listed as "pending" in PAU quarterly reports and never approved by the commissioner. Thirteen enrollments took place in these four trials.[691] Of the 34 enrollments in these two categories, 10 occurred outside of foster care but participation extended into a stay in foster care.

The MAP did not review 30 (52 percent) of the 58 medical intervention trials in which foster children participated and that required review. Forty-six children (11 percent) participated in these trials. In 18 of the 30 trials, a single child in foster care participated. Although there was no MAP review in two of these trials, Vera found that a single consultant reviewed and recommended the trials. Ten children participated in these two trials. In two other trials, a single consultant reviewed and recommended against participation of foster children. In one of these trials (PACTG 1024) a single child was enrolled prior to entering foster care. In the other (PACTG 1020A), three children participated. In another two trials, a child enrolled after a referral to the National Institutes of Health (NIH). Vera found no evidence of external review in the remaining 24 trials with 46 enrollments. HRA/Children's Services' written clinical trial approval documents did not mention any separate process for trials with small enrollments or other situations that allowed the agency to circumvent the MAP review process.

The unreviewed trials differ from the MAP reviewed and approved trials in several ways. On average, fewer than two children in foster care participated in these trials, compared with an average of 22 children in each of the approved trials. Five of the trials were expanded access programs; none of the approved trials are in this category. In addition to the five expanded access program trials, Vera staff determined that eight of the unreviewed studies were sponsored by pharmaceutical companies. In contrast, each of the MAP reviewed and approved trials were sponsored by NIH.

Figure 10.4 lists the MAP reviewed medication trials that enrolled New York City foster children. Figure 10.5 lists medication trials *not* reviewed by the MAP that enrolled New York City foster children.

[691] Each of the reviews of these four trials all took place in the late 1990s after the child welfare agency lawyer working on clinical trials reviews raised questions about the policy. See Chapter 7 of this report.

Figure 10.4 Medication Trials Reviewed by the Medical Advisory Panel in which New York City Foster Children Enrolled

	Reviewed by MAP					
Policy period	**Recommended**		**Not recommended**		**Pending or tabled**	
	Trial	**Enrollment**	**Trial**	**Enrollment**	**Trial**	**Enrollment**
1991-1994	PACTG 138	11	PACTG 218	3		
	PACTG 144	29				
	PACTG 152	123				
	PACTG 179†	1				
	PACTG 182	1				
	PACTG 190	19				
	PACTG 240	32				
1994-1998	PACTG 225†	1	PACTG 247	10	PACTG 345	9
	PACTG 239	3	PACTG 254‡	8	PACTG 366	1
	PACTG 245	16			PACTG 382	2
	PACTG 292†	4			PACTG 403	1
	PACTG 300	46				
	PACTG 327	11				
	PACTG 338	19				
	PACTG 377	14				
1999-2005						
Total	**15**	**330**	**3**	**21**	**4**	**13**
Enrollments while in foster care		**293**		**9**		**11**

† Members of the MAP were split on whether children in foster care should participate in PACTG 179, PACTG 225, and PACTG 292. For each trial, the recommendation sent to the commissioner that was prepared by HRA's Office of Legal Affairs recommended approval of the trial only with parent consent.
‡ Members of the MAP did not recommend PACTG 254. The recommendation that HRA's Office of Legal Affairs sent to the commissioner recommended approving the trial only with parent consent.

Figure 10.5: Medication Trials Not Reviewed By the Medical Advisory Panel in which New York City Foster Children Enrolled

	Not reviewed by MAP (Enrollments in parentheses)				
Policy period	**No outside review located**	**Trials at NIH**	**Recommended by single consultant**	**Rejected by single consultant**	**Reviewed under new policy (2005)**
1991-1994	PACTG 178 (1)	PACTG 103 (2)			
	H-LR Open Label ddC (2)	NCI G-CSF-Erythropoietin (2)			
	GCO Hib vaccine (2)				
	GCO pneumococcal vaccine (4)				
	BMS d4t Parallel Track (5)				
1994-1998	PACTG 076 (1)*		G-W ABV-LMV-ZDV (6)		
	PACTG 265 (2)		G-W APV (4)		
	PACTG 316 (1)*				
	PACTG 356 (4)				
	PACTG 725 (1)*				
	PACTG 727 (4)*				
	WinRhoSD-UNX-800 (1)				
	Pertussis IG Study (1)				
	Pneumovax Study (3)				
	ICC Growth Study (1)				
	H-LR Enfuvirtide (2)				
	G-W Abacavir (2)				
	AG Nelfinavir (6)				
	Merck IDV+2NRTIs-01 (1) Merck IDV+2NRTIs-10(1) Merck IDV+2NRTIs-20 (1)				
	BI Open Label NVP (1)				
	AG NFV Exp. Access (1)				
	Pentamidine Study (1)				
1999-2005	GSK Open Label APV (1)			PACTG 1020A (3)	Pfizer Maraviroc (1)
	PACTG 1006 (1)			PACTG 1024 (1)	NCI Lymphoma (1)
	PACTG 1008 (1)				
	PACTG 1015 (1)				
Trials	28 (24 required MAP review)	2	2	2	2 (No MAP review required)
Enrollments	53 (46 enrollments in trials with MAP review required)	4	10	4	2 (0 enrollments in trials with MAP review required)
Enrollments while in foster care	41	3	4	3	2

Note: For many of the trials in this table, the abbreviated version of the trial name is used. Refer to the table of contents of Appendix X (The clinical trials) for the full name of the trial, and for more information on the trial.

* These studies were either transmission trials (PACTG 076 and PACTG 316), in which a mother enrolled herself and her baby during pregnancy, or sub-studies of larger studies that the MAP reviewed and approved (PACTG 725 and PACTG 727). Vera staff determined that a MAP review would not have been expected for these trials.

Vera reviewers identified 14 observational research studies in which 95 foster children participated after the MAP review policy was instituted. HRA/Children's Services staff made a distinction between clinical trials that tested new medications or medical interventions and "research protocols" that Vera describes as observational research studies. The MAP did not review the observational research studies. Observational studies often involved extra blood draws and/or diagnostic tests that would appear to qualify as human research according to state regulations.[692]

There is room for interpretation for what constitutes a clinical trial as opposed to an observational research study. The written documents did not contain a detailed definition that would have guided staff in determining which studies required MAP review. None of the 14 studies were reviewed by the MAP and Vera staff did not characterize the lack of MAP review as a policy violation.

Three studies were approved by the commissioner, two after an internal review by child welfare staff (PACTG 219 and PACTG 188) and a third (PACTG 219C) after an internal review by staff and a review by a single external consultant. In each of these three studies, the commissioner's approval was provided only if researchers obtained informed consent from the birth parent and foster parents assented to the child's participation. The 81 enrollments in these three studies made up 85 percent of the enrollments in observational research studies during this period.

Three studies of the remaining 11 studies were reviewed and recommended by a single consultant, though Vera reviewers did not find evidence that the commissioner formally approved the study.[693] One of the remaining 11 studies was reviewed and rejected by a single external consultant—the one foster child who participated in that trial, PACTG 1010, enrolled prior to entering foster care. Vera reviewers found no evidence of a review for the remaining seven studies.[694]

[692] Some policy documents refer to New York State Public Health Law Article 24-A. That section of the law defines human research as "any medical experiments, research, or scientific or psychological investigation, which utilizes human subjects and which involves physical or psychological intervention by the researcher upon the body of the subject and which is not required for the purposes of obtaining information for the diagnosis, prevention, or treatment of disease or the assessment of medical condition for the direct benefit of the subject. Human research shall not, however, be construed to mean the conduct of biological studies exclusively utilizing tissue or fluids after their removal or withdrawal from a human subject in the course of standard medical practice, or to include epidemiological investigations" (PHL Article 24A(2)).

[693] These three studies included NCI Respiratory Infections Study 94-C-0049, the MRS in Pediatric AIDS Dementia Study, and PACTG 1045.

[694] These studies included NIH NMR Scanning Study 84-CC-0058, PACTG 360, PACTG 803, a study of metabolic rates, an observational psychiatric study at Metropolitan Hospital, a study of renal manifestations, and an ICC Growth study. Vera reviewers found little information on the latter four observational studies.

Enrollment Procedures in Medication Trials that Did Not Undergo Standard Trial Review

This section describes only the 129 enrollments in medication trials that occurred outside of the standard trial review policy. For the period 1988 to 1991, this refers to the 22 enrollments in medication trials that the commissioner did not approve. For the period 1991 to 2005, this refers to the 34 enrollments in trials reviewed by the MAP but not approved by the commissioner and the 73 enrollments in trials that were not reviewed by the MAP. Of the 129 enrollments, Vera confirmed that 31 enrollment took place outside of foster care.[695] HRA/Children's Services' written policies did not address how such situations should be handled. For example, the policy did not indicate if these children should continue in the trial once in foster care, whether the commissioner needed to approve continued enrollment, if the trial needed to be reviewed by the MAP, if the participating hospital needed to sign a letter of agreement with the child welfare agency, or if a parent needed to sign a new informed consent form upon entering foster care.

Of the remaining 98 enrollments that were not clearly outside of foster care, Vera reviewers found enrollment dates for 80 enrollments (see Figure 10.6). Without an enrollment date, Vera staff often could not tell if the enrollment took place inside or outside of foster care, or before or after the termination of parental rights. Though the analysis does not include these enrollments, Vera staff believes that state regulations and child welfare policy required that an enrollment date be recorded in the child welfare files.

Parental Rights Intact. Vera reviewers found that 59 enrollments in unapproved trials took place while parental rights remained intact, as shown in Figure 10.6. Of these 59 enrollments, 29 included informed consent forms signed by parents. In eight enrollments, the commissioner's delegate—the PAU director—approved the enrollment although parental rights remained intact. In at least three of these eight enrollments, the location of the parent was known, but the information in the files indicated that the circumstances surrounding the enrollment led to the delegate signing the approval. These circumstances included a parent incarcerated for the sexual assault of a child's sister, a parent who had ceased to plan for the child's return but caseworkers had determined that termination of parental rights was not in the child's best interest, and a child taken care of by her grandmother—who approved of the enrollment—but the mother lived several hours from New York City. In one instance, the foster care agency approved the enrollment though parental rights remained intact. In 21 enrollments with parental rights intact, no one from the city's child welfare agency approved the enrollments, though in two of these 21 enrollments the agency was notified of the enrollments.

[695] The 129 enrollments include the nine enrollments in the six trials that the MAP would not have been expected to review. However, the two enrollments in PACTG 076 and PACTG 316 are among the group that took place outside of foster care. Vera staff included the remaining enrollments because although MAP review was not expected, the need to obtain informed consent remained.

Figure 10.6: Mechanism for Entering Trials That Did Not Follow the Standard Review Process

Enrollments in Unapproved Trials				
	With parental rights intact		Parental rights severed*	
Enrollment approval	Enrollments	% Enrollments**	Enrollments	% Enrollments**
Parent or guardian	29	49.2	0	0.0
Commissioner delegate	8	13.6	12	57.1
Foster care agency/joint guardianship	1	1.7	7	33.3
Notification only	2	3.4	0	0.0
No form of approval found	19	32.2	2	9.5
Total enrollments	**59**	100.1	**21**	99.9

*Parental rights are considered severed through death, surrender, or termination of parental rights.
** Percentages do not total 100.0 due to rounding.
Source: Vera file review.

In these latter 21 enrollments, Vera reviewers did not locate an informed consent or approval form. Regulations and policy required that the form be in the child welfare file. The absence of the form, however, does not mean that an informed consent process did not take place and that a signed informed consent form does not exist in the clinical trial research file. Because the New York State Department of Health refused to exercise its supervisory authority to allow review of these files, the Vera review could not determine whether a valid informed consent document exists for these enrollments. Analyses below contain similar situations.

Parental Rights Severed. Twenty-one enrollments occurred after the severing of parental rights. In 12 of these 21 enrollments, the commissioner's delegate approved the enrollment though the trial had not been approved. Seven of the 21 enrollments were done through joint guardianship. These enrollments conformed with HRA/Children's Services' clinical trials consent policy. However, the joint guardianship policy created situations in which children participated in trials that the MAP had reviewed and not recommended, including three enrollments in PACTG 218 as described in Chapter 7 and two in PACTG 254. For two of the 21 enrollments, Vera reviewers could not find consent forms.

Enrollments in Medical Intervention Trials That Followed the Standard Trial Review Process

This section describes how consent for enrollment was obtained for foster children who were enrolled in medication clinical trials that had been reviewed and approved according to policy. For the period from 1986 to 1991, Vera reviewers located 109 enrollments of children who participated in three approved trials while in foster care. From 1991 to 2005, 330 foster children were enrolled in 15 trials. These two periods are analyzed separately because the policy for enrollment was different in each period.

Enrollments in Approved Medication Trials and Expanded Access Programs, 1986-1991. From 1986 to 1991, 109 foster children participated in three trials approved by the commissioner (PACTG 045, PACTG 051, and the Burroughs Wellcome AZT Treatment IND). Of the 109 enrollments, 87 took place in foster care. In 81 of those 87 enrollments, Vera reviewers identified an enrollment date. The six enrollments where Vera reviewers could not determine an enrollment date (again, regulations and policy called for an enrollment to be recorded in the file) are excluded from Figure 10.7 and the analysis that follows.

Figure 10.7: Enrollments in Commissioner-Approved Medication Studies, 1986-1991

Mechanism for Enrollment in Commissioner Approved Trials, 1986-1991				
	With parental rights intact		**Parental rights severed***	
	Enrollments	**% Enrollments****	**Enrollments**	**% Enrollments**
Parent or guardian	25	36.2	0	0.0
Commissioner delegate	28	40.6	10	83.3
Notification only	1	1.4	0	0.0
No form of approval found	15	21.7	2	16.7
Total enrollments	69	99.9	12	100.0

*Parental rights are considered severed through death, surrender, or termination of parental rights.
** Percentages do not total 100.0 due to rounding.
Source: Vera file review.

Of the 81 enrollments, 69 occurred with parental rights intact. In 25 of these enrollments (36 percent) a parent or guardian signed the consent form. In 28 enrollments (41 percent), the commissioner's delegate (the PAU director) signed the consent form. These approvals were consistent with policy. In one situation, HRA received notification that a child was enrolled, but no other consent forms were found. In 15 enrollments (22 percent), Vera did not find any informed consent or approval forms in the child welfare documents.

In 12 of the 81 enrollments, the enrollment occurred after parental rights were severed. In 10 enrollments, the commissioner's delegate signed the informed consent as the child's guardian as allowed by the policy. In two enrollments, Vera reviewers did not locate any informed consent or approval forms in the child welfare documents.

Enrollments in MAP Reviewed and Recommended Medication Trials, 1991-2005. The policy for this period is described in detail in Chapter 7. To review, once the commissioner approved a trial, researchers were responsible for obtaining informed consent from parents whose parental rights had not been terminated. If the researchers could not locate the parent, they could ask the contract foster care agency to do a "diligent search" for the parent, and contract agency staff could obtain consent from the parent to enroll the child. If the contract foster care agency did not locate a parent, then the policy allowed the researcher to notify the PAU that the parent could not

be located, certify that a search for the parent had been conducted, and enroll the child in the trial.

The analysis below examines 277 of the 330 enrollments that occurred during this time. Of the 330 enrollments, 293 occurred while the child was in foster care. Of those 293 enrollments, Vera reviewers could determine the enrollment date for 277 enrollments from the information in the child welfare files, as illustrated in Figure 10.8. Without an enrollment date, Vera staff could not determine if a child was enrolled while in foster care or if parental rights were intact. Without this information, Vera staff could not analyze whether the enrollment complied with the policy for enrolling children in approved trials.

Figure 10.8: Approvals for Children Entered MAP Recommended and Commissioner Approved Trials, 1991-2005

In-Care Enrollment in MAP Recommended Trials				
	Parental rights intact		Parental rights severed*	
Approval	No.	%	No.	%
Parent or legal guardian	77	38.1	4	5.3
Notification	84	41.6	44	58.7
Foster care agency/joint guardianship	1	0.5	7	9.3
Commissioner delegate	4	2.0	2	2.7
No form of approval found	36	17.8	18	24.0
Total	202	100.0	75	100.0

*Parental rights are considered severed through death, surrender, or termination of parental rights.

PARENTAL RIGHTS INTACT: The majority of the children who enrolled in approved trials did so while parental rights remained intact (202 children or about 73 percent) (see Table 10.8). Vera reviewers found a consent form signed by a parent or legal guardian in 77 of these enrollments (38 percent). For 84 enrollments (42 percent), the clinical trial researcher notified the PAU of an enrollment in an approved trial after the parent could not be located, as the policy required. In four enrollments, reviewers found a commissioner delegate approval. For 36 enrollments (18 percent), Vera reviewers did not find any documents pertaining to consent or approval.

Vera reviewers examined the following enrollments in which the commissioner's delegate or a foster care agency signed an informed consent form even though parental rights had not been terminated:

- The contract foster care agency signed the informed consent form. According to the Vera reviewer's notes, it appears that at the time of original enrollment, the child was living with his grandfather in kinship foster care, but case managers mistakenly believed that the child had been adopted by his grandfather. The notes discuss a consent form being signed, but this form was not found. When the child's

grandfather suffered a stroke, the child "re-entered foster care," and the agency medical director signed an informed consent for the child to remain in the trial. The child's mother, who was incarcerated at this time, surrendered her parental rights later that year.

- Two enrollments were of a pair of siblings whose mother was deceased. The siblings had different fathers, one of whom had never been located. The other father had been out of contact with the agency for several years. Prior to the mother's death, she requested that caseworkers not inform the father of the child's HIV status because she feared his abuse. Despite the lack of contact, neither fathers' parental rights had been terminated when the commissioner's delegate signed the consent for the siblings' enrollment in PACTG 377. These enrollments were reviewed by an independent physician as required by the commissioner.
- In a fourth instance, the notes say the mother verbally consented to the child's enrollment but did not go with an agency worker to the hospital to sign the consent. She agreed to accompany the caseworker at a later time but was not home on the day of the appointment. When the mother did not respond to a mailgram asking her to consent for the trial, the commissioner's delegate signed the consent.

PARENTAL RIGHTS SEVERED: In 75 enrollments, a child entered a trial after parental rights were severed. In these situations, policy called for the clinical trial researcher to notify the PAU—commissioner approval for the trial had already been provided through the MAP review and commissioner approval process. In 44 of the 75 enrollments (59 percent), Vera reviewers found that the researcher had sent a notification of enrollment to the PAU as required. For joint guardianship enrollments, the foster care agency was required to notify the PAU. In seven enrollments (9 percent), the child entered through the joint guardianship provision of the policy—the foster care agency signed the consent as guardian and notified the PAU.

In 18 (24 percent) of the 75 enrollments Vera reviewers did not find a valid consent or approval documents. In two of these 18 enrollments, the birth parent signed a consent form even though parental rights were severed. In two additional enrollments, Vera reviewers could not determine the name of the person who signed on the parent/legal guardian line of the form.[696] In three of the 18 enrollments, a kinship foster parent signed the informed consent although that foster parent had not adopted the child, and no other form of consent or approval was found. For the purposes of clinical trials consent, kinship foster parents are treated the same as other foster parents and, therefore, are not authorized to sign informed consent forms. In one of those three enrollments, the physician's notes indicate that the child was enrolled in the control group and the child did not receive the experimental vaccine. In another of the three enrollments, the

[696] It is possible that these two signatures were by foster care agency staff as joint guardianship enrollments. Vera staff did not request and Vera reviewers did not have access to rosters of foster care agency staff who were authorized to sign consents as joint guardians.

mother's parental rights had not been severed when the kinship foster parent signed the consent.[697]

Enrollments Prior to Obtaining Informed Consent or Approval

In 16 enrollments, Vera reviewers found information suggesting that children were enrolled in a trial prior to its approval by HRA/Children's Services. This information should be viewed with caution, however: without access to clinical trial research records, Vera staff often had difficulty confirming the enrollment date. In some situations, Vera reviewers used the consent date or calculated the enrollment date based on other information, such as a laboratory result or progress note labeled "week x of trial y". To be conservative in this analysis, Vera staff only analyzed enrollments dated ten or more weeks before HRA/Children's Services approved the trial.

Eleven of these enrollments were in PACTG 327. PACTG 327 was a "rollover study"—it enrolled children previously enrolled in PACTG 240 (a study recommended by the MAP and approved by the commissioner). PACTG 240 compared treatment with Stavudine (also known as d4T) and treatment with AZT. PACTG 240 was unblinded and enrollment ended earlier than planned in February 1995 on the recommendation of its Data Safety Monitoring Board. The Board acted based on the results of PACTG 152, which found AZT as a single drug therapy to be less effective and more toxic than a combination of AZT and ddI. Children enrolled in PACTG 240 had the option of continuing on their study medications or changing medications and continued to be followed in the study.[698]

The PACTG 327 trial continued the research on the effectiveness of Stavudine that had been started in PACTG 240. The trial compared Stavudine alone with a combination of Stavudine plus ddI..[699] When PACTG 240 ended in August 1996, Stavudine had not yet been approved by the FDA for use in children; therefore, children leaving PACTG 240 would have had to either discontinue treatment or enroll in the Stavudine parallel track to continue on the medication. Eleven children in foster care, all previously enrolled in PACT 240, were enrolled in PACTG 327 during a three-week period near the end of August 1996. In two enrollments, a foster care agency representative signed the informed consent form as a joint guardian, and as such, did not have to wait for the commissioner to approve the trial. In three other enrollments, a birth parent signed the informed consent form. Vera reviewers did not find consent or approval documents in the other six enrollments in PACTG 327, which closed to new enrollments in October 1996. The commissioner approved the trial in January 1997.

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[697] In two other enrollments in observational trials (PACTG 219 and PACTG 219C), kinship foster parents signed the informed consent forms.

[698] Kline, M., Van Dyke, R., Lindsey, J., Gwynne, M., Culnane, M., McKinney, R., A Randomized Comparative Trial of Stavudine (d4T) Versus Zidovudine (ZDV, AZT) in Children with Human Immunodeficiency Virus Infection., *Pediatrics*, 1998; 101;214-220.

[699] NIAID, ACTG 327, Trial of Stavudine (D4T), Plus Didanosine (DDI) in Children on Long Term Stavudine Monotherapy, and Stavudine vs. Stavudine Plus Didanosine in Children on Long Term Zidovudine Monotherapy: A Roll Over Protocol for ACTG 240 Partixipants and Children receiving Prescription Zidovudine, Version 1.0 Final, June 24, 1996.

Three other enrollments that appear to have taken place while a child was in foster care but prior to the commissioner's approval of the trial took place in PACTG 051—one of the first trials considered by HRA. In two of those enrollments, the birth parent consented. In the other enrollment, Vera did not find consent documents.

In other situations, clinical trial researchers asked birth parents to sign informed consent forms weeks or months prior to a child's enrollment, and in at least one instance, asked for the parent to sign multiple informed consent forms for different clinical trials. In many of these situations, narratives by Vera reviewers indicated that birth parents were often hard to locate.

Compliance with Other Aspects of Trial Policy

The section below addresses three specific elements in HRA/Children's Services policy:

- searches by contract foster care agencies for parents not initially available to discuss consent,
- commissioner conditions for approval of enrollments in some trials reviewed and recommended by the MAP, and
- trials the MAP or the PAU disapproved and in which no children in foster care enrolled.

Search. Children's Services' policy called for foster care agencies to search for parents when clinical trials researchers could not locate them. A search consisted of a personal visit and a mailgram to the last known address. In 84 enrollments into medication trials Vera reviewers confirmed a search was necessary. In 26 of these 84 enrollments, reviewers found the notes and the mailgram receipt indicating the caseworkers carried out a search for parents who could have consented.[700] In 10 of the 84 enrollments, reviewers found documentation of a search for one parent but not the other. In six of the 84 enrollments, the child's mother was deceased, and the agency did not attempt to search for a father whose name was known but who the agency believed had never been involved in the child's life.

In 39 of the remaining 42 enrollments, reviewers found evidence such as case notes or correspondence in which the researcher or caseworker stated that a search for the parent took place, but the files lacked substantiating evidence, such as copies of correspondence and details such as dates and descriptions of attempts to visit the home. In four of these 39 situations, nursing, physician, or caseworker notes indicated that parental consent for the child's enrollment had been obtained, but no consent was found in the file.

[700] Vera staff classified some parents as legitimately unavailable to consent. This group was comprised of parents known to be deceased and fathers whose name the mother either did not know or refused to give to Children's Services. One other parent classified as 'legitimately unavailable' was a mother who had a severe mental illness and had been adjudicated in family court as mentally unfit to surrender her rights or to sign medical consents for the child.

In the remaining 3 enrollments, documentation contradicted the assertion that the parents were unavailable or had been searched for. In one enrollment, the notice of enrollment said that the parents were deceased when the mother was, in fact, alive and known to Children's Services (though not to the agency). In another, the enrollment letter stated that a search was not necessary because the child was in the guardianship of the commissioner, but reviewers noted that the parents' parental rights had not yet been severed. In the final enrollment, during the initial conversation with the caseworker about the clinical trial, the mother had refused to sign consent, citing concerns about the experimental nature of the drugs. When the mother did not respond to the caseworker's subsequent attempts to discuss enrolling the child in the clinical trial, the caseworker wrote that she had completed a search.

Medication Trials Approved with Conditions. The commissioner approved four medication trials in which children could be enrolled if specific conditions were met. This section describes how well the agency complied with those conditions. The conditions pertained to a limited number of enrollments, and staff often complied with these conditions. However, Vera found several instances that did not comply with the conditions the commissioner set for his approval of enrollments.

The commissioner required parental consent for foster children to enroll in PACTG 179 and PACTG 225. One child was enrolled in each trial, and both enrollments had parental consent. The commissioner approved PACTG 300 only for foster children who were more than mildly symptomatic with HIV/AIDS; mildly symptomatic children could enroll only with parental consent.[701] Vera reviewers checked for informed consent forms signed by parents when the children were mildly symptomatic. Reviewers identified 41 children who were enrolled in PACTG 300 while in foster care.[702] The disease stage of eight children could not be determined from available information. Although Vera staff cannot say whether or not these enrollments met the commissioner's conditions, policy and regulations required staff to record the child's disease stage in the child's file.

Of the remaining 33 children, two children were asymptomatic or mildly symptomatic. In one instance, the parent signed the consent form. In the other enrollment, the commissioner's delegate signed the informed consent after an independent consultant reviewed the situation and recommended enrollment based on the child's declining T-cell count. On the date the commissioner's delegate approved the enrollment, however, parental rights were still intact. Five

[701] The approval for PACTG 300 reads "Consent does not apply to those foster children in CDC HIV Category A1 whose only two conditions are dermatitis and recurrent or persistent upper respiratory infection, sinusitis or otitis media; they may participate only with parental consent." The Centers for Disease Control (CDC) classification takes into account both the severity of symptoms (graded N, A, B, C) and the immune function (Graded as 0, 1, 2, 3). Children with no symptoms are classified as N. Children in Class A have mild symptoms, including dermatitis, recurrent respiratory infections, enlarged liver, enlarged spleen, enlarged parotid glands, and enlarged lymph nodes. Because commissioner approval required parental consent for all children in class N and some children in class A, Vera medical reviewers examined these cases to determine which ones required parental consent.

[702] Five other children participated in PACTG 300 while in foster care. Two enrolled while outside of foster care, and the date of enrollment could not be determined for three children.

months after the consent, the PAU received a notification of enrollment certifying that a diligent search had been completed without locating the parent. Yet three weeks later, a Uniform Case Review submitted by the foster care agency indicated that the mother occasionally visited the child's siblings.

The commissioner also approved enrollment of foster children in PACTG 377 but required either parental consent or the recommendation of the child's physician, the researcher, and an independent physician. Vera reviewers identified 12 children who enrolled in PACTG 377 while in foster care during an eight-month period.[703] Three enrolled with parental consent. Two children were enrolled by the foster care agency under the joint guardianship provision (policy did not require that commissioner conditions had to be met). Of the 7 enrollments that required review by an independent physician, Vera reviewers located letters from an independent physician indicating that he had reviewed the child's medical history and recommended enrollment in the trial in five enrollments. Two other children were legally free at the time of enrollment and in the joint guardianship of a foster care agency. Vera found no consent documentation for these two enrollments.

Disapproved Trials with No Enrollments. The early part of this chapter describes trials in which foster children participated, despite the fact that the MAP had recommended against participation and the commissioner had not approved them for foster child participation. However, there are also examples of HRA/Children's Services upholding policy. HRA/Children's Services refused to approve or even to consider the enrollment of foster children in many medication trials; Vera reviewers found no evidence that children in foster care participated in those trials.

In two of these trials, PACTG 170 and PACTG 381, the MAP reviewed and did not recommend the trial and no foster children participated. In another trial, PACTG 1018, a single physician reviewed the trial and recommended against foster child participation. The agency refused requests to consent to at least six other trials. Vera reviewers found less information on these trials because no foster children enrolled in them.

Some trials that did not meet the criteria established by HRA/Children's Services were not forwarded to the MAP or an external physician for review because PAU staff determined that the protocol did not meet HRA/Children's Services' criteria. In several letters from the National Institute of Child Health and Human Development to HRA/Children's Services that discussed new developments in PACTG trials, Dr. John Moye noted that he knew that the child welfare agency did not consider Phase I trials.

In other situations, refusals to approve enrollments were based on an external consultant's review of the trial and the child's medical history. A letter to a foster care agency from HRA's general associate counsel describes why, after consulting with an external physician, HRA rejected a request to enroll a foster child in a pharmaceutical-company-sponsored trial (Glaxo Research Institute Open Label Protocol for 3TC):

[703] Two other children participated in PACTG 377, but they were enrolled prior to entering foster care.

> *The HRA lawyer wrote "current standard treatment would be to treat him with DDI, unless there are specific contra-indications. We have not been told of any contra-indications. Moreover, the use of 3TC, without having tried DDI cannot be considered a compassionate use. Therefore, we will not consent to this treatment and strongly urge your agency to do the same."*

Because the Vera review list only included children for whom Children's Services felt there was evidence of clinical trial participation, Vera staff cannot determine how often refusals to approve enrollment occurred.

Elements of the Trial Review Policy that Vera Did Not Systematically Review

There were some elements of the policy that Vera did not systematically review due to a lack of information or time constraints. These include required documentation of trial protocols for each trial, IRB approvals for each trial, and letters of agreement with each medical center for each approved trial. Vera reviewers found significant numbers of each type of document. However, in trials that were not approved by the MAP, Vera staff did not find letters of agreement and other required documentation.

The information presented above focuses on numerical measurements of compliance with policy. These numbers, however, do not capture the process of implementing the policy. This is described below.

The Consent Process. Vera reviewers wrote narratives based on information in the child welfare files that described the process by which informed consent for a clinical trial enrollment was obtained. This included information in case notes and medical progress notes; correspondence between foster care agencies, Children's Services, researchers, and parents; and copies of notification of enrollments, informed consent forms, and handwritten parental consent letters. Information from child welfare files is not equivalent to observing the informed consent process, so this information should be interpreted with caution.

Vera reviewers found information in the files that suggested that the process used to obtain informed consent met regulatory and policy requirements in many instances. In other situations, however, some or all of the process did not meet those requirements. This section discusses several issues: the knowledge of clinical trial researchers about the consent process for foster children; communication between researchers, foster care staff, and parents; and incentives to participate in clinical trials.

KNOWLEDGE OF CONSENT POLICY AND REGULATIONS: The information found in the file review and the interviews Vera staff conducted indicates that many HRA/Children's Services staff, contract foster care agency staff, and clinical trial researchers were aware that federal regulations and child welfare agency policy required that informed consent be obtained before a

child could be enrolled in a clinical trial. Many pediatric HIV physicians and clinical trial researchers knew which children they saw were in foster care and that enrolling a foster child in a clinical trial involved special procedures. The review of correspondence between clinical trial researchers and the PAU indicates that some clinical researchers knew details of the policy as well. In the first narrative excerpt below, the clinical trial researcher knew that the commissioner had to approve the enrollment even though the parent had given consent. In the second, the clinical trial researcher understood that a kinship foster parent could not provide consent.

> *The files contained a request for consent from the researcher. He writes "Dear [PAU Director], This [child] is a 7 month old female with HIV infection. During the last few months, she required several hospitalizations due to pneumonia, sepsis with meningitis group C, failure to thrive, esophagitis, oral thrush, septic arthritis, and synovitis. The infectious disease unit carefully evaluated this patient and we feel she can benefit from protocol [PACTG] 051. An informed consent was obtained from the mother and pre-entry blood work will be done in the next few days.*

> *The doctor wrote to the PAU,"[Name of child] is an 8 year old in kinship care. Her mother is deceased and she has been with her grandmother since the age of 2. She has been on AZT for several years. Recently she has dropped her T cell count [to] <200 and has several bacterial infections as well as loss of appetite. She is eligible for ACTG 245. This is a salvage protocol for children who have failed previous antiretroviral treatment. It offers different combinations of AZT, DDI and nevirapine. Her maternal grandmother is interested in enrolling. She is ready to sign an informed consent. Although [name of child] has been with her for years I understand that CWA is the legal guardian. I am asking for consent.*

In some instances, the child welfare files contain information indicating that the policy and possibly regulations were not followed. The Vera reviewer wrote:

> *The child was enrolled in clinical trial PACTG 190 in 1992. Three months after the enrollment the foster care agency nurse wrote a letter to the child's doctor requesting to know "when ZDV was discontinued and when ddC and ZDV was started and who gave permission to do so." The physician replied that the child and her sibling "are followed by us at the immunology clinic as they are part of the clinical trial groups. Before participating in this clinical trial, they were on AZT. Upon enrollment a second drug was added on to what they were already getting, that is ddC. These combination therapies are found to be more beneficial to HIV infected patients. We understand that these children are in foster care, so that appropriate permission from ACS about these medications given to them is in progress." A notification letter is seen in the PAU files dated a month and a half after the physician's letter to the foster care agency. No consent is found in files reviewed.*

Vera's interviews with clinical trial researchers and information in the child welfare files suggest that the clinical trials researchers who participated regularly in MAP reviews appeared to

have a better understanding of the special issues involved in obtaining informed consent to enroll children in foster care than their peers who did not participate in MAP reviews.

COMMUNICATING WITH PARENTS: Vera's review found that communicating the required information for an informed consent to the parents of foster children who were being considered for clinical trials enrollment was fraught with challenges. These challenges included locating parents, ensuring that parents understood the risk of possible harm and the anticipated benefits of a trial, and responding to situations that arose frequently but were not covered by the written policy.

LOCATING PARENTS: Though the information in the files indicates that some parents kept in regular communication with medical providers and foster care agency staff, many others did not. Parents often did not have stable addresses or lived on the street, in homeless shelters, or were incarcerated, and often did not have the resources to travel to appointments. The Vera reviewer wrote:

> *In 1999 the agency nurse sent a letter to the mother stating, "your daughter is very ill and we need to speak with you—please call; I am enclosing a token; you may come directly to the agency—we have papers to be signed; it is very urgent." The next day the mother signed a letter giving consent for her daughter to receive Amprenavir "under study by Glaxo Wellcome."*
>
> *The child's T-cell count was 54, and the doctor requested that the child be placed on AZT therapy as soon as possible. Consent was to be obtained from the mother and from HRA. The case worker visited the mother at the hospital, where she had been admitted for pneumonia. She appeared weak, but alert and oriented. She was counseled about the consent process and she signed the consent form the following day. Her doctor attested to her ability to sign and understand the consent form.*

In some instances, the files documented that the case workers made efforts to locate parents that were unsuccessful. This example illustrates both the types of efforts made and some of the difficulties involved in communicating and maintaining confidentiality. The Vera reviewer wrote:

> *In 1992, a letter from a caseworker to the child's mother requests her permission for the child to enter the trial. One week later, the agency case worker wrote to the physician, "I have made the required diligent efforts to contact the [mother], seeking her permission to participate in protocol 152. I first attempted to contact her through a mailgram…[The next day] I personally went to her last known address carrying a letter which explained the protocol and the need for consent, and the medical consent form. There was however no answer when I rang the doorbell. I rang other doorbells in the building in an attempt to get inside the front door and to the mailboxes, but no one would let me in. After half an hour of waiting outside, I put the letter and the consent form inside an envelope,*

> *addressed it to the mother and slid it under the door. I have waited four business days but have gotten no response…please contact PAU to seek approval through them."*

Vera reviewers also found notes showing that HRA requested proof of a diligent search. The reviewer wrote:

> *In a letter in 1991, HRA refused to give consent, reminding the agency of the regulations governing informed consent, emphasizing that HRA would consent only after the agency had provided proof of a diligent search for mother.*

Sometimes foster care staff located a parent, but the parent missed one or more appointments to discuss the clinical trial. The policy allowed the clinical trial researcher to enroll the child when the parent "could not be located," but in several instances the files indicate that this was also applied to situations where the parent had been located but was unavailable for discussion with the agency or with the researcher. In one enrollment, a parent missed four appointments to discuss the clinical trial. In several situations where parents missed appointments with researchers or foster care staff, children were enrolled in trials.

UNDERSTANDING THE RISKS AND ANTICIPATED BENEFITS OF A TRIAL: When either research or foster care staff made contact with a parent, they had to explain complex medical information to the parent. Parents also faced challenges in understanding the decision that researchers and child welfare workers were asking them to make. Though the federal regulations say the informed consent forms "shall be in language understandable" to the person being asked to sign, Vera reviewers found this was often not the case.[704] In some trials, the informed consent form included a simplified, one or two page version in common language. Vera reviewers, however, usually did not find simplified versions of the informed consent forms in the child welfare files. Instead, informed consent forms were often six to ten pages long and contained technical language that would be difficult for people without a medical background to understand.

Vera saw several instances where a child was not enrolled in a trial because either a parent refused a request to sign an informed consent form or had the opportunity to sign an informed consent form and did not. The Vera reviewer wrote:

> *The mother met with the doctor in 2001; during this meeting she was informed of her child's HIV status, and she was appropriately sad. The mother asked questions about the protocol (PACTG 345) and took home a copy of the consent form to look over and bring back the next week. According to hospital notes, she did not come back. The child did not participate in the trial.*

[704] 45 CFR 46.116.

In at least one enrollment, foster care agency staff who could not obtain informed consent from one parent asked the other parent. The Vera reviewer wrote:

> *In 1990, physicians requested consent to place the child in the B-W AZT IND. The mother signed the informed consent form and then withdrew her consent the next day. Agency staff located the father and he signed the consent form. The mother was described in agency progress notes as exhibiting bizarre behavior at times and using phencyclophenidate ("angel dust").*

Communicating with parents who were actively using drugs or suffered from medical and mental health problems presented a challenge to the informed consent process. The federal regulations described in Chapter 6 call for a person approached to consider signing an informed consent for a child to have "sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence."[705] In some enrollments where a child's parent was a substance user, there is a note in the file that specifically indicates that the parent was sober during the discussion about the trial and when consent was signed. At its most extreme, the notes describe medical or mental health issues that made the parent incompetent to sign. The Vera reviewer wrote:

> *The caseworker visited her in the hospital to explain PACTG 152 and wrote of the visit, "she looked thinner; she didn't want to talk to me and seemed preoccupied. I explained why I was there. She agreed to sign consent for protocol 152. She said, 'I have to get rid of these leeches inside of me' – told me she's scratching all the time because they are inside her." Other notes indicate that the mother "completely loses track of conversations."*

SITUATIONS NOT ANTICIPATED BY THE WRITTEN POLICY AND IRREGULAR CONSENTS: The narratives describe many variations in the consent process that do not follow standard practice. In several files, there were handwritten notes signed by parents for enrollment in specific trials or agreeing to clinical trial participation generally, but there was no IRB-approved signed informed consent form. The narratives also describe situations where clinical trial researchers enrolled children after discussing the trial and receiving verbal consent on the telephone. In some of these situations, the files documented efforts to obtain consent, contained explanations of why obtaining consent was difficult, and/or had requests to the PAU asking how to proceed. The Vera reviewer wrote:

> *The files contain a letter from the clinical trial researcher (who was also the child's pediatrician) that read "I would like to update you regarding the status of [ ], an HIV infected infant currently residing in an agency foster home. I have received verbal permission from his mother to enroll him in clinical trial #152. The mother states that she is physically abused by FC's father and that he does not allow her to leave her home.*

[705] 45 CFR 46.116.

> *This is why she has been unable to come in for appointments. I have referred her to a battered women's shelter. Please let me know if there is any other documentation required to begin [ ] on treatment.*

INCENTIVES TO PARTICIPATE IN CLINICAL TRIALS: Vera reviewers were instructed to record any instance of incentive payments or gratuities for clinical trial participation. Vera reviewers found no evidence of incentive payments to parents, children, foster parents, foster care agencies or staff, or HRA/Children's Services staff or the agency itself.[706] Where Vera staff obtained protocols for clinical trials, staff found no evidence in the protocols of incentive payments to children in foster care, foster parents, birth parents, foster care agencies or staff, or HRA/Children's Services staff or the agency itself for participation in clinical trials. During interviews with Vera staff, some researchers indicated that the budget for conducting a clinical trial included funds used for children and their caregivers to travel to and from appointments and for meals taken while at a clinic appointment.

Participants in clinical trials received enhanced monitoring available through clinical trials that would not otherwise be covered by Medicaid.[707] Vera found no indication in trial protocols that caregivers for children in foster care were to be treated differently than parents and other caregivers of children who were not in foster care. Vera found no evidence that foster parents whose foster children were enrolled in clinical trials were treated or received different financial support than foster parents caring for HIV-positive children not enrolled in a clinical trial. Any foster parent taking care of an HIV-positive child qualified for a "special exceptional rate"—a higher rate than the typical foster care reimbursement designed to compensate these foster parents for the higher costs of taking care of an HIV-positive child. The rate was not connected with clinical trials participation.

Access to free medication was often cited as one of the benefits of clinical trials enrollment. For example, one Vera reviewer wrote:

> *A "Placement medical history" form dated 1989 located in the case planning files states that "doctor advised nurse of need for social worker, doctor, and the mother to meet for discussion and consent of treatment. Possibilities discussed by doctor were 1) IV immunoglobulin q mo 2) AZT at a cost of $10,000 per year 3) AZT or placebo…"*[708]

[706] In one instance, the notes say a clinical trials researcher "took the mother out to lunch" where she signed an informed consent form granting permission to enroll her child in a clinical trial and that the researcher referred her to a medical clinic for her own treatment. The notes do not describe any cash payments taking place. In one other case, the child welfare files contain a letter from a doctor to a parent of a child in foster care asking for the parent to consent to a child's enrollment in a clinical trial. The letter said that the child would receive "free medical care" as a result of participation. Children in foster care qualify for Medicaid, making the promise of free medical care irrelevant.

[707] Monitoring included more frequent visits to a physician and more frequent laboratory tests. See Chapter 8 for more information on clinical trials monitoring.

[708] The names of the nurse, the social worker and the mother, which appear in the original quoted material, were removed to preserve the child's confidentiality.

Until New York State revised its reimbursement policy for the cost of HIV/AIDS medications for children in foster care in the early 1990s, some foster care agencies incurred substantial costs for children prescribed antiretroviral medications outside of a clinical trial. In an interview, an executive director at one foster care agency with a specialized HIV placement program recalled telephoning New York State officials to tell them that the agency could no longer afford to pay for HIV/AIDS medications as doing so jeopardized the agency's survival. Soon after the call, the State agreed to pay for HIV/AIDS medication for foster children.

Vera did not attempt to examine whether or not pharmaceutical companies made contributions to foster care agencies and did not request documents pertaining to charitable donations to foster care agencies. Neither the policy documents nor the child welfare files mention any contributions to foster care agencies from pharmaceutical companies.

Appointments of Independent Advocates. As described in Chapter 6, federal research regulations require the hospital institutional review board to appoint an independent advocate for foster children enrolled in some types of clinical trials. In brief, trials that the IRB approved under 45 CFR 46.406 or .407 required an independent advocate; trials approved under 45 CFR 46.404 or .405 did not. The letter of agreement between HRA/Children's Services and medical centers discussed in Chapter 7 mandated that hospitals appoint independent advocates when required by 45 CFR 46.409.

Vera did not have access to IRB minutes from medical centers that conducted the trials. (Efforts by Children's Services to arrange access to this information are described in Chapter 2.) Without the IRB minutes, Vera could not identify the trials in which an IRB approved a trial under 45 CFR 46.406 or .407. HRA/Children's Services' policy required that each institution produce proof of IRB approval, but the policy did not require that the institution identify the category under which the IRB approved the research.[709] The PAU did not appear to systematically collect this information, though PAU staff sometimes knew that a particular trial at a particular institution required the appointment of an independent advocate for each foster child.

Findings Regarding Independent Advocates. Vera reviewers recorded the names of independent advocates when they were noted on enrollment notifications or other forms. Vera reviewers found documentation that independent advocates had been appointed for 152 enrollments in medication trials and for 167 enrollments overall.[710] Most independent advocates (91 percent) were appointed in medication trials. Independent advocates were also appointed for 14 enrollments in observational trials and one enrollment in the Burroughs Wellcome AZT Treatment IND (see Figure 10.9).[711]

[709] In MAP recommended and commissioner approved trials, Vera found numerous IRB approval forms from many different hospitals. Vera did not systematically analyze this information.
[710] Vera also identified independent advocates in 14 enrollments in observational trials.
[711] The federal regulations suggest that an independent advocate would not be required for the child enrolled in the Burroughs Wellcome AZT Treatment IND. As a treatment IND, the trial would not appear to fit the criteria for 45

Figure 10.9: Assignment of Independent Advocates for In-care Enrollments

	In-care enrollments	In-care enrollments with independent advocate	
	No.	No.	Percent
Medication trials	397	144	36.3
Expended access programs	68	1	1.5
Total	**465**	**145**	**37.8**

Independent advocates were assigned to children in 13 of the 65 medication trials in which children in Vera's review were enrolled (see Figure 10.10). Vera staff cannot determine, however, if independent advocates were required in any of the trials in which they were not appointed. Furthermore, Vera staff cannot determine if an independent advocate might have been required at one clinical trial site but not at another site for the same trial. IRBs at different sites might have approved the same trial under different categories in the federal regulations. An IRB that approved a trial under 45 CFR 46.405 would not have to appoint an independent advocate, but an IRB that decided to approve the trial under 45 CFR 46.406 would have to appoint an independent advocate.[712] Of the 13 trials with independent advocates, 11 were approved by the commissioner.

Figure 10.10: Assignment of Independent Advocates by Trial

Clinical trial	Phase	In-care enrollments**	In-care enrollments with independent advocate appointed	
		No.	No.	Percent
NCI 91-C-01	UTD*	1	1	100.0
PACTG 218	I	3	1	33.3
PACTG 138	II	6	1	16.7
PACTG 190	II	17	11	64.7
PACTG 240	II	31	12	38.7
PACTG 327	II	10	3	30.0
PACTG 338	II	18	3	16.7
PACTG 152	III	108	77	71.3
PACTG 245	I/II	15	3	20.0
PACTG 377	I/II	13	2	15.4
PACTG 045	II/III	13	1	7.7
PACTG 144	II/III	25	14	56.0
PACTG 300	II/III	41	15	36.6
Total		301	144	47.8

*Vera staff were unable to determine the phase of this trial.

** This table excludes enrollments where Vera staff could not determine if the enrollment occurred while the child was in foster care or out of foster care.

CFR 46.406 or .407 since, by definition, it involved the possibility of direct benefit. It has been excluded from the analysis below.

[712] See Chapter 6 for a description of when an independent advocate is required.

In reviewing policy documents and correspondence between the PAU and the clinical trials researchers, Vera found documentation that, in some situations, the PAU actively checked whether or not an advocate had been appointed and requested the advocate's name. The following letter is in reference to several children enrolled in PACTG 152:

> *I have not received enrollment forms for [child's name]. Additionally, if there are other children enrolled in a clinical trial for which you are Principal Investigator [clinical trial researcher], please send to me a completed enrollment form for each. Finally, may I ask you to re-read the letter of agreement to enrollment of foster care children in clinical trials you signed and entered into on October 10, 1991 particularly with respect to an enrolled child's Independent Advocate… For several of the children for whom you submitted enrollment forms, CWA was inappropriately identified as the child's independent advocate. Please review copies of the completed forms you have sent me to date to appropriately identify the independent advocate for the children enrolled in trials.*

The researcher to whom it was addressed responded by giving the name of an independent advocate who, the researcher says, "sits on the local Institutional Review Board and goes over the protocols along with other members of the board." The regulations allowed independent advocates to serve on the IRB.

Whenever possible, Vera medical reviewers recorded the name of the independent advocate and the relationship of that person to the child, the agency, or the medical facility. If the relationship was not clear, Vera staff did an electronic search for the person.

Vera found that some of the independent advocates did not appear to meet the federal regulation requirement that the advocate be a person "who is not associated in any way (except in the role of as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization."[713] Among the people listed as independent advocates were foster parents, research nurses, researchers and physicians at the hospital where the research was conducted, and hospital social workers. Vera project staff were unable to identify some of the people named as independent advocates. In at least six enrollments where Vera reviewers found that an independent advocate had been appointed, the independent advocate had relationships with the researchers, the institution, or the foster care agency that the federal regulations specifically bar.

Vera staff attempted to interview three of the people who were listed as independent advocates and were able to interview two. One person declined Vera's request for an interview, saying that he/she did not recall being an independent advocate. A second person listed as an independent advocate was interviewed by Vera staff but did not recall having been an

[713] See 45 CFR 46.409. As discussed in Chapter 6, the regulations are open to interpretation in some cases regarding the types of associations. For example, the regulation is not clear as to whether a physician at the same institution and in the same department as the clinical trial researcher or other members of the research team could be considered to be associated with the research.

independent advocate. The other independent advocate that Vera reviewed described a lack of clarity as to what was expected of him/her in this role.[714]

Vera reviewer narratives described only one child for whom the independent advocate played an active role. The mother had, at times, expressed disagreement to the foster care agency with the child's participation in the trial, but she had repeatedly failed to keep appointments with the child's doctor to discuss the child's medical care, including the trial. The independent advocate recommended that the child remain in the clinical trial.

To summarize, Vera found that the regulatory requirements for the independent advocate were poorly understood by IRBs and by clinical trials researchers. Because project staff were unable to review IRB minutes from most of the institutions where clinical trials were conducted, the categories under which the IRBs approved the trials are unknown. Therefore, this report cannot determine whether or not independent advocates were required for compliance with federal regulations and Children's Services policy.

Conclusion

This chapter describes compliance with a complex set of procedures and regulations that changed over time and depended on the status of parental rights, the availability of the parent, and the type of trial involved. The record of complying with these procedures and regulations was mixed. In some situations, particularly in commissioner approved studies, clinical trials researchers, child welfare staff, and foster care agency staff commonly followed the procedures outlined in policy documents as well as state and federal regulations. In other situations, few of the written the rules and regulations were followed. Like the procedures and regulations themselves, assessing compliance is a complex undertaking.

The next chapter summarizes the findings from this study and offers Vera's recommendations for future clinical trials policy.

[714] Vera is not revealing the gender of the person because the person interviewed anonymously.

Chapter 11: Findings and Recommendations

Chapter Summary

This chapter begins with a summary of the key findings of the Vera study. It then discusses the implications of the findings for clinical trials policy and presents perspectives on this controversy. Finally, the chapter presents the recommendations of the Vera Institute of Justice and the Vera Clinical Trials Advisory Board that stem from the findings.

During the course of this study, Vera staff learned of an array of perspectives on whether children in foster care should participate in clinical trials. These perspectives range from the view that foster children should never participate in clinical trials to the view that children in foster care should have the same access to developing treatments as any other children. Although the perspectives Vera staff heard often took one of these two positions, in practice a continuum of situations exists in which foster children might be considered for participation in a clinical trial. Jurisdictions must decide where to locate policy on that continuum and then provide the resources to enable their policy to be carried out effectively.

This chapter discusses this continuum with the premise that these decisions rest with elected representatives and appointed officials, with input from the affected communities and other stakeholders, such as advocacy organizations and medical and child welfare professionals.

Summary of Findings

Starting in the late 1980s, New York City's child welfare agency decided to allow children in foster care to participate in HIV/AIDS clinical trials under certain conditions. Commissioners of social service under four administrations approved this policy. The Vera Institute's review of the child welfare files of 796 children identified 532 New York City foster children who participated in 88 clinical trials and observational studies between 1985 and 2005.

Vera researchers found little or no evidence for some of the concerns described in Chapter 1 that prompted Children's Services to initiate this study.

1. Many children—inside and outside of foster care and clinical trials—died because of complications of HIV/AIDS during the late 1980s and 1990s. Eighty of the 532 children who participated in clinical trials or observational studies died while in foster care; 25 of them died while enrolled in a medication trial. Vera staff did not identify any child death caused directly by taking a clinical trial medication. A detailed review found that 22 of these 25 children had developed multiple AIDS related complications prior to their enrollment in a clinical trial; several were enrolled in "salvage protocols" and expanded access programs when no other treatment options were available. Three children who were mildly to moderately symptomatic from

HIV disease died while enrolled in clinical trials—one from meningitis, one from pneumonia, and one from a respiratory illness.[715]

2. As part of this project, Children's Services asked the New York City Department of Health and Mental Hygiene (DOHMH) to identify the mortality rate of children in Vera's review with that of all children in New York City with HIV.[716] DOHMH databases contained information on 531 of the 796 children on Vera's review list. Twenty-nine percent of these children had died by 2006 compared to 35 percent of all HIV-infected children born in New York City between 1981 and 2004. Though not conclusive, these data suggest that HIV-positive foster children who were enrolled in clinical trials and/or observational research studies did not experience an increased risk of death from their enrollment.
3. The child welfare files contained information indicating that some children experienced serious toxicities, such as reduced liver function or severe anemia, related to clinical trial medications—especially AZT.[717] The toxicities Vera staff identified were consistent with toxicities described in published articles about the trials. Most of the severe toxicities took place during the late 1980s and early 1990s, when few or no FDA-approved treatment options existed for children with HIV/AIDS. For children for whom Vera reviewers found documentation of toxicity from the clinical trial medications, the reviewers also found records indicating that physicians in charge of the clinical trial made adjustments to the children's treatment as required by the clinical trial protocols. Citing confidentiality laws, the New York State Department of Health (DOH) refused a request from Children's Services to use its supervisory authority to allow staff from the Vera Institute or Children's Services to review clinical trial research or medical records. The DOH refused subsequent requests from Children's Services that sought to allay the confidentiality concerns the DOH raised. This limited Vera staff's ability to fully document the frequency and severity of toxicity or the individual outcomes of trial participation for the children in the review.
4. Each clinical trial protocol included a set of inclusion criteria related to the child's age, documentation of HIV status, and degree of illness.[718] Children who did not fit the inclusion criteria were not supposed to enter the trial. Trial protocols also had a set of exclusion criteria, and children having any of those criteria could not participate in the trial. Where documentation allowed reviewers to make a determination, children in foster care met age, HIV status, and disease stage criteria for entering the specific trials in which they were enrolled. Of the 532 children who participated in clinical trials or observational research studies while in foster care, reviewers found

[715] Chapter 9 of this report describes how Vera made this finding.
[716] Chapter 5 discusses these data in more detail.
[717] Chapter 9 and Chapter 2 of this report describe these findings.
[718] Chapter 9 discusses inclusion and exclusion criteria.

two children who appeared to meet exclusion criteria (one child whose birth weight was below the required minimum and one child with abnormal liver function tests) for the medication trials in which they were enrolled.

5. Of the children who participated in trials for HIV-infected children, Vera staff identified two children who participated in a trial who were HIV exposed, where evidence suggested that the children *might* not have been infected with HIV.[719] Vera project leaders informed Children's Services about these children. Children's Services subsequently responded that inquiries to state and local agencies had confirmed a diagnosis that made it appropriate for one of the children to participate in the clinical trial. Children's Services has not provided additional information on the second child, but the child welfare files indicated that the child died of causes unrelated to clinical trials participation.
6. In 1988, when New York City officials first considered the participation of foster children in clinical trials, the agency conducted a year-long review of state and federal research regulations. The social services commissioner and his staff were aware of concerns about the participation of African American and Latino children in medical research and they consulted with several medical experts, including the National Medical Association (an organization of physicians of African descent). The standard that New York City's child welfare agency developed for approving trials—that every child in foster care enrolled in a trial have the possibility of benefit—exceeded the standard required by federal regulations. The policy also required that researchers obtain informed consent from a birth parent where parental rights remained intact.[720]
7. To speed the approval process, the child welfare agency changed its policy in 1991. The new policy called for a medical advisory panel (MAP) of physicians to review and make a recommendation to the commissioner on whether a trial met Children's Services standards for approval. Seventy-six percent of all foster child enrollments in medication trials were in 15 trials recommended by the MAP and approved by the commissioner. In trials where the commissioner authorized approval only under specific conditions, the conditions were followed in most circumstances.[721]
8. Once the commissioner approved a trial, Children's Service's policy required researchers to obtain informed consent from a parent if parental rights were intact. If a researcher could not locate a parent, then policy required the foster care agency staff to search for the parent. If this search proved unsuccessful, then Children's Services would approve the enrollment after the researcher certified that the foster care agency staff had made a search. If parental rights had been terminated or the parents were

[719] Chapter 9 of this report describes how Vera made this finding.
[720] Chapter 7 of this report describes how Vera made this finding.
[721] Chapters 7 and 10 of this report discuss the medical advisory panel and its compliance with standards set by child welfare staff.

deceased, consent was given by the commissioner, a delegate of the commissioner, or the foster care agency (for children in joint guardianship).[722] In MAP-recommended and commissioner-approved trials, this consent process took place most of the time. Of 202 enrollments in MAP-recommended medication trials where parental rights remained intact and Vera reviewers identified an enrollment date, reviewers found informed consent forms signed by a parent or legal guardian in 77 (38 percent) of the enrollments. In 81 (40 percent) of the 202 enrollments, Vera reviewers saw evidence of a search for parents, although a parent was not located (many of these parents did not have fixed addresses and at times lived in shelters or on the street). In the remaining 44 enrollments (22 percent), Vera reviewers did not find informed consent or approval documents.

9. In many files Vera staff found documentation indicating that researchers discussed the risks and potential benefits of trial enrollment with a birth parent and that the parent then gave permission to enroll the child. In several instances, parents did not want their children in a clinical trial and the child did not participate in the trial.[723]
10. Children in foster care did not appear to participate in HIV/AIDS clinical trials at rates that suggest they were specially targeted for enrollment. Foster children made up 30 percent of all New York City enrollments in 16 trials of medical interventions for which New York City-level data were available (all sponsored by the National Institutes of Health). The few estimates of the percentage of HIV-exposed and -infected children who spent any time in New York City foster care during this period are between 20 and 40 percent. Children in the Vera review group were not a majority of participants in any of these clinical trials. Thirteen percent of all medication trial enrollments identified by Vera reviewers occurred prior to the child's entry into foster care and extended into the period when the child was in foster care.[724]
11. Children in foster care who participated in HIV/AIDS clinical trials were predominantly African American and Latino (64 percent were African American and 30 percent were Latino).[725] This demographic profile parallels the demographics of children with HIV infection in New York City (58 percent were African American, 35 percent were Latino). Compared with the demographics of children with HIV in the United States, however, white children are underrepresented and Latino children are overrepresented as a group in New York City and in the group of children in the Vera study.
12. The Vera review found no instances of children being removed from their families by Children's Services because a parent refused to consent to the child's participation in a clinical trial.[726] For three of the 796 children in Vera's review, the files included

[722] Chapter 7 of this report describes these policies. Chapter 10 discusses how often the policies were followed.
[723] Chapter 10 of this report discusses this finding in more detail.
[724] Chapter 8 of this report describes how Vera made this finding.
[725] Chapter 5 of this report describes how Vera made this finding.
[726] Chapter 5 of this report describes how Vera made this finding.

discussions of clinical trial participation during a child protective investigation. These three investigations did not result in removals, however. Child protective investigations of abuse and neglect of children in Vera's review were most commonly triggered by positive drug screens of newborn babies. A majority of children in Vera's review entered foster care from hospitals as infants and three quarters of the children in Vera's review entered foster care before age one year. Parents of the children in clinical trials faced many problems, including poverty, substance use, unstable housing, unemployment, and social isolation. These challenges were exacerbated in many cases by the impact of HIV and AIDS on child and parental health and by a lack of available, appropriate, or effective social services.

13. Several files documented differences of opinion between child welfare staff and both birth and foster parents concerning antiretroviral medications prescribed *outside of clinical trials* and *after the approval* of the medication by the FDA. In these situations, child welfare staff followed New York State policy concerning medical neglect that mandated that parents administer medications prescribed by a doctor to their children. The differences of opinion were resolved on a case-by-case basis. Sometimes this involved continued monitoring and alternative treatments. In other situations, concerns that children might develop resistance to medications if the medications were not taken consistently or evidence that a child's condition was worsening (increased viral load or dropping CD-4 cell counts) resulted in child removals and placement transfers.[727] None of the removals or transfers resulted from a parent's refusal to administer medications distributed through a clinical trial, however.
14. The Vera review found no evidence that children, parents, foster parents, foster care agencies or staff, or child welfare agencies or staff received incentive payments for children to participate in clinical trials.[728] Vera's study of this issue was limited to information in child welfare, policy files, and public information from the NIH on the funding of their clinical trials.

The Vera review also found evidence that supported some concerns about the participation of foster children and their families in clinical trials. This evidence includes violations of state regulations, Children's Services' own policies for clinical trial review and enrollment, and federal regulations for protecting human subjects. [729]

1. Child welfare agency policy after 1991 called for a review of clinical trials by a Medical Advisory Panel and approval by the commissioner. This was a widely

[727] Chapter 5 of this report describes how Vera made this finding.
[728] Chapter 10 of this report describes how Vera made this finding.
[729] Chapter 7 of this report describes Children's Services' clinical trials policy from 1985 to 2005. Chapter 6 describes federal regulations regarding the participation of people in research. Chapter 10 of this report identifies violations of specific regulations and policies.

disseminated policy distributed on three separate occasions under three different commissioners. This review policy was not followed in 37 medication trials in which 80 children in foster care participated:

a. Twenty-one children participated in three medication trials that the MAP reviewed and did *not* recommend and the commissioner did not approve. Thirteen of these enrollments took place before the children entered foster care.
b. Thirteen children participated in four medication trials that had been reviewed by the MAP but a recommendation was not forwarded to the commissioner. Two of these enrollments took place before the children entered foster care.
c. Sixty-four children participated in 30 medication trials that were not reviewed by the MAP reviewed. Thirteen of these enrollments took place before the children entered foster care.

Of the 30 medication trials not reviewed by the MAP, four were reviewed, instead, by an independent physician consultant. A consultant recommended two of the four trials, and ten foster children participated in these two trials. A consultant reviewed and did *not* recommend the other two trials, and four foster children participated in these two trials. Written child welfare policy did not mention this alternative review process. Two of the 30 medication trials not reviewed by the MAP took place at the National Institutes of Health. Twenty four medication trials received no review by an independent consultant or by the MAP. Forty-six foster children participated in those 24 trials.[730]

2. Regulations and policy required the child welfare agency have on file the informed consents, commissioner approval documents, and other documentation for each trial and each enrollment. No informed consent or approval documents were found in the child welfare files of 21 percent of the enrollments in medication trials that Vera reviewers confirmed took place while the children were in foster care. Some consent documents were incomplete and did not have required signatures or dates.
3. Each trial sponsored by the National Institutes of Health was monitored by an organization charged with ensuring that an informed consent document was present in the research records for each child. Without access to clinical trial research records, which the New York State Department of Health denied, it is not possible to say whether or not an informed consent document existed in every case or that the legally authorized person signed the informed consent form for the child to enroll in the trial.[731]

[730] Chapter 10 of this report describes how Vera staff made this finding.
[731] Chapter 2 discusses efforts made by Children's Services to arrange access to clinical trials research records and hospital medical records.

4. In at least 16 enrollments in medication trials, Vera staff found that children in foster care appeared to have been enrolled in a trial *prior* to the commissioner approving the trial. In four of these enrollments, the parent signed the consent form, and in one enrollment a commissioner delegate approved the enrollment. In 11 of the 16 enrollments, Vera reviewers did not find consent documents in the child welfare files. In addition, a small number of reviewer narratives discuss requests for backdating consents or consents requested retroactively—though notes indicate that these requests were denied. In some of these instances, the Human Resources Administration/Children's Services spent several months reviewing the trial before approving the trial.[732]
5. In at least seven enrollments, a person who was not legally authorized to do so signed an informed consent form. In two of these enrollments, the birth parent signed although parental rights had been terminated. In at least five enrollments, the foster parent signed the informed consent. In four of these enrollments, the child was in a kinship placement.[733]
6. Federal regulations required informed consent forms to be written in accessible language. Many informed consent forms contained technical language difficult for people without a medical background to understand.[734]
7. The role and requirements of the independent advocate described in federal research regulations were not well understood by clinical trials researchers and, in some situations, child welfare staff. Child welfare staff knew that federal research regulations required hospital Institutional Review Boards(IRBs)—which review research to ensure that it complies with federal research regulations—to appoint independent advocates for foster children in certain types of clinical trials. Letters of agreement with medical centers conducting clinical trials referenced the regulation, and hospital IRBs appointed an independent advocate in 152 enrollments in medication trials.[735] The information that the child welfare agency collected, however, did not allow child welfare staff or Vera reviewers to identify when an independent advocate was required. This is a particular concern, given that the Office for Human Research Protections conducted several investigations into this issue at institutions across the nation and found that 19 IRBs neglected to make these determinations.[736] Thus, Vera staff could not determine if an independent advocate was appointed in all instances where an independent advocate was required. In at

[732] Chapter 10 discusses how Vera staff made this finding.
[733] Chapter 10 discusses how Vera staff made this finding.
[734] Chapter 10 discusses how Vera staff made this finding.
[735] Chapter 6 of this report describes the regulations concerning independent advocates. Chapter 7 describes the letter of agreement.
[736] The Office for Human Research Protections (OHRP) is part of the federal governments Department of Health and Human Services and is responsible for enforcing federal research regulations regarding people participating in research. Chapter 6 describes the determinations made by OHRP cited here.

least six enrollments where Vera reviewers found that an independent advocate had been appointed, the person appointed had relationships with the researchers, the institution, or the foster care agency that the federal regulations specifically bar. Two of the people listed on consent forms as independent advocates did not recall serving as an independent advocate. Based on interviews and narratives, independent advocates did not actively monitor foster children in clinical trials.[737]

8. Child welfare files described several deviations from the processes required by federal regulations and Children's Services' policy. These situations included handwritten notes for informed consent instead of official documents, consent accepted over the phone, and parents whose consent was sought or obtained but who appeared not to have been competent to provide informed consent. In at least two instances, the notes indicate that parents' wishes were ignored. In several situations, parents were described as "unable to be located" after they missed one or more appointments to discuss clinical trials. In two instances, clinical trial researchers reported inaccurate information on a parent's legal status, though Vera staff could not determine if this was done intentionally or unintentionally. In some situations, the request for consent was made in ways that might have been perceived by parents to be coercive. The situations described in this finding were often unique or had other circumstances that made compliance with policy and regulations challenging. Nonetheless, the informed consent process in these situations did not conform to federal regulations or child welfare agency policy.[738]
9. Although state regulations mandated that Children's Services ensure the retention of most of the child welfare files that Vera staff was asked to review, for 30 percent of the children, some part of the child welfare file was lost, destroyed, or otherwise unavailable. In most of these situations, the unavailable material was a contract agency case planning file. In some situations, such as a documented instance of a warehouse fire, the records' absence is understandable. In others, the documents were missing without reasonable explanation. Though case planning files are maintained by contract foster care agencies, state regulations make Children's Services ultimately responsible for their retention and maintenance. The files of agencies that no longer provide foster care were especially difficult to locate.
10. Records often did not contain documentation mandated by state regulations. In some instances, documents covering years of a child's stay in foster care were missing. Other files did not meet state requirements for recording medical information about a child in foster care.[739]

[737] Chapter 10 discusses how Vera staff made this finding.
[738] Chapter 10 of this report and its appendix describes these situations.
[739] Chapter 10 describes the regulations and the content and availability of files. Chapter 10 describes the impact of this finding on this study.

11. Although New York State regulations required child welfare agencies to collect information related to HIV testing, HIV medical care, and clinical trials enrollment, the record keeping at the Pediatric AIDS Unit (PAU), especially after 1995, did not allow child welfare and public health officials to know consistently or accurately the number of foster children tested for HIV, their HIV status, whether they were enrolled in clinical trials, or the trials in which they were enrolled. Problems with the PAU's record keeping after 1995, including defects in the unit's electronic database, were noted in the unit's quarterly reports to supervisors and state officials, including the AIDS Institute.[740]
12. Vera reviewers found informed consent documents and approval letters signed by foster care agency staff for at least 14 enrollments of children who were in the joint guardianship of the commissioner and the foster care agency. Although conforming to the technical requirements of the policy, this resulted in the enrollment of several foster children in trials that the Medical Advisory Panel had either recommended against or which the commissioner had not yet approved. Three children were enrolled through the joint guardianship provision in a Phase I clinical trial of an HIV vaccine (PACTG 218) that the MAP reviewed and did not recommend, and the commissioner did not approve.[741]

Results of Clinical Trials. For 15 medications that were part of clinical trials in which New York City foster children and other children participated, the FDA reviewed trial data, determined that it showed the drugs were safe and effective, and approved the medications for widespread use by children living with HIV.[742] Of the medications tested in clinical trials in which foster children participated, five antiretroviral medications and three HIV vaccines have not been approved by the FDA for pediatric use. All five of the antiretrovirals (but not the vaccines) have been approved by the FDA for use in adults. There were many reasons that they were not approved for children, including the need for frequent dosing, the availability of less toxic alternatives, a lack of proven efficacy, high toxicity profiles, and the absence of a formulation such as a syrup or powder that is acceptable for use in children.[743]

Discussion and Implications

These findings identify many serious issues for future clinical trials policy in New York City and elsewhere. The conditions under which these issues are considered in the future are likely to be difficult. Child welfare agencies across the country commonly struggle to attract, train, and retain qualified staff; to ensure budgets that support effective services; and to hold themselves and

[740] Chapters 7 and 10 discuss this finding.
[741] Chapter 7 discusses the policy for joint guardianship enrollments and the enrollments in PACTG 218. Chapter 10 discusses other instances of children entering trials through joint guardianship.
[742] Chapter 8 of this report describes how Vera staff made this finding.
[743] Chapter 8 of this report describes how Vera staff made this finding.

those they contract with accountable for the wellbeing of children in their care. The performance of child welfare agencies can and does change, often dramatically, and agencies often adhere rigorously to policy.

But even during periods with relatively few children in foster care and a strong economy, child welfare agencies face enormous challenges. This state of affairs creates an ethical dilemma. Somewhere, sometime, some children in foster care will suffer from serious and potentially fatal health conditions that will result in physicians recommending they participate in a clinical trial. Knowing that implementing any clinical trials policy will be difficult and might be inconsistent, what is a responsible policy for jurisdictions to adopt?

In the course of this project, Vera staff heard many perspectives on clinical trials policy. Some feel that child welfare agencies should not allow children in foster care to participate in any clinical trials. In support of their position, they often cite the history of medical research involving African American and Latinos and the vulnerability of foster children. Others feel that children in foster care, including African American and Latino children, should have the same chance to participate in the development of new treatments as other children and that they should not be denied access to a promising new medication because they are not in their parents' care. The words of people Vera staff interviewed provide a framework for this discussion.

Edward Handlesman, pediatrician and clinical trials researcher:

> *I know exactly what I was doing, I know exactly what my motivation was, I know exactly the motivation of most of the people who I was directly working with [at the foster care] agencies…Those things I know directly and I know absolutely, positively, without any doubt, the only reason we were putting kids in trials was to save their lives or to make their lives better and that's it…there were probably some things which technically may not have been done exactly according to the letter of the law, but they were done according to the spirit of the law…the reason it was done was because it would save time and potentially save lives.*

Hermann Mendez, pediatrician and clinical trials researcher:

> *There are regulations, safeguards, legal safeguards that were put in place, that were not followed. Put in place years before. Most of us were [acting in] good faith, like pediatricians we [acted in] good faith, with the good intention to help, right? [But] we were part of a system that was not being too careful in protecting the rights of the children…A system…that did not enforce the existing regulations.*

Stephen Nicholas, pediatrician and clinical trials researcher:

> *So, it sounds almost self-serving by anybody to say at this point, "Well, you should have had better record keeping. You shouldn't have lost those records." That's true. But should any part of the process have been clearly different? I don't think so. I think this is a success story by a lot of good people doing their best. And I don't think there's any regrets in that regard, you know? We didn't hurt kids, we saved them. I rest my case.*

Roger Wareham, human rights attorney in private practice and member of the December 12th Movement:

> *[W]e thought that the questions that were raised were very legitimate, and in terms of the history of [African American] people in this country, just raised the specter of the type of experiments that went on with the syphilis experience around Tuskegee…The issue was not around whether people see a connection between AIDS and HIV. It's the issue of the experimentation.*

Megan Mclaughlin, policy strategist, consultant, and former executive director/CEO, Federation of Protestant Welfare Agencies:

> *You know, the Tuskegee experiment floats around in people's minds. All kinds of distrust floats [around]. So when these issues come up, we have to be honest about it and open about it and take it head on, address head on the vestiges of the historical context if you will, vestiges of past wrongs. Now I have said to people, this is not a Tuskegee situation. It's the opposite. Medication wasn't withheld. Medication was given.*

Vera Sharav, executive director, Alliance for Human Research Protection:

> *These kinds of experiments would not have been done on middle class children whose parents would have access to a second opinion to investigate what risks, in fact, are involved. The city consented [the children] like animals in a herd. They consented them en masse …[W]hatever dignity a human being is supposed to have compared to an animal, the children were not given that dignity. These children were treated, and I'll repeat it, like throwaway children. They were nobody's children.*

James Purcell, executive director, Council of Family and Child Caring Agencies:

> *Doing these [foster boarding home] HIV programs would be one of my two things that I put on my resume from my time at the New York State Department of Social Services. It is one of the things I am most personally proud of. It's one of the reasons I was so personally angry about [this controversy], because I thought we did a great job. The question I would ask…those kids who weren't enrolled in trials, why not?...[If we had not allowed these children into the trials,] the more damning question would have been, "What were you thinking that you didn't enroll these kids in trials? I mean—at that time— you knew they were going to die." With the trials, maybe they wouldn't.*

David Lansner, partner, Lansner and Kubitschek, and board member of the Family Defense Center:

> *[This controversy] didn't surprise me because the [Children's Services'] foster care system keeps parents out of things enormously. My understanding is that there were children with HIV for which they didn't have any cure and so they gave them this experimental medicine which may have saved some of their lives, in which case it may*

> *have been a good thing to do. But I certainly believe that a lot of parents weren't told about what was going on.*

Director of a program for foster children:[744]

> *In the late 80s, you sat at the bedside of dying children because you had no available treatment for them. You watched mothers sign for trial medication and you watched those children leave the hospital and go home with their parent. Your children were leaving for the cemetery. You would beg to have those medications for the children so they could have a chance at life too.*

Alan Fleishman, senior vice president, New York Academy of Medicine:

> *If agencies create regulations to not allow foster children into research…then we will risk children and their future lives if we have another epidemic in which you can only get clinical treatment through clinical trials…[F]oster children shouldn't be discriminated against. In a well-intentioned approach to protect them, we could protect them to their detriment.*

Adoptive parent:

> *Clinical trials are what kept our kids alive. And not just that, but Incarnation Children's Center kept our kids—my kid alive.*

Children's Services employee:

> *When I first came to work at [Children's Services] and I heard that the kids were in clinical trials my first reaction was, "You've got to be kidding."…obviously kids in institutions are very vulnerable. Minorities are vulnerable. Wards of states are vulnerable. And also, HIV is like the new frontier where a lot of ambitious people are hoping for the Nobel Prize…After I was at [Children's Services] and looked at the issues more closely, I thought and I still believe that we did the right thing.*

It is not the Vera Institute's role to recommend a specific policy. New York City and other jurisdictions will determine clinical trials policy through the policymaking process. Over the course of this study, however, Vera staff and advisors have accumulated a large body of knowledge to inform that decision. Elected officials representatives, appointed officials, families, advocates, physicians, researchers, and communities with a stake in this issue and with a capacity to influence policy should understand that there are multiple options for clinical trials policy. Developing such a policy is more complex than a single decision to either bar foster child participation in clinical trials or to provide unfettered access to newly developing treatments.

[744] Some people Vera staff interviewed opted to speak anonymously. Therefore, this report does not list their names or other identifying information.

A Continuum of Situations. Clinical trials are conducted in a variety of situations and for many different purposes.[745] Some HIV/AIDS clinical trials, including many cited in this report, tested new treatments to suppress the virus, some tested treatments to prevent complications associated with HIV, and some sought to prevent transmission from mother to baby. Other studies were observational, allowing scientists to learn more about the virus and the course of the disease in order to improve diagnosis and treatment.[746] Indeed, without clinical research, public health authorities, patients, physicians and others cannot know whether new treatments are effective or harmful. Given the range of possible clinical research activity, officials need to consider many factors when deciding upon the conditions that could apply when enrolling a vulnerable group such as foster children—if they decide that foster children should be allowed to participate at all.

In addition to existing federal research regulations and state law, there are at least four medical dimensions to consider in thinking about when and how foster children might be allowed to participate in clinical trials:

1. The seriousness of the child's disease: A fatal disease or one with serious and permanent consequences might prompt a different set of decisions when compared to one that is not life-threatening or a disease that has unpleasant but temporary effects.
2. The existence, efficacy, and safety of existing treatments: In some situations there may be no existing treatment that is effective and safe. Clinical trials that address conditions for which standard medical treatments are effective and have relatively few side effects might be viewed differently than those that treat conditions for which the standard treatment may be effective but have side effects that make them undesirable.
3. The risks and potential benefits of a study: Does the trial offer the possibility of benefit over the best available treatment outside of a clinical trial? What are the potential toxicities of study medications over standard treatment?
4. The stage of development of experimental treatment (for trials of new treatments): As discussed in Chapter 8, clinical trials of new treatments usually follow three phases and may be available while under development through expanded access programs.

In addition to these medical considerations, at least two child-specific and child welfare factors also might influence a decision to allow foster children to participate in a clinical trial:

[745] In addition to the Vera review, this section of the report draws on discussions between Vera staff and the Vera Clinical Trials Advisory Board, information gathered by Vera staff attending conferences on the participation of children in clinical research, Vera staff interviews with advocates and activists, and published articles and books on the subject, especially Eric Kodish, *Ethics and Research with Children: A Case-Based Approach* (New York: Oxford University Press, 2005); and Marilyn Field and Richard Behrman, eds., *Ethical Conduct of Clinical Research Involving Children* (Washington DC: The National Academies Press, 2004).

[746] Children in observational trials received care and treatment from their own physicians and could also have been enrolled in medication trials.

1. Placement stability and capacity: Trials place varying demands on caregivers. Some observational trials require little more from caregivers than answering a few questions. Medication trials, on the other hand, can require frequent visits to medical centers or complicated schedules for administering medication. Some foster parents have fewer responsibilities or a greater capacity to take on complex tasks than others. In systems that contract out foster care services, like New York City, a contract agency's stability and capacity to monitor a child through the course of a trial might be part of a decision. A child with a history of frequent placement transfers, moreover, might be less likely to complete a clinical trial. If the risks or potential benefits of a trial are linked to completion, then a child's placement stability should be a consideration in decisions about participation.
2. The trajectory of the foster care case: Foster care is meant to be a temporary stop on the path to a permanent family—either a return to a parent or an adoption. Though predicting the outcome of a foster care case can be difficult, if a child is on the cusp of reunifying with a parent, a brief delay that allows the clinical trials decision to be made solely by a parent might be considered. In other instances, a child may have little or no prospect of returning home, and adoption resources might not be readily available. In those situations, the child welfare agency will have to make a decision on its position regarding a possible trial enrollment.

These dimensions create many possible combinations. Some jurisdictions may decide not to allow children in foster care in any clinical trials without a judge's approval. Other jurisdictions might approve of enrollments of a fatally ill child who has no treatment options to enroll in clinical trials of new treatments for his or her disease—but not in a Phase I trial to test the safety of a new medication. The same jurisdiction might decide that clinical trials of treatments that have unpleasant but temporary effects are inappropriate for children in foster care.

Complicated and important decisions such as these are part of any child welfare system. Social workers, managers, judges and many others make life-altering decisions every day, from returning a child to a parent to severing a parent's rights, from placing a child in one foster home as opposed to another to approving an adoption or deciding a placement transfer is a better option for a particular child. A critical difference between these decisions and participation in a clinical trial, however, is that clinical trial participation is voluntary and not solely the domain of child welfare system staff if a birth parent retains his or her rights.

Recommendations

The knowledge gathered throughout this study provides a basis for the Vera Institute and its Clinical Trials Advisory Board to make the following recommendations should policymakers decide to allow foster children to participate in clinical trials. These recommendations are aimed in part at remedying the problems that this report identifies. The recommendations can be seen as

a set of benchmarks for child welfare staff, elected representatives, and community advocates to measure progress in addressing the concerns this report raises.[747]

1. Respect Parental Decision Making

Concern: Parental rights were not respected in every case.

Recommendation: Make researchers and their staff—not foster care agency staff—responsible for obtaining permission for a foster child's participation in a clinical trial. Clinical trials policy should respect parents' right to determine whether they want their children to participate in a clinical trial. The relationship between child welfare staff (including contract foster care agency staff) and parents is complex and varies from case to case. Yet there is always a fundamental imbalance of power between a parent and child welfare staff: a request by even the most sensitive and well-informed child welfare staff member comes freighted with the knowledge that the person making the request may influence the course of the parent's child welfare case.

*Recommendation: In instances where the parents cannot be engaged and the child welfare commissioner feels it is imperative that a child enroll in a clinical trial, a person representing the child's interest and not connected to either the foster care agency or the medical institution, such as a law guardian or family court judge, should provide a written determination that participation in the clinical trial is in the child's best interest***.** Vera reviewers read many files in which child welfare or medical staff found locating or working with parents challenging. Many parents may have found working with child welfare and medical staff difficult as well. In some situations, child welfare agencies certified that parents could not be located and the city's child welfare commissioner consented to enrollment. The regulations allowed this approval.

2. Make Detailed Policy

Concern: New York City's clinical trials policy in the 1980s and 1990s did not detail procedures for how to handle many issues, and the policy documents reviewed by Vera staff did not anticipate several frequently occurring situations. This forced medical and child welfare personnel to improvise in a pressured environment that involved legally and ethically complex decisions.

Recommendation: Create detailed policy guidelines that can apply across a range of child welfare and medical/public health circumstances. In other areas of government, creating detailed policies can hamper efficiency, performance, and innovation. However, given the

[747] By clinical trials, this section refers to research that involves medical interventions or testing. Children's Services and the New York State Office of Children and Family Services have an oversight regime for observational studies and behavioral research already in place.

sensitivity and complex regulatory framework associated with enrolling foster children in clinical trials, it is essential to have a detailed policy that anticipates common situations, acknowledges potential problems, and provides procedures for handling those situations. Establishing this policy prior to facing these situations will allow for broader input in the policymaking process, faster and more informed decision making, and will allow less room for individual interpretations of the policy during implementation.

Vera recommends that specific, detailed policy be developed to address the following issues:

1. The circumstances in which a birth parent can enroll a foster child in a clinical trial without Children's Services permission;
2. The process for determining a parent's competence to participate in an informed consent process, and the procedures staff should take if a parent is deemed incompetent;
3. The procedures to follow when a child was enrolled in a clinical trial prior to entering foster care, including the required documentation (beyond a copy of the signed informed consent form which should be required in every case);
4. The steps child welfare staff should take if they find that a child became enrolled in a clinical trial while in foster care without child welfare or research staff having followed the required procedures, or if other violations of the policy are discovered. These steps should pertain to policy violations by foster care agency staff and medical institutions; and
5. The conditions and authority under which child welfare staff can take actions not anticipated by the written policy.

3. Ensure that Staff Understand and Agree to Abide by the Rules

Concern: The 2001 Congressional report on research involving children found that knowledge about and application of federal regulations for the participation of children in research was inconsistent. Vera staff found that many people at Children's Services and its predecessor agencies had studied the federal regulations and applied them to their requests to have foster children participate in research. However, knowledge and application of the regulations and policies was not consistent. As the Department of Health and Human Services' Office for Human Research Protections' (OHRP's) investigation of Columbia University Medical Center and other institutions across the country found, IRBs did not always know about or fulfill all their responsibilities when it came to some HIV/AIDS clinical trials involving children who were "wards of the state."[748]

[748] See Chapter 6 for a discussion of OHRP findings.

Recommendation: Child welfare and medical staff involved in the participation of foster children in clinical trials should obtain periodic certifications indicating that they understand and agree to follow the applicable rules and regulations. Today, there are many resources that provide guidance for the participation of children in research. These include extensive published literature, government reports, OHRP's web site, accreditation for Institutional Review Boards, and online research ethics training programs. Vera staff recommends that *at a minimum*, key staff in child welfare and medical institutions complete certification courses in the federal regulations.

4. Increase Transparency and Community Involvement

Concern: The policy that allowed the participation of foster children in HIV/AIDS clinical trials was discussed publicly and disseminated to physicians, foster care agency staff, and staff in New York City's child welfare agency. Child welfare officials received input from many medical experts and child welfare professionals. However, there is little evidence that community constituents, including parent and child advocacy organizations, were involved.

Recommendations: Given community concerns about medical research and specifically about the participation of foster children in medical research, Children's Services should take steps to ensure that clinical trials policy development and oversight involve child and community advocates and representatives of African American, Latino, and other constituencies as well as medical and child welfare professionals. Child welfare policy is a contentious arena in which officials must have time and space to make decisions, and time pressures often constrain officials in seeking advice. The deeply held concerns about this issue indicate that transparency and community involvement in the policies that pertain to clinical trial enrollments, the number of children enrolled, and the types of trials involved—while respecting the individual confidentiality of children and their families—are essential to building public trust.

5. Maintain Commissioner Control of Trial Enrollments for Children in Guardianship

Concern: For a period in the 1990s, foster care agencies approved enrollments of foster children in joint guardianship with the assent of prospective adoptive parents but without the approval of the child welfare agency.

Recommendation: Only the commissioner of Children's Services should have the right to approve or reject trial enrollments for foster children in the sole or joint guardianship of the commissioner.

6. Document Activities

Concern: The clinical trials examined in this report were conducted during a difficult period for New York City and for the city's child welfare agency. Nonetheless, the violations of regulations concerning file documentation and retention prevented child welfare officials from fully informing former foster children, caregivers, participants, the New York City Council, advocacy groups, and the general public about the HIV/AIDS clinical trials Vera staff examined.

Recommendations: Children's Services should provide public reports to demonstrate that the agency is ensuring that regulations regarding record keeping and retention for all foster children are being followed. The creation and retention of accurate records is a fundamental responsibility of the child welfare system. Child welfare records often contain the only comprehensive accounting of a child's social and medical history. They are also an essential tool of child welfare officials charged with holding staff and contract agencies accountable for their actions. Some may blame violations in fulfilling this responsibility to insufficient resources, unclear policy, staff turnover, and other factors.

Government must ensure that the law is followed and that child welfare personnel have the resources to adequately staff operations to accomplish this work. Standards for documentation and record-keeping by contract foster care agencies and by Children's Services for children enrolled in clinical trials should be reviewed and enhanced. To ensure that standards are followed, Children's Services should consider retaining an independent entity to conduct periodic, public audits of files pertaining to children enrolled in clinical trials.

7. The New York State Department of Health Should Authorize the Review of Medical Records

Concern: The New York City Law Department determined that only the New York State Department of Health (NYSDOH) has the right to conduct or authorize a review of the medical and clinical trial records of foster children who participated in HIV/AIDS clinical trials—even when hospitals agree to have the files reviewed. Children's Services requested that NYSDOH exercise this supervisory authority on several occasions and in several ways. The NYSDOH declined all of its requests. As a result, the findings in this study have several limitations.

Recommendation: *The NYSDOH should either authorize Children's Services to obtain copies of the informed consent forms used to permit children to enroll in the clinical trials Vera staff examined and other relevant information that Children's Services may request or conduct its own investigation.* Children's Services, the New York City Council, and the Office for Human Research Protections have each spent considerable time and money addressing the subject of this report. City, state, and federal legislative bodies have each held hearings on this issue. Only a review of medical and research records can settle some of the issues discussed in this study. The

state department of health's refusal to exercise its supervisory authority undermines public confidence in medical research and child welfare services. To avoid a conflict of interest in making this recommendation, the Vera Institute declines to participate in subsequent analysis of any information that the NYSDOH might release.

8. Actively Manage Clinical Trials Issues

Concern: In the late 1980s and early 1990s, HRA invested considerable resources in expanding the number of PAU employees, hiring staff with strong credentials. The agency developed computerized tracking systems and conducted several types of activities to gather information from contract foster care agencies and medical providers and to keep this broad network of people engaged with the unit. The performance of the PAU, however, declined after 1995. Over time, the unit's capacity to perform its assigned tasks diminished.

Recommendations: Children's Services should actively manage clinical trials issues. In addition to providing the staff and resources needed to manage clinical trials issues, Children's Services should conduct regular reviews of clinical trials policy during times of increased trial participation. The complex issues raised by foster children's participation in clinical trials—issues that multiply with the numbers of children and trials involved—require proactive management. Child welfare officials must ensure that the staff are performing their work adequately. For staff involved with clinical trials, management should ensure that at a minimum:

1. Data on enrollments are reliable and verified with contract agency staff and hospitals.
2. Researchers have informed the agency of the Subpart D section (45 CFR 46.404-407 and 21 CFR 50.51-54) under which the IRB approved a clinical trial.
3. Staff confirm that for trials approved under 46.406:
    a) an independent advocate who meets the criteria set by the regulations is appointed;
    b) the independent advocate has planned a set of appropriate activities; and
    c) the independent advocate files a written report on his or her activities periodically (depending on the nature and design of the trial) and no less than once a year.
4. Copies of IRB approvals, consent forms, and trial protocols are archived at Children's Services and are readily available for review.
5. Caseworkers are regularly informed about a child's progress and medical condition by the child's physician while the child is participating in a trial.

Some may argue that federal regulations mandate that hospital IRBs carry out these responsibilities. This is true. When IRBs fail to carry out their responsibilities, however, the enforcement mechanisms in the federal regulatory oversight system are primarily reactive:

federal enforcement usually occurs only when complaints are received. The particular vulnerability of children in foster care requires child welfare staff to play a *proactive* role in ensuring their safety and proper treatment. Children's Services should take responsibility to ensure that rules, regulations, and policies are followed with regard to children in foster care.

9. Use High Standards for Clinical Trial Enrollment

Concern: The standard for enrollment in a clinical trial that HRA/Children's Services policy used was that a trial must offer a potential treatment benefit to *every* foster child who might enroll in it.

Recommendation: For each foster child who might enroll in a clinical trial, Children's Services should ensure that the anticipated benefits outweigh the risks of harm. Vera urges the agency to restrict the approval of foster child enrollment to trials where the chance to receive a clinical benefit is not otherwise available outside the clinical trial. There are many perspectives about the risks and potential benefits that accrue to people who participate in medical research. Given that foster care is designed as a temporary measure until a permanent home is found, Children's Services should allow foster children to participate in trials only when participation offers the possibility of benefits not found outside of the trial.

10. Manage Conflicts of Interest

Concern: Medical Advisory Panel reviewers had significant influence on whether HRA/Children's Services approved or disapproved enrollment in specific trials. During the early period of pediatric HIV/AIDS, there were few medical specialists with expertise in pediatric HIV/AIDS. In turning to experts on pediatric HIV/AIDS to participate on the MAP and provide consulting services, HRA had little choice but to draw from a small circle of people who had strong professional relationships with each other. That the MAP recommended disapproval of many trials does not eliminate the appearance of a conflict of interest.

A single person at Incarnation Children's Center served as executive director of the facility, a clinical trial investigator, a pediatrician, a faculty member, a consultant to the Pediatric AIDS Unit, and a Medical Advisory Panel member. The city's child welfare agency requested that this person assume many of these roles—which, in combination, created real and apparent conflicts of interest. This person's colleagues and Children's Services' staff have high regard for the physician's knowledge, ability, and integrity; this physician recommended against HRA/Children's Services' approval of several clinical trials in his role as a MAP member and PAU consultant; he received small remuneration for his consultancy; and he recommended that Children's Services stop approving the enrollment of foster children in clinical trials without birth parent consent years before this controversy arose.

Recommendation: Children's Services should adopt a conflict of interest policy relating to research. The agency needs and will continue to need advice from medical experts to carry out its charge of ensuring the health of the children in its care. In some cases, particularly in the advent of a newly discovered disease, few people may know much about a disease or condition and the small pool of experts available might have positions or consultancies that create conflicts. The conflict of interest policy should ensure that Children's Services receives advice from physicians not involved in clinical research on clinical trials issues when it is practicable, as the agency did in many instances after 1999. Furthermore, to minimize the appearance of a conflict of interest, Children's Services should keep the roles of foster care facility director separate from consultant or clinical trials investigator.

Conclusion

This report presents information on the participation of foster children in HIV/AIDS clinical trials in New York City. The information it presents will not settle many of the issues that led to this report. Perspectives on the information contained in this report will diverge and conflict. Broader debates about the status and identities of those who bear the burdens and receive the benefits of medical research will continue.

For nearly five decades, the Vera Institute of Justice has provided stakeholders and the general public with information and nonpartisan recommendations useful to the reform and improvement of public policy. The authors of this report and their advisors have sought to stay true to this tradition. Vera staff and their advisors hope that the information presented here will inform the debates that are sure to follow and, through this exchange of information and ideas, lead to improvements in the services that people rely on for justice and safety.

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